



Article

A Properly Balanced Reduction Diet and/or Supplementation Solve the Problem with the Deficiency of These Vitamins Soluble in Water in Patients with PCOS

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Abstract: Polycystic ovary syndrome (PCOS) is an increasingly common problem for women in the reproductive age throughout the entire world. A reduction diet with a low glycaemic index (GI) has proved to support the treatment of PCOS. The aim of the study was to analyse the influence of the diet on the level of vitamins soluble in water. The study included 55 women, 40 of which suffered from PCOS (identified by means of the Rotterdam Criteria) and 15 healthy women of the Caucasian race. The level of vitamins before and after the dietary intervention was measured. The diet was a reduction diet with a reduced glycaemic index (GI). Biochemical analyses were made on the basis of liquid chromatography—Infinity 1260 Binary liquid chromatography (LC) Agilent Technology. The level of vitamins in the serum was analysed together with the consumption before and after the dietary intervention. A higher level of vitamin C in the plasma was observed before and after the dietary intervention in the PCOS group in comparison to the control group despite the lower intake of this vitamin in the PCOS group. The remaining vitamins were at a comparable or lower level (B1, B3, B5, B6 and B12). After the dietary intervention, only B1 and B9 were at a clearly lower level (a trend of $p = 0.093$ and $p = 0.085$). A properly balanced reduction diet with reduced GI improves the supply of vitamins in women with PCOS. An additional recommendation should be the additional supplementation of B1, niacinamide and the combination of folates with inositol. The level of vitamin C in the plasma may not be a good marker of its supply in the PCOS group.



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1. Introduction

Polycystic ovary syndrome (PCOS) is diagnosed on the basis of at least two out of three Rotterdam Criteria from 2003 [1]:

- hyperandrogenism,
- or its clinical manifestations, such as androgenic baldness, hirsutism, menstruation and ovulation disorders,
- enlarged (ovary volume $> 10 \text{ cm}^3$) or polycystic ovaries (at least 12 follicles) visible in an ultrasound image.

When it comes to metabolism, PCOS is characterised by disorders in carbohydrate metabolism, which is accompanied by insulin resistance [2]. Furthermore, the fat build-up of internal organs, particularly, the presence of NAFLD, is the domain of women [3,4]. A study published in 2017 proved that the implementation of a reduction diet combined with physical activity had an influence on the reduction in body mass in patients and on the improvement of biochemical parameters, mainly of the lipid profile, which is often disturbed [5]. Therefore, it seems that PCOS is a syndrome that includes numerous

disorders that originate in metabolic defects leading to the development of obesity. The presence of the symptoms depends on the effective functioning of the entire organism, while the dysfunction of ovaries is a consequence of metabolic disorders. Women with PCOS are also in the risk group of developing type 2 diabetes, which makes more sensitive to insulin. This is why metformin is often used in the treatment of PCOS. Unfortunately, this medicine has an influence on the reduction in vitamin B₁₂ levels after just a few months of intake and is accompanied by an increase in the concentration of homocysteine [6]. Moreover, the inability to get pregnant and random stillbirth in women with PCOS may also be a consequence of the clinical deficiency of B12 [7]. In addition, in patients with hyperhomocysteinemia, stillbirth was observed more frequently than in women with correct homocysteine concentration [8].

The authors have a hypothesis that vitamins soluble in water that have antioxidant properties and participate in metabolic transformations as regulators may be supplemented together with a reduction diet, thus being beneficial in the treatment of PCOS. In the available literature, we did not find information on the influence of a balanced reduction diet on the supplementation of nutritional deficiencies with regards to vitamins soluble in water in women with PCOS. We were interested whether the supply combined with a properly balanced reduction diet proves sufficient to negate the differences with the control group, whether this type of diet should also additionally include supplementation and if so—what vitamins should be selected. We were interested whether the supply with an appropriately balanced reduction diet is enough to eliminate the difference in comparison to the control group or whether this type of diet should also include supplementation with specific vitamins (which ones?).

We decided to check whether the reduction diet with a low glycaemic index (GI), but rich in vitamins can improve the status of vitamins soluble in water in women with PCOS. To do this, we compared the results to those of women with PCOS who did not decide to change the diet, as well as to healthy women with excluded PCOS.

2. Material and Methods

The study was approved by the Bioethics Committee of the Pomeranian Medical University in Szczecin and was conducted in accordance with the provisions of the Declaration of Helsinki, institutional policy, and national law. All study participants consciously expressed their consent to participate in the study.

2.1. Study Group

In total, 55 women of the Caucasian race participated in the study—40 patients aged 32.52 ± 7.12 years with polycystic ovary syndrome (PCOS-I) diagnosed on the basis of the Rotterdam criteria: 2 out of 3 of the following criteria—rare ovulations or lack of ovulations and/or biochemical symptoms of hyperandrogenism and/or image of polycystic ovaries in USG (Ultrasound Voluson 730, GE, Switzerland). The control group (CG) consisted of 15 women aged 31.23 ± 6.3 years and the correct BMI of 22.1 ± 1.5 without PCOS. All participants of the study were subjected to the measurements of anthropometric bioelectrical impedance (Akern, BIA-101, Firenze, Italy).

Only 18 women with polycystic ovary syndrome who followed the recommendations and diet were qualified for stage 2 of the study (PCOS-II). The verification was conducted on the basis of a nutritional interview and body mass reduction—a minimum of 2 kg in 3 months. Lastly, the measurement of the content of vitamins in the plasma was conducted and compared between the groups in accordance with Figure 1. All of the women were in the childbearing age and their anthropometric parameters are presented in Table 1.

2.2. Quantitative Dietary Assessment

The following methods were used to gather data on product consumption: food diary referring to the last 3 days at the start of the study. The focus was on a one-day food record from the last 24-h dietary interview when the patient returned for a control visit. The

data collected from the diaries and interviews included the following: quantity, way of preparation, the time of consumption of each meal and the ingredients that were used. The menus were taken on Thursday and Friday as well as on Saturday or Sunday. Using computer software Dieta 6D (National Food and Nutrition Institute, Warsaw, Poland), we analysed a total of 162 dietary menus of women suffering from PCOS.

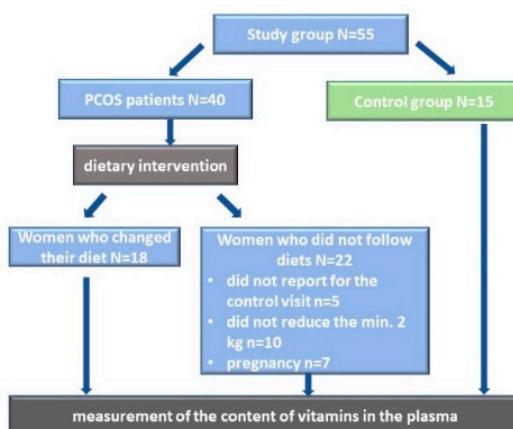


Figure 1. Study design.

Table 1. The characteristics of the study group and the control group.

Parameter	PCOS Patients	Control Group (CG)	p
Age (year)	32.52 ± 7.12	30.23 ± 6.31	NS
Height (m)	1.67 ± 0.06	1.68 ± 0.06	NS
Body mass (kg)	82.75 ± 15.6	62.76 ± 6.67	1×10^{-6}
BMI (kg/m^2)	29.65 ± 6.76	22.22 ± 1.52	1×10^{-6}
Fat mass (%)	39.54 ± 8.08	25.65 ± 3.96	1×10^{-6}
Waist circumference (cm)	99.87 ± 15.65	74.75 ± 5.01	1×10^{-6}
Hip circumference (cm)	109.45 ± 8.96	95.85 ± 4.88	1×10^{-6}
WHR	0.92 ± 0.08	$0.78 \pm 0.03 *$	1×10^{-6}

WHR—waist-to-height ratio; BMI—body mass index; *—it does not seem necessary to apply WHR in patients with correct body mass; NS—no statistically significant differences.

2.3. Dietary Intervention

Recommendations pertaining to the change of lifestyle and a 7-day menu were provided to each female participant [9,10]. The caloricity of the diet was reduced by 600 kcal with reference to the daily caloric needs. Moreover, 5 meals per day were included in the diet, and the products were given in grams. Sources of carbohydrates (5 portions per day) included: brown rice, oatmeal, coarse-grained groats, wholegrain rye bread or graham bread and—sporadically—potatoes as well as wholemeal pasta featuring lowered glycaemic indexes. The diets recommended the following products as sources of proteins: lean meat without skin (turkey or chicken), fish (sole, salmon and tuna), eggs, semi-skimmed milk (fat content: 2%), dairy products (quark and natural yoghurt) and legumes (soy, red lentils, beans or peas). Fat sources (2 portions per day) included—nuts and seeds (pumpkin seeds, almonds, sunflower seeds, sesame seeds, and chia seeds), oily fruits, e.g., avocado, and raw cold oils (e.g., linseed oil, olive oil, and rapeseed oil). From October to April, it is recommended to consume cod liver oil as Poland is situated in a temperate, warm transitional climate as people here often have problems with vitamin D deficiency.

Low GI fruits and vegetables were also included in the menus with the aim of supplementing the diet with minerals and vitamins. The recommended methods of food

preparation were braising, roasting, cooking in water and steaming. Furthermore, every participant was advised to drink about 2 L of fluids every day, especially water and herbal infusions. The final recommendation was to increase physical activity to a minimum of 3 h a week.

2.4. Reagents for Biochemical Analyses

Reagents (NaHCO_3 , NaOH , HK_2PO_4 , methanol and acetonitrile) of the highest HPLC quality were purchased from Sigma Aldrich (St. Louis, MO, USA). Millipore water (Millipore, Billerica, MA, USA) was used to prepare the buffers. Vitamins were isolated using amber-coloured Eppendorf tubes. To secure vitamins against photo-oxidation, the samples were isolated in a dark room in amber Eppendorf tubes. After the collection of 400 μL of blood plasma, an equal amount of acetonitrile was added together with 100 μL of internal standard (100 ng/mL theobromine). The reagents were mixed for 2 min and then centrifuged for 15 min at 4000 rpm. The formed supernatant was then transferred to new tubes in order to evaporate the acetonitrile. The water phase was moved to solid phase extraction columns that included a C-18 silica cartridge (Thermo Scientific, Waltham, MA, USA), which was activated earlier by means of 1 mL of methanol and 1 mL of clear water. The contents of the columns were subjected to elution using 85% methanol with 1.5 mL water. The formed solution was vacuum dried and—directly before HPLC analysis—was diluted in 100 μL buffer, 25 mM HK_2PO_4 [11,12].

2.5. The Analysis of Vitamins Soluble in Water with HPLC

HPLC Infinity 1260 Binary LC (Agilent Technologies, Waldbronn, Germany) was used to conduct the analysis. Subsequently, vitamins were separated using the gradient method with 25 mM HK_2PO_4 buffer with the pH of 7.0 and 100% methanol buffer. A and B buffer proportions for the times 0.0, 2.5 and 16 min were 97%:3%, while for 7.2 and 14 min they were 70%:30%. The separation of vitamins was conducted using BDB Hypersil C-18 (Thermo Scientific) column at 35 °C. The buffers moved through the column at the rate of 0.9 mL/min, and the injection volume was 10 μL [13]. The identification of specific vitamins in the studied samples was conducted on the basis of the observation of retention times of standard peaks. The data were analysed using ChemStation taking into account standard curves (ascorbic acid-C, thiamine-B1, riboflavin-B2, nicotinic acid-B3, calcium pantothenate-B5, pyridoxine-B6, biotin-B7, folic acid-B9, cyanocobalamin-B12, niacinamide-PP) with a correction for the internal standard (theobromine with the concentration of 100 mg/mL) [14].

2.6. Statistical Analysis

Statistica 12.0 (StatSoft, Cracow, Poland) was used to analyse the results. The average values (Avg) and standard deviation (SD) were calculated. As the distribution in most cases deviated from normal (Shapiro–Wilk test), non-parametric tests were used: the Mann–Whitney test for group comparisons (PCOS and CG) in which $p < 0.05$ was considered statistically significant.

3. Results

The average consumption of vitamins in the analysed diets in the PCOS-I group and—especially—in the PCOS-II group significantly differed in comparison to the control group (Table 2). The participants of the PCOS-I group consumed less vitamins in comparison to the control group, but statistical significance was observed only in terms of vitamin C and folates. The PCOS-II group consumed statistically significantly higher amounts of all of the analysed vitamins in comparison to PCOS-I. When comparing the consumption of vitamins in PCOS-II with the control group, statistically significant differences or trends were also observed in terms of the higher consumption of vitamins, except for cobalamin (Table 2).

Table 2. The comparison of the consumption of vitamins with reference to the analysed groups (PCOS-I, PCOS-II, and CG).

Vitamins	PCOS-I N = 40	PCOS-II N = 18	CG N = 15	P PCOS-I vs. PCOS-II	P PCOS-I vs. CG	P PCOS-II vs. CG
C (mg)	68.53 ± 38.22	234.61 ± 87.3	101.37 ± 73.04	1 × 10 ⁻⁶	0.017	1 × 10 ⁻⁵
B1 (mg)	1.21 ± 0.33	1.64 ± 0.29	1.12 ± 0.32	1 × 10 ⁻⁶	0.195	1 × 10 ⁻⁵
B2 (mg)	1.33 ± 0.29	1.76 ± 0.59	1.41 ± 0.39	0.0004	0.564	0.041
niacin (mg)	15.42 ± 4.18	21.2 ± 4.65	15.06 ± 4.58	1 × 10 ⁻⁶	0.771	0.0001
B6 (mg)	2.08 ± 0.63	2.64 ± 0.78	2.16 ± 0.91	0.002	0.718	0.049
Folates (μg)	221.2 ± 65.4	321.3 ± 72.3	262.8 ± 78.56	1 × 10 ⁻⁵	0.041	0.074 *
B12 (μg)	3.30 ± 2.13	3.72 ± 1.05	3.03 ± 2.34	0.323	0.651	0.168

PCOS I—polycystic ovary syndrome group before dietary intervention; PCOS II—polycystic ovary syndrome group after dietary intervention; CG—control group; *—trend.

When investigating the supply of vitamins soluble in water, we based our analysis on their concentration in blood plasma. After the dietary intervention, the concentration of some of the vitamins changed significantly (Figure S1A–C; Table 3). Most vitamin levels in the analysed cases were significantly different between PCOS-I and the control group (CG) (Figure S1B; Table 3). This was true for vitamin C, thiamine, B3, B5, pyridoxine, folates and cobalamin—in the last case, a trend was observed. However, the concentrations of vitamin C and B3 were lower in the control group. After the introduction of a balanced reduction diet, vitamin C and B3 levels in the PCOS-II group still remained significantly lower than in CG (which was surprising), but they did improve insignificantly (Figure S1C; Table 3). Furthermore, the average level of the remaining vitamins was increased in comparison to PCOS-I, but the results were not statistically significant (Table 3).

Table 3. The average concentration of vitamins analysed in the plasma before and after the dietary intervention with reference to the analysed groups (PCOS-I, PCOS-II, and CG).

Vitamin [μg/mL]	PCOS-I N = 40	PCOS-II N = 18	CG N = 15	P PCOS-I vs. PCOS-II	P PCOS-I vs. CG	P PCOS-II vs. CG
C	1.032 ± 1.236	1.006 ± 0.581	0.667 ± 0.115	0.287	0.043	0.050
B1	0.256 ± 0.275	0.336 ± 0.282	0.560 ± 0.416	0.241	0.023	0.095 *
B2	0.004 ± 0.002	0.005 ± 0.002	0.006 ± 0.004	0.279	0.112	0.428
B3—nicotinic acid	0.496 ± 0.449	0.153 ± 0.367	0.062 ± 0.050	0.018	0.001	0.370
PP—niacinamide	0.721 ± 0.212	0.756 ± 0.163	0.849 ± 0.201	0.418	0.173	0.292
B5	0.479 ± 0.230	0.606 ± 0.191	0.722 ± 0.192	0.126	0.002	0.116
B6	0.568 ± 0.283	0.758 ± 0.240	0.809 ± 0.217	0.046	0.042	0.770
B7	0.253 ± 0.321	0.262 ± 0.169	0.264 ± 0.256	0.189	0.674	0.419
B9	2.016 ± 0.465	2.130 ± 0.441	2.480 ± 0.616	0.385	0.035	0.083 *
B12	0.056 ± 0.029	0.072 ± 0.073	0.080 ± 0.055	0.386	0.064	0.559

PCOS I—polycystic ovary syndrome group before dietary intervention; PCOS II—polycystic ovary syndrome group after dietary intervention; CG—control group; *—trend.

4. Discussion

When analysing vitamin levels in the plasma, we took into account their supply and the needs of the human body depending on age, physical activity and accompanying illnesses associated with increased needs. The polycystic ovary syndrome is associated with the presence of a chronic inflammation and increased oxidative stress. This is why,

the supply of antioxidants, including vitamins, is particularly important. Vitamins that have antioxidant properties include ascorbic acid, the fastest reacting antioxidant, as well as vitamin E, carotenoids and flavonoids [15]. Ascorbic acid (AA) is present in high concentrations in the pituitary gland. Therefore, it can play a significant role in the secretion of the anterior pituitary hormones, including follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL) [16]. Moreover, it has been determined that AA deficiency (caused by low consumption) increases insulin resistance, which accompanies women with PCOS. This is why, the diet offered to women with PCOS was rich in this constituent (the average consumption of 230 mg/day/person). In our opinion, the observed higher concentration of vitamin C in the plasma of women with PCOS both before and after the dietary intervention is associated with the organism's response to oxidative stress and the competition with glucose for the joint transporter GLUT1 and GLUT3 to cell interior [17]. Due to the fact that vitamin C level in the plasma—regardless of its supply with the diet—remained at the same level (PCOS-I and PCOS-II), it seems that the measurement of AA levels in the plasma of these patients cannot serve to measure the supply of this vitamin to the organism. The problem was already described earlier by the authors in 2019 [14]. Additionally, in the same study group, an increased level of several eicosanoids was observed after the introduction of a reduction diet with reduced GI. The same authors explained the mechanism as activation/amplification of repair processes [18].

Group B vitamins belong to the category of vitamins whose main function is regulation, which means that they participate in important processes and reactions located within tissues and cells. Due to the possibility of dysbiosis in the course of PCOS, it seems very important to supplement the supply of these vitamins [14,19]. In the study, in the case of most B vitamins, the increase in their supply with the diet lead to the expected result in the form of their increased level in the plasma of women with PCOS. This effect was not observed for vitamin B3, and the levels of B2 and thiamine were not as satisfactory as in the case of the remaining vitamins. This is why the authors decided to analyse the cause of this effect. It has been documented that the insufficient supply of vitamin B₃ is associated with the development of inflammatory diseases [20]. Some examples of this type of disorders that accompany the pathogenesis of PCOS include insulin resistance and lipid disorders that promote atherosclerosis, as well as the increased risk of cardiovascular diseases [21,22]. Therefore, the delayed removal of fat from circulation in women with PCOS is another factor supporting the occurrence of this syndrome. It has been shown that nicotinic acid therapy reduces the frequency of occurrence of stroke and myocardial infarction and alleviates coronary artery revascularisation in patients suffering from the metabolic syndrome [23]. Niacin is important for the increase in HDL, the decrease in plasma TG and low-density lipoprotein (LDL) [24]. Radmila Lyubarova et al. (over 3000 patients) state that extended-release niacin (ERN) is associated with the decrease in the activity of lipoprotein-associated phospholipase A₂ (LpPLA₂) and hence, with the risk of cardiovascular (CV) events [25]. Furthermore, nicotinamide and its metabolite N1-Methylnicotinamide (MNAM) alleviate endocrine and metabolic abnormalities in ovarian and fat tissues in the rat model of PCOS [26]. It has been observed that MNAM production is significantly higher in the cumulus cells of PCOS patients. It has also been demonstrated that its administration in the rat model of PCOS helped solve the problem of hyperandrogenism and ovarian adenosine monophosphate-activated protein kinase (AMPK). This is possible via aldehyde oxidase 1 (AOX1), which is a detoxifying enzyme that metabolises MNAM through the transient elevation of ROS [27]. Nicotinamide is a direct precursor used in the synthesis of NAD⁺ and NADP⁺, which are important coenzymes of redox reactions. Data shows that nicotinic acid is not formed from nicotinamide in the human body. On the contrary, nicotinic acid has to be transformed into nicotinamide [28]. Therefore, in our study, due to the protective effect with reference to vascular endothelium and the antithrombotic potential, it seems that the introduction of a balanced reduction diet rich in antioxidants lead to the activation of repair mechanisms resulting in the observation of a reduction in the level of nicotinic acid in the plasma of women with PCOS. Therefore, it seems that additional supplementation of

women with PCOS would be recommended, especially with the methylated form [29,30]. It is known that, in this group, there is a higher probability of women with the adverse methylene tetrahydrofolate reductase (MTHFR) polymorphism [30].

Contrary to expectations, the concentrations of the two remaining vitamins (thiamine and folates) in the plasma did not increase. Thiamine plays a key role in metabolism because it is a cofactor in the transformation reactions of carbohydrates, fats, and amino acids with a branched chain [31]. Due to the disorders of fat and carbohydrate metabolism in women with PCOS, thiamine deficiency supports the development of type 2 diabetes, cardiovascular diseases and dyslipidaemia in patients with PCOS [32]. Other authors have also observed that thiamine level is inversely related to the level of glucose and that it is an important factor in the prevention of the adverse processes of glycation with the production of advanced glycation end products (AGE) [33]. It has also been observed that hyperglycaemia and oxidative stress accelerate the formation of AGE [34]. Furthermore, thiamine supplied with food is a compound that is soluble in water, which makes it more difficult to absorb and it is rather quickly removed from the body through kidneys. This is why it is recommended to supply PCOS patients with benfotiamine, similarly to patients suffering from diabetes [35]. Benfotiamine is a synthetic derivative of thiamine, soluble in fats, that eventually becomes an active form of vitamin B1—thiamine diphosphate, which participates in tissue enzymatic systems of metabolic processes. Thiamine deficiency is associated with the presence of diabetic neuropathy. Diabetic neuropathy is the damage of peripheral nerves in women with PCOS in the early stages before diabetes. The proof of this is the observed elevated level of nerve acid in women with PCOS, also in this particular study group [36]. Women with PCOS and carbohydrate metabolism disorders are often treated with metformin that normalises glycaemia. Its chronic intake is additionally associated with the deficiency of thiamine and cobalamin [7,37]. This is why one of the ideas promoted by the authors of this article is to include supplementation with thiamine and/or benfotiamine while remembering that proper bioavailability in tissues requires the application of high doses [38]. The potential activation of transketolase through benfotiamine contributes to the inhibition of 3 out of 4 mechanisms that damage blood vessels, reducing the risk of cardiovascular disease (CVD) [39]. Another CVD factor in PCOS is the frequently existing elevated level of homocysteine in the plasma [40]. Furthermore, in women with PCOS, the level of homocysteine is inversely correlated with the level of transporting protein (SHBG), with circulatory system diseases and infertility [40]. In order to reduce the level of homocysteine, the triplet of vitamins—B6, B9 and B12 is supplied, and it is worth highlighting that folic acid has the highest influence on the normalisation of its level. Other studies have shown that the synergistic effect of myo-inositol, L-tyrosine, selenium and chromium after 6 months of use restores proper menstruation cycle and ovulation, and it also reduces the body mass of these patients [41,42]. Inositol was introduced as a new agent sensitising towards insulin and androgens in the treatment of patients with PCOS. Contrary to metformin, it does not cause any side effects [43,44]. Furthermore, L-methylfolate increases peripheral sensitivity to insulin, maintaining stable folatemia, thus restoring the normal level of homocysteine. Contrary to folic acid, L-methylfolate has higher bioavailability, no drug/food interference and high absorption level and is stable with reference to the effect of UV-A rays [45]. The supplementation with MI and folic acid has a positive influence on metabolic parameters, especially insulin resistance and the cardiovascular profile in women after 30 years of age, suffering from PCOS [46]. Supplementation with 5 mg of folate every day resulted in the reduction in Hcy in the HOMA-B plasma and a reduction in the concentration of high-sensitivity C-reactive protein (hs-CRP) and in malondialdehyde (MDA) in blood in comparison to folic-1 acid and placebo groups. Moreover, a significant increase in the total antioxidant capacity (TAC) in the plasma and glutathione levels (GSH) was also observed [47].

5. Conclusions

To summarise, it is necessary to include antioxidants in the diet of women with PCOS. A proper balanced reduction diet with low GI supplements the level of vitamins soluble in water. However, it is also recommended to include additional supplementation with thiamine (in the form of benfotiamine), niacinamide and folates with inositol, which increase peripheral sensitivity to insulin. The level of vitamin C in the plasma may not be a good marker for its supply in the PCOS group.

Supplementary Materials: The following are available online at <https://www.mdpi.com/2072-6643/13/3/746/s1>, Figure S1: The average concentration of vitamins in the plasma with reference to the analysed groups [$\mu\text{g}/\text{mL}$].

Author Contributions: Conceptualization, M.S.; methodology, M.S.; software M.S.; validation, M.S., I.S. and J.N.-R.; formal analysis, M.S.; investigation, M.S.; resources, M.S.; data curation, M.S., I.S. and J.N.-R.; writing—original draft preparation, M.S.; writing—review and editing, M.S., I.S. and J.N.-R.; supervision, M.S.; project administration, M.S.; funding acquisition, M.S., I.S. and J.N.-R. All authors have read and agreed to the published version of the manuscript.

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A Study on identification of risk factors in developing Poly Cystic Ovarian Syndrome among teenagers and minimizing them by Life Style Modifications through Advanced Patient Counselling by Doctor of Pharmacy

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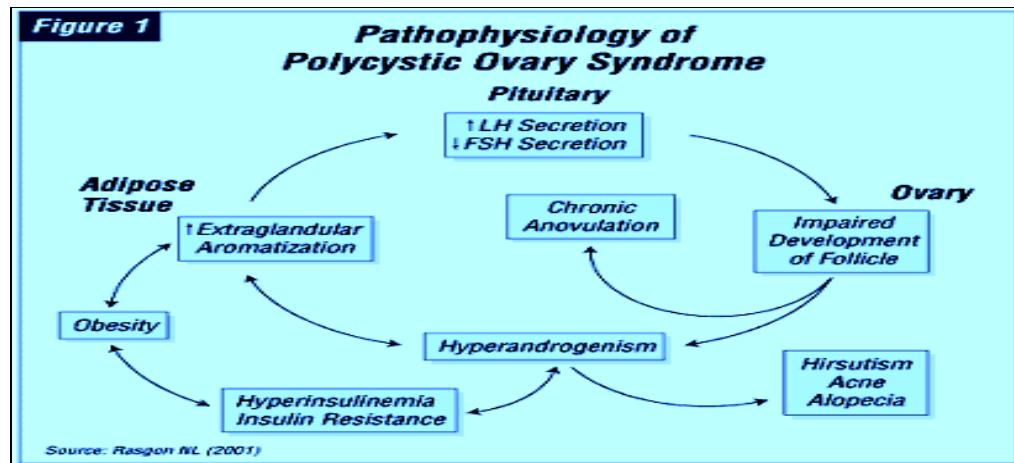
ABSTRACT

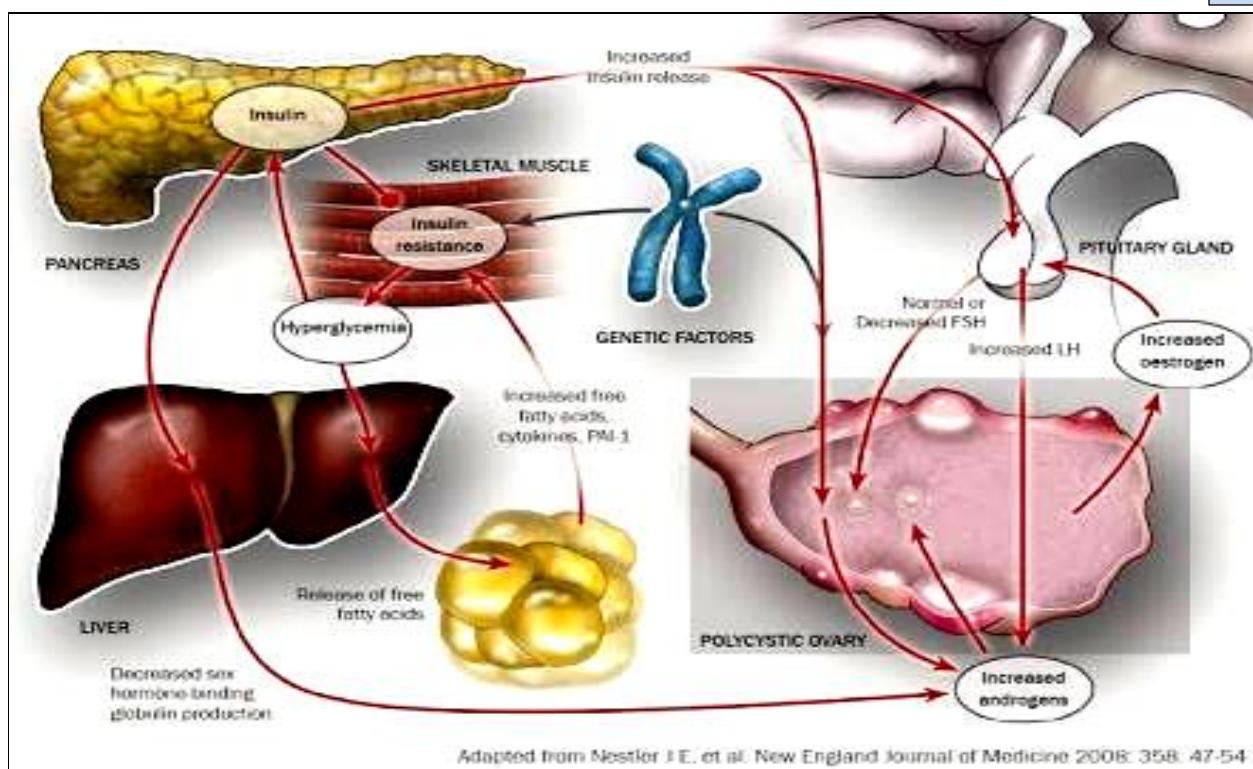
Poly-Cystic Ovary Syndrome (PCOS) is characterized by multiple small ovarian cysts, obesity, hypertension, diabetes, insulin resistance, and Hirsutism. The Study Aims to assess the role of Doctor Of Pharmacy in identification of risk factors in developing poly cystic ovarian syndrome among teenagers and minimizing them by life style modifications through advanced Patient counseling. The Main Objective of the present study is to prevent the following: To prevent the complications of PCOS who are suffering with PCOS in early of their age. To prevent the occurrence of PCOS to early females who are nearer for its occurrence. To minimize the symptoms and to improve the quality of life of females suffering with PCOS. Study Design: It is a observational and interventional study. Study Period: The Present study was conducted for a period of 6 months from January 2nd 2017 to July 31st 2017. Study site : The Present study was conducted in BAHUDHA WOMENS HOSTEL affiliated to Annamacharya college of Pharmacy, Rajampet, Kadapa, Andhra Pradesh, India. In The Present Study Out of total 600 women 530 enrolled to participate in the present study. After the collection of information by PCOS self assessment forms the scoring is given as 271 with scoring > 5 with percentile 51.1320 are with Chance for getting PCOS, 159 with scoring > 10 with percentile 30.01 are with high Chance for getting PCOS, 100 with scoring < 5 with percentile 18.8679 are Unpredictable to PCOS. The present study concludes that Doctor Of Pharmacy is very helpful in assessing the risk factors responsible in developing PCOS and also minimizing them by life style modifications through advanced patient counseling.

INTRODUCTION

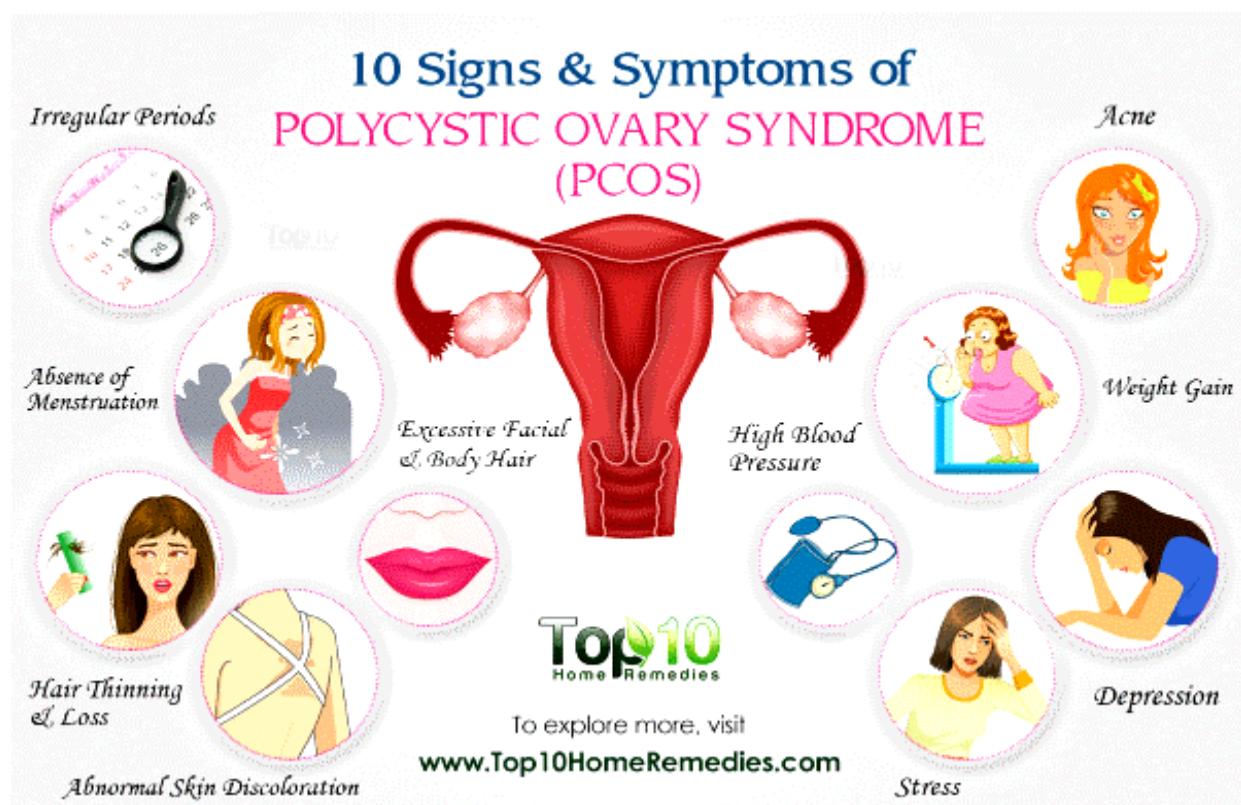
DEFINITION: Poly-Cystic Ovary Syndrome (PCOS) is characterized by multiple small ovarian cysts, obesity, hypertension, diabetes, insulin resistance, and Hirsutism.

SEQUENTIAL DIAGRAMATIC REPRESENTATION ETIO-PATHOPHYSIOLOGY OF PCOS:





DIAGRAMMATIC REPRESENTATION OF SIGNS AND SYMPTOMS



COMPLICATIONS

- Complete Infertility or in some cases difficulty to conceive.
- Cardiovascular diseases like hypertension ,atherosclerosis and other heart problems
- Type-2 diabetes mellitus.
- Hirustism which leads to unusual hair growth on body.
- Hormonal imbalances which leads to endocrine disorders and hyper-androgenism, etc.,,

ROLE OF DOCTOR OF PHARMACY IN MINIMIZING THE RISK FACTORS IN GETTING PCO

Doctor of pharmacy are health care professionals with complete knowledge on both disease/dicorder and treatment involved as well as on patient counselling and non pharmacological therapy that is helpful to prevent or reduce the complications of a particular disease/disorder, here in this study as a doctor of pharmacy student I have taken a study to control /to reduce/prevent the complications of PCOS in my hostel where I have been 5 years of my study.

AIM:

The Study Aims to assess the role of Doctor of Pharmacy in identification of risk factors in developing poly cystic ovarian syndrome among teenagers and minimizing them by life style modifications through advanced Patient counseling.

OBJECTIVES:

The Main Objective of the present study is to prevent the following:

- To prevent the complications of PCOS who are suffering with PCOS in early of their age.
- To prevent the occurrence of PCOS to early females who are nearer for its occurrence.
- To minimize the symptoms and to improve the quality of life of females suffering with PCOS.

METHODOLOGY:

Study Design: It is an observational and interventional study.

Study Period: The Present study was conducted for a period of 6 months from January 2nd 2017 to July 31st 2017.

Study site: The Present study was conducted in BAHUDHA WOMENS HOSTEL affiliated to Annamacharya college of Pharmacy, Rajampet, Kadapa, Andhra Pradesh, India.

Sample size: 600 women with age group ranging from 18-24 were selected for this study.

Source of Data: All the required data was collected through risk factors assessment forms.

Inclusion criteria:

Females aging between 18-24 and who are willing to participate in the study. ,(Out of total 600 530 were willing to participate in the present study).

Exclusion criteria:

Females aging between 18-24 and who are not willing to participate in the study,(Out of total 600 70 were not willing to participate in the present study).

PCOS SELF ASSESSMENT FORM**SELF TEST: DO YOU HAVE PCOS?**

(Poly-Cystic Ovary Syndrome (PCOS) is characterized by multiple small ovarian cysts, obesity, hypertension, diabetes, insulin resistance, and Hirsutism.)

NAME: _____ AGE: _____ OCCUPATION: _____

BODYWEIGHT: _____ HEIGHT: -----

ALREADY HAD PCOS: YES NO

QUESTIONARY FORM TO BE FILLED:

- YES NO 1. I crave carbohydrates and sugar.
- YES NO 2. I have had continuous weight gain.
- YES NO 3. I have always had difficulty with losing weight.
- YES NO 4. My waistline is greater than 35 inches.
- YES NO 5. I have or had problems in the past with acne.
- YES NO 6. My periods last longer than 35 days.
- YES NO 7. My periods are unpredictable.
- YES NO 8. My periods last longer than a week.
- YES NO 9. My periods are very heavy or prolonged.
- YES NO 10. I have with excess facial hair.
- YES NO 11. I feel extremely hungry, irritable, sleepy, or fatigued after eating sweets.
- YES NO 12. I have noticed skin color or pigmentation changes.
- YES NO 13. I have unusual amount of hair on my breasts.
- YES NO 14. I have hair growth on my upper thighs.
- YES NO 15. I have pubic hair that grows up my abdomen and around the navel.
- YES NO 16. My acne is worse at different times of my cycle.
- YES NO 17. I use to work/study under extreme stress conditions.

SCORE: ≥ 10 **high risk to get PCOS;** ≥ 5 **Chance for getting PCOS**

≤ 5 Unpredictable to PCOS.

NOTE: This Questionnaire form is prepared based On WHO Guidelines and Standard Text Books written to assess The Risk Factors Of PCOS.

RESULTS

Table1.1 AGE WISE DISTRIBUTION OF FEMALE POPULATION IN BAHUDHA HOSTEL.

AGE GROUP	NUMBEROF FEMALES	PERCENTAGE
18	95	17.9245
19	89	16.7924
20	87	16.4150
21	60	11.3207
22	40	7.5471
23	70	13.2075
24	89	16.7924
TOTAL=530.		TOTAL=100%

Fig 1.1 DIAGRAMATIC REPRESENTATION OF AGE WISE DISTRIBUTION OF FEMALE POPULATION IN BAHUDHA HOSTEL.

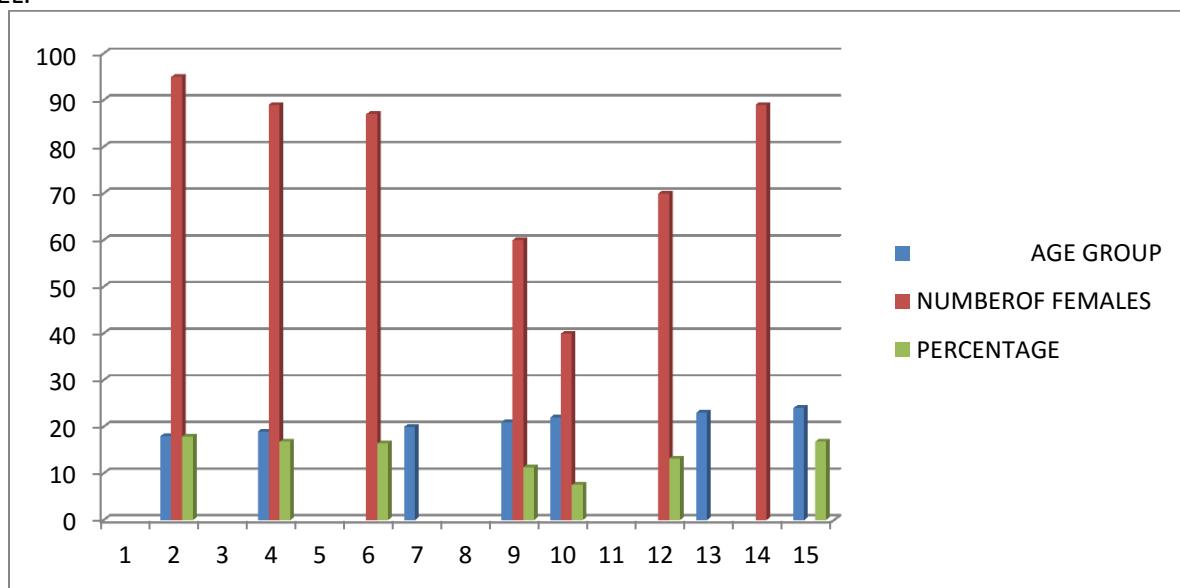
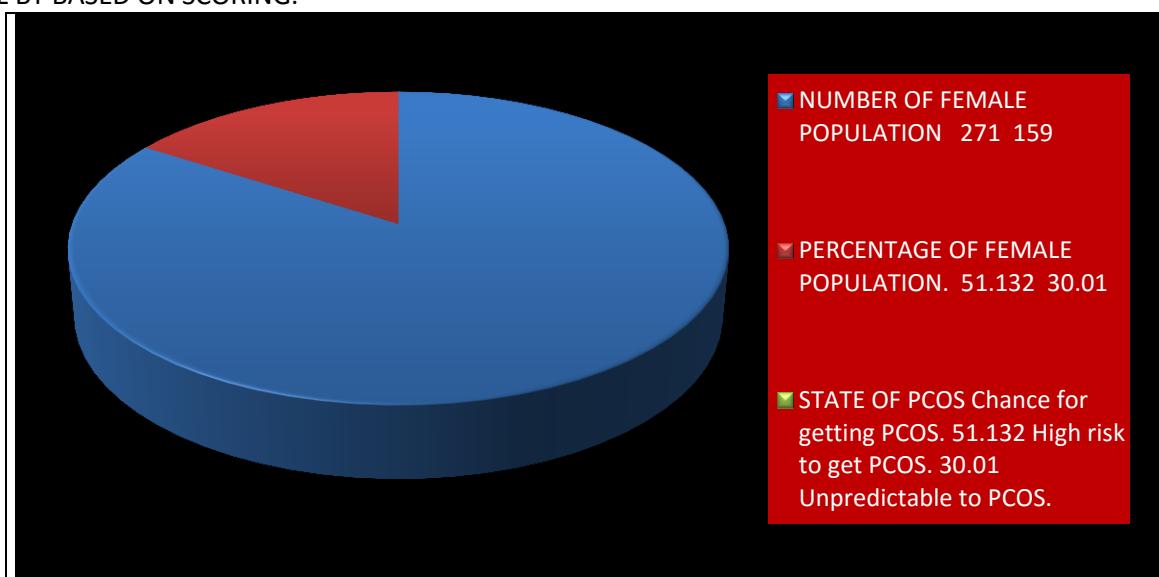


Table1. ANALYSIS OF PCOS STATE IN FEMALE POPULATION OF BAHUDHA HOSTEL BY BASED ON SCORING

NUMBER OF FEMALE POPULATION	SCORING	PERCENTAGE OF FEMALE POPULATION	STATE OF PCOS
271	≥ 5	51.1320	Chance for getting PCOS.
159	≥ 10	30.01	High risk to get PCOS.
100	<5	18.8679	Unpredictable to PCOS.
TOTAL=530			

Fig 1.2 DIAGRAMATIC REPRESENTATION OF ANALYSIS OF PCOS STATE IN FEMALE POPULATION OF BAHUDHA HOSTEL BY BASED ON SCORING.



PATIENT COUNSELLING TIPS ALONG WITH LIFE STYLE MODIFICATIONS PROVIDED BY DOCTOR OF PHARMACY TO FEMALE POPULATION WHO ARE AT CHANCE AND RISK OF GETTING PCOS

- Every women should Perform self test every month in order to assess the state of PCO occurance.
- Always reduce the intake of carbohydrate which can help to regulate menstrual cycles in regular manner.
- Always reduce the intake of fats with very low density lipoproteins that can helps to weight gain ultimately leads to insulin resistance.
- Always perform regular exercise& yoga to minimize the complications of PCO.
- Always should maintain proper BMI (body mass index).
- Use CARICA PAPAYA before one week of your menstruation date that can help to stimulate the growth of female Hormones like Oestrogen that will help to maintain proper menstruation cycles.
- Diet rich in iron like dates and fibre rich contents along with fruits and fresh vegetables must be taken .
- A balanced diet must be taken by based on body weight for example plate model meal.
- If one found if the complications are heavy they should immediately consult a Gynaecologist.

HOW DOCTOR OF PHARMACY IS HELPFUL IN ASSESING PCO?

Doctor of pharmacy are health care professionals with deep knowledge in assesing the risk factors, disease status, complications, drug selection, patient counseling. Here in this study a separate self assessment form is produced by doctor of pharmacy professionals as per standard guidelines of W.H.O and other international authorized guidelines, which is helpful for individuals to asses PCO on their own.

DISCUSSION

In The Present Study Out of total 600 women 530 enrolled to participate in the present study. Among them 95 were under the age group of 18 with percentile 17.9245, 89 were under the age group of 19 with percentile16.7924, 87 were under the age group of 20 with percentile 16.4150, 60 were under the age group of 21with percentile11.3207, and 40 were under the age group of 22 with percentile 7.5471, 70 were under the age group of 23with percentile 13.2075, 89 were under the age group of 24 with percentile 16.7924. After the collection of information by PCOS self assessment forms the scoring is given as **271 with scoring >5** with

percentile **51.1320** are with **Chance for getting PCOS, 159** with scoring ≥ 10 with percentile **30.01** are with **high Chance for getting PCOS, 100** with scoring ≤ 5 with percentile **18.8679** are **Unpredictable to PCOS**.

CONCLUSION

The present study concludes that PCOS occurrence is more in teenager females which can serve as major hurdle for their healthy life which ultimately leads to infertility as it is due to major risk factors like changes in the diet, stressful life, and unbalanced improper and unhealthy life style in females, hence the present study concludes that Doctor Of Pharmacy is very helpful in assessing the risk factors responsible in developing PCOS and also minimizing them by life style modifications through advanced patient counseling.

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Measures of health-related quality of life in PCOS women: a cross sectional study from Saudi Arabia

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Abstract. – **OBJECTIVE:** Polycystic ovary syndrome (PCOS) is the most common endocrine-gynecologic disorder affecting women of childbearing age. It has a wide range of clinical manifestations, including menstrual irregularity, infertility, hirsutism, acne, and obesity. Studies have confirmed that PCOS can significantly reduce a patient's health-related quality of life (HRQoL). The pathophysiology of PCOS is poorly understood, but it is believed to be caused by the interaction of several factors. Moreover, there is a lack of information about HRQoL among PCOS women in Saudi Arabia. This study aims to assess the HRQoL of PCOS patients by using the Arabic Version of the Polycystic Ovarian Syndrome Health-Related Quality of life Questionnaire (AR-PCOSQ) in Riyadh city.

SUBJECTS AND METHODS: A descriptive cross-sectional study was conducted on 281 women in Riyadh city using the translated questionnaire (AR-PCOSQ) to explore PCOS quality of life among Saudi females. The eligibility criteria were Saudi female who had been diagnosed with PCOS, living in Riyadh city, aged 18 and above, and willing to participate. The sample size was estimated using the 10-events-per-variable rule for prediction models (REF). Informed consent was taken from all participants and a Google Form was used to create the survey and collect data.

RESULTS: The higher score represents poor QOL. However, the analysis revealed that higher scores of the weight-related QOL had the greatest impact on patients' quality of life in older age groups, including women aged 26 to 35 ($\beta = 0.143$, 95% CI, 0.023 to 0.304, p -value = 0.046) and women aged > 35 ($\beta = 0.229$, 95% CI, 0.039 to 0.428, p = 0.011). Other domains of QOL, such as emotions, body hair, infertility, and menstrual problems, were not significant-

ly predicted by any of the women's demographic characteristics.

CONCLUSIONS: The findings revealed that PCOS-related conditions such as weight problems, menstrual irregularity, and infertility were associated with a reduction in quality of life.

Key Words:

Quality of life, Arabic, PCOS.

Abbreviations

Polycystic ovary syndrome (PCOS), health-related quality of life (HRQoL), Arabic Version of the Polycystic Ovarian Syndrome Health-Related Quality of life Questionnaire (AR-PCOSQ), quality of life (QOL), Princess Nourah Bint Abdulrahman University (PNU).

Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine-gynecological disorder and affects women at their reproductive age¹. It is widely spread in most parts of the world, with large variations between different regions. A retrospective study shows that the prevalence of PCOS is estimated between 4% and 20% worldwide². Moreover, the prevalence of PCOS is 16% among Saudi females³. The name polycystic ovary syndrome describes a condition where numerous small cysts in the ovaries produce elevated level of androgens, which can cause irregular menstrual cycle and many symptoms of PCOS⁴. According to ESHRE/ASRM criteria, PCOS is defined as the presence of two or more of the following three criteria: polycystic ovaries, oligo-/anovulation, and/or clinical or biochemical evidence of hyperandrogenism⁵. The

wide range of clinical manifestations, including menstrual irregularity, infertility, hirsutism, acne, and obesity, are all significant sources of psycho-social distress and lead to a reduction of life quality⁴. Numerous studies⁴⁻⁶ confirm the symptoms of PCOS can lead to a significant decrease in patients' health-related quality of life (HRQoL). According to a study conducted in Iran⁶, infertility is considered one of the most distressing symptoms of PCOS. In addition, a thorough review of the literature conducted by Bazarganipour et al⁷ show that hirsutism and menstruation are the main causes of HRQOL impairment in PCOS patients. The interaction between multiple factors is believed to be the cause of the hormonal disturbance seen in PCOS patients⁸. Additionally, genetic mutations are linked to PCOS, along with hypothalamic-pituitary dysfunction⁹. A genetic mutation of the aromatase enzyme deficiency may affect ovary functioning and elevate androgen level, leading to PCOS⁹. Despite this, research done to assess the quality of life of patients with PCOS is minimal, especially in Asian countries, even though it is the most common endocrine disorder in young females^{10,11}. Upon literature review, there has been minimal research assessing the HRQoL of PCOS patients in Saudi Arabia. HRQoL is culturally dependent⁶; therefore, the unique characteristics of social and cultural life contexts suggest that information on the HRQoL of PCOS patients in Saudi Arabia may be different from that of Western countries. Since there is a scarcity of information about the HRQoL among PCOS women in Saudi Arabia. This study aims to assess the HRQoL of PCOS patients by using the Arabic Version of the Polycystic Ovarian Syndrome Health-Related Quality of life Questionnaire (AR-PCOSQ) in Riyadh city. We hypothesize that women with PCOS, would show worse HRQoL compared to women without PCOS.

Subjects and Methods

A descriptive cross-sectional study using the translated questionnaire (AR-PCOSQ) was conducted to explore PCOS quality of life among the Saudi female population, through an anonymous online questionnaire using a snowball convenience sampling technique from January 2023 to March 2023. The eligibility criteria to participate in this study were Saudi females who had been diagnosed with PCOS, living in Riyadh city, aged 18 and above, and willing to participate in the study. Since we planned to conduct a multivariate

linear regression model of the primary outcome variable (QOL score), the sample size was estimated using the 10-events-per-variable rule for prediction models¹². Given that the PCOSQ scale consists of 26 items, a sample of 260 women was required in the current study. The total sample size comprised 281 participants. Before starting the study, approval was obtained from the Institutional Review Board (IRB) at Princess Nourah bint Abdulrahman University (PNU), Riyadh, Saudi Arabia (IRB log number: 23-0077). Informed consent was taken from all participants after being explained briefly about the study's objectives and informed that they have the full right to withdraw from the study without any obligation. A Google Form was used to create the survey and collect data. The link was then shared and circulated randomly across different social media platforms (i.e., WhatsApp, Telegram, Instagram, and Twitter). The majority of participants were strongly encouraged to share the invitation link with their personal and professional contacts.

Data Collection

In the current study, we employed the PCOSQ scale, which consists of 26 items and 5 domains, including emotions (eight items), body hair (five items), weight (five items), infertility (four items), and menstrual problems (four items)¹³. The mean scores of each domain were computed based on the items allocated to each domain after validation. Each item was graded on a seven-item Likert scale, where higher scores indicated a poorer quality of life. Since the scores of each domain are based on the mean values of respective items, they ranged between 1 and 7.

Statistical Analysis

The normal distribution of the QOL score was assessed using a Shapiro-Wilk test, which revealed non-normally distributed data (p -value = 0.0001). Statistical analysis was performed using RStudio (R version 4.2.2): Integrated Development for R. RStudio, PBC, Boston, USA. Categorical variables were expressed as frequencies and percentages, whereas numerical variables were presented as median and interquartile range (IQR). To assess the predictors of poor quality of life among PCOS participants, we carried out a bootstrapped partial least squares structural equation modeling technique using the five subscales as endogenous variables and the demographic characteristics of the participants as predictor variables. The internal consistency reliability of the model was asses-

sed using Cronbach's alpha coefficients and rhoC rhoA values. Furthermore, we used the average variance extracted (AVE) as a measure of the convergent validity in order to assess the degree to which each construct could have converged to express the indicators' variance. Beta coefficients and their respective 95% confidence intervals (95% CIs) were used to present the results of the structural model, and statistical significance was deemed at p -value < 0.05 .

Results of the structural paths showed that higher scores of the weight-related QOL (poor QOL due to weight concerns) were predicted by older age categories, including 26 to 35 years women ($\beta = 0.143$, 95% CI, 0.023 to 0.304, $p = 0.046$) and > 35 years women ($\beta = 0.229$, 95% CI, 0.039 to 0.428, $p = 0.011$). Other domains of QOL, including emotions, body hair, infertility, and menstrual problems, were not significantly predicted by any of the demographic characteristics of women (Table I).

Results

Demographic Characteristics

The responses of 281 women with PCOS were analyzed in the current study. All the participants were Saudi women residing in Riyadh city. The majority of them were between 18 and 25 years old (70.1%), were singles (72.2%), and had a bachelor's degree (73.7%). Approximately two-thirds of the participants were students (61.6%) and had an average monthly income of $< 5,000$ SAR (68.7%).

Out of the 26 items of the PCOSQOL survey, 24 items showed adequate loadings to their original constructs (bootstrapped factor loadings > 0.5). Therefore, two items were excluded from the validated model, including one item from the body hair subscale (QOL_11) and one item from the menstrual problem subscale (QOL_24). Furthermore, we combined single, divorced, and widowed categories into one category (single) and unemployed and retired categories into another category (unemployed/retired) to avoid the zero-variance error in the bootstrapped model. The final model exhibited excellent reliability indicators since the Cronbach's alpha values ranged between 0.751 and 0.935, and the values of rhoC and rhoA exceeded 0.70. Additionally, the AVE values of subscales were generally above 0.50, ranging between 0.551 and 0.794. This indicates that the constructs explained at least 55.1% of the

indicators' variance that formed the construct. Finally, there was no risk of multicollinearity since the values of the variance inflation factor (VIF) were generally below the threshold of 5 (Table II).

Validity and Reliability

Description of the PCOSQOL scale and subscales

The median (IQR) quality of life score for all the participants was 4.2 (2.8 to 5.2). Weight-related QOL had the highest median score (median = 4.8, IQR = 2.8 to 6.0), followed by menstrual problems-related QOL (median = 4.7, IQR = 3.3 to 5.3) and infertility-related QOL had the lowest score (median = 3.3, IQR = 2.0 to 4.8, Figure 1).

Discussion

PCOS HRQoL has been previously studied worldwide¹⁵⁻¹⁸. The purpose of this paper was to assess the PCOS HRQoL and to identify the predictors of poor HRQoL in a sample of Saudi females. It was found that women with PCOS have a lower HRQoL. This finding could be attributed to the fact that PCOS has metabolic, reproductive, and psychological features and consequences on health across the lifespan¹⁹. In this study, weight problems were the greatest concern reported by PCOS women. These results were in line with previous studies¹⁵⁻¹⁸. One possible explanation for this finding is that women with PCOS often report extreme difficulty in losing weight and maintaining weight loss, and interventions to lose weight are often failed and linked to high rates of weight gain¹⁷. Furthermore, two studies^{20,21} have reported that PCOS women have a worse body image and are dissatisfied with their weight, and consequently, have a poor quality of life. Noticeably, a weight reduction appears to improve HRQoL significantly²². Additionally, our study demonstrates that the weight-related QOL was significantly predicted by older age categories, including 26 to 35 years and > 35 years women. On the other hand, a systematic review by Jones et al²² revealed that weight-related QOL is significantly associated with the adolescent age group. It might be because there are few data on HRQoL in women with PCOS during their late reproductive years, with most prior studies focusing on women at younger ages²³.

Although menstrual disorders demonstrate a high negative association in PCOS patients on a

Table I. Outcomes of the structural models.

Parameter	Category	Emotions		Body hair		Weight		Infertility		Menstrual problems	
		Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Age	18 to 25	Ref		Ref		Ref		Ref		Ref	
	26 to 35	0.072 (-0.198 to 0.237)	0.258	0.026 (-0.149 to 0.212)	0.387	0.143 (0.023 to 0.304)	0.046	0.122 (-0.051 to 0.285)	0.091	-0.077 (-0.229 to 0.110)	0.819
	> 35	0.129 (-0.266 to 0.355)	0.199	-0.013 (-0.217 to 0.183)	0.551	0.229 (0.039 to 0.428)	0.011	0.144 (-0.082 to 0.355)	0.102	-0.042 (-0.235 to 0.189)	0.651
Marital status	Single* Married	Ref -0.092 (-0.273 to 0.141)	0.811	Ref -0.125 (-0.292 to 0.055)	0.925	Ref -0.125 (-0.301 to 0.049)	0.922	Ref -0.005 (-0.203 to 0.201)	0.521	Ref -0.019 (-0.207 to 0.145)	0.581
Highest	School Bachelor Post-graduate	Ref -0.100 (-0.223 to 0.103)	0.882	Ref -0.151 (-0.279 to -0.026)	0.992	Ref -0.025 (-0.150 to 0.106)	0.647	Ref -0.039 (-0.166 to 0.093)	0.720	Ref 0.015 (-0.134 to 0.184)	0.426
Occupation educational level	Student	Ref		Ref		Ref		Ref		Ref	
	Housewife	0.026 (-0.182 to 0.218)	0.399	-0.004 (-0.158 to 0.144)	0.519	-0.013 (-0.171 to 0.147)	0.564	0.019 (-0.195 to 0.200)	0.425	0.087 (-0.097 to 0.250)	0.167
	Employed	0.106 (-0.098 to 0.283)	0.136	0.102 (-0.062 to 0.262)	0.116	0.081 (-0.110 to 0.256)	0.195	0.046 (-0.148 to 0.212)	0.305	0.117 (-0.098 to 0.282)	0.126
	Unemployed / Retired	0.064 (-0.081 to 0.206)	0.192	0.117 (-0.030 to 0.246)	0.053	0.062 (-0.090 to 0.206)	0.203	0.031 (-0.122 to 0.169)	0.338	0.126 (-0.022 to 0.259)	0.051
Average monthly income	< 5,000 5,000 to 10,000 > 10,000	Ref -0.075 (-0.252 to 0.086)	0.808	Ref -0.105 (-0.241 to 0.047)	0.925	Ref -0.132 (-0.279 to 0.014)	0.964	Ref -0.016 (-0.168 to 0.140)	0.581	Ref 0.019 (-0.129 to 0.179)	0.400
		-0.054 (-0.202 to 0.116)	0.749	-0.088 (-0.221 to 0.049)	0.893	-0.160 (-0.302 to -0.011)	0.986	-0.110 (-0.223 to 0.026)	0.962	-0.117 (-0.240 to 0.036)	0.945

*The category single indicates that the participant was single/divorced/widowed.

Measures of health-related quality of life in PCOS women in Saudi Arabia

Table II. Convergent validity and construct reliability of the bootstrapped model of the used PCOSQ survey

Domains/items	BFL	VIF	alpha	rhoC	rhoA	AVE
Emotions			0.903	0.905	0.865	0.551
QOL_1	0.789	2.621				
QOL_2	0.655	2.578				
QOL_3	0.651	2.636				
QOL_4	0.706	1.940				
QOL_5	0.666	1.648				
QOL_6	0.817	3.734				
QOL_7	0.748	2.499				
QOL_8	0.814	2.841				
Body hair			0.901	0.930	0.937	0.769
QOL_9	0.802	2.033				
QOL_10	0.860	2.434				
QOL_12	0.931	4.697				
QOL_13	0.907	3.979				
Weight			0.935	0.951	0.941	0.794
QOL_14	0.881	3.111				
QOL_15	0.860	2.814				
QOL_16	0.924	4.543				
QOL_17	0.885	3.313				
QOL_18	0.905	3.618				
Infertility			0.863	0.892	0.947	0.692
QOL_19	0.908	3.714				
QOL_20	0.941	4.853				
QOL_21	0.926	3.419				
QOL_22	0.570	1.235				
Menstrual problems			0.751	0.853	0.832	0.660
QOL_23	0.746	1.407				
QOL_25	0.834	1.574				
QOL_26	0.802	1.575				

AVE: average variance extracted; Alpha: Cronbach's alpha; VIF: variance inflation factor; BFL: Bootstrapped factor loading.

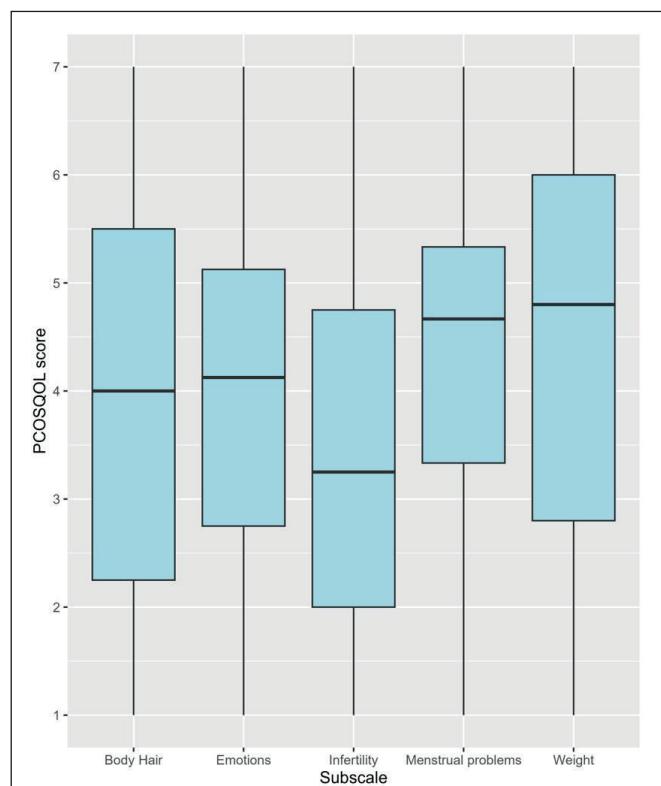


Figure 1. Description of the overall PCOSQOL scale and subscales.

clinical and biochemical basis²⁴, in some studies, it was not in the top three most affected domains⁷. The infertility outcome of this study shows the lowest score among the other domains. This finding explains that most of our participants are single, and infertility is not a big concern in this group. Another similar study²⁵ found an extremely low score for infertility in comparison to the other domains, although there is a significant negative impact on the quality of life of PCOS cases in relation to psychological distress, and this is because maternity has an effective role in the identity of women and the acceptance of society following marriage. Therefore, PCOS women can have sexual function issues where they sense less sexual satisfaction and desire due to long-term infertility and psychological stress¹⁵. Moreover, the Iranian study²⁶ displays the lowest score for infertility. Accordingly, infertility was detected as a concern of HRQOL because of the social pressure for childbearing.

Our study did not investigate a specific age group, but all females above 18 were included, which may affect the results since older females are more susceptible to health problems like metabolic syndrome. Also, symptoms might be affected by other factors, such as social stressors. Future studies should focus on specific age groups for a more accurate result.

Another limitation of the study is that the diagnoses of the disease were self-reported by the participants. This can be avoided by a validated diagnostic questionnaire to identify women with PCOS or by distributing the questionnaire from the primary healthcare and gynecological clinic to patients with a confirmed diagnosis of PCOS.

It should be noted that this study did not investigate any biochemical correlation related to PCOS cases and their HRQOL. Thus, it is suggested that future studies explore further correlations between HRQOL and PCOS cases.

The sample size was limited, and most participants were highly educated and might have had good health education regarding their self-care and health-seeking behaviors. Future researchers need to use large samples with various education and socioeconomic statuses.

Conclusions

In conclusion, this study provides evidence that HRQOL in patients with PCOS is impaired mostly by weight problems and menstrual irregularity,

while concerns about infertility had the lowest impact. Therefore, these problems must be considered by professional healthcare providers when dealing with PCOS patients, and more services need to be implemented to minimize the impact of PCOS on affected females.

Authors' Contributions

HAS has conceptualized the study and played a primary role in compiling, analyzing, and interpreting the data. RAS, BV, and CJJ did the manuscript preparation. SOA and RHA did the manuscript editing. JAA, LAA and MSA approved the final draft. RHA, JAA, MSA and LAA did the data cleaning and data analysis. LSMA and NA did the data collection. All the authors take complete responsibility for the content of the manuscript, and read and approve the final version of the manuscript.

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Ethics Approval

The ethical approval was obtained from the Institutional Review Board (IRB) at Princess Nourah bint Abdulrahman University (PNU), Riyadh, Saudi Arabia (IRB log number: 23-0077).

Informed Consent

Informed consent was obtained from the participants before initiating the study.

Data Availability Statement

The data can be made available by the corresponding author on request.

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Melatonin and its correlation with testosterone in polycystic ovarian syndrome

ABSTRACT

CONTEXT: Polycystic ovarian syndrome (PCOS) is considered to be the most common endocrine disorder affecting women. Melatonin, a small lipophilic indoleamine, and reproductive hormones may be interrelated. Melatonin influences sex steroid production at different stages of ovarian follicular maturation as melatonin receptors have been demonstrated at multiple sites in ovary and in intrafollicular fluid. It plays role as an antioxidant and free radical scavenger which protects follicles from oxidative stress, rescuing them from atresia, leading to complete follicular maturation and ovulation. **AIMS:** To study the role of melatonin in PCOS and to investigate its correlation with testosterone in patients suffering from PCOS. **SETTINGS AND DESIGN:** A total of 50 women with PCOS (Rotterdam criteria, 2003) and 50 age and weight matched healthy controls were selected and serum melatonin estimation was done in both the groups and correlated with serum total testosterone levels. **MATERIALS AND METHODS:** In a case-control study, detailed history, clinical examination and hormonal evaluation [basal levels of leutinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, prolactin, insulin, total testosterone, progesterone and melatonin] were carried out in all the participants including both cases and controls. For melatonin estimation, blood samples were collected between 12:00 am and 04:00 am on day 2nd of menstrual cycle and analyzed by using commercially available enzyme-linked immunosorbent assay kit. **STATISTICAL ANALYSIS:** Student's t-test was used to compare the significant difference in mean values between cases and control groups. Chi-square test was used to test the significant association between the qualitative variables. Linear correlation coefficient and regression analysis were done to see the amount and direction of relationship between quantitative variables. **RESULTS:** The mean melatonin level was observed to be significantly increased in patients (63.27 ± 10.97 pg/mL) than in controls (32.51 ± 7.55 pg/mL). Melatonin was found to be raised in all the cases of PCOS (above cut-off value of ≥ 45 pg/mL, $P < 0.001$). Total testosterone level was also raised in 72% of patients. Melatonin levels were found to be positively associated with increased testosterone ($P < 0.001$). In regression analysis using melatonin as dependent variable and testosterone as an independent variable, the value of $R^2 \times 100$ (percent variation) was found to be 72.1%. **CONCLUSIONS:** Women with PCOS have significantly raised serum melatonin levels and hyperandrogenemia along with increased number of atretic follicles. Further studies are required to establish a definite role of melatonin in PCOS cases with disturbed hormonal milieu. This could open up the way for therapeutic role of melatonin in treatment of patients suffering from PCOS.

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KEY WORDS: Hyperandrogenemia, infertility, melatonin, Polycystic ovarian syndrome

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is considered to be the most common endocrine disorder affecting women.^[1] It is the most common cause of anovulatory infertility and hirsutism.^[2,3] About 15% women of reproductive age group are affected.^[4] Women with PCOS in long term are known

to exhibit adverse Cardiovascular risk profile such as obesity, dyslipidemia, hypertension, insulin resistance and hyperinsulinemia,^[5] with an increased risk of premature coronary artery disease.^[6]

The role of melatonin (N-acetyl-5-methoxytryptamine), a small lipophilic indoleamine,^[7] in human reproduction is

still unknown. A large body of information suggests that melatonin and the reproductive hormones are interrelated. This concept is based on observation of increased melatonin levels in hypogonadal patients with gonadotropin-releasing hormone (GnRH) deficiency,^[8] in patients of hypothalamic amenorrhea, and in anorexia nervosa.^[9] Increased melatonin has been seen to influence sex steroid production at different stages of ovarian follicular maturation.^[10]

Melatonin, as well as its metabolites, are claimed to be broad-spectrum antioxidants and free radical scavengers,^[11,12] and their role is to quench reactive oxygen species (ROS) as well as reactive nitrogen species.^[13] Elevated melatonin in preovulatory follicles, as seen in normal women, is likely to protect granulosa cells and oocyte from free radicals that are induced during ovulation. In addition, melatonin regulates the antioxidant enzymes and antiapoptotic/proapoptotic protein gene expression.^[10]

Melatonin is detectable in virtually every compartment of body and its wide distribution allows melatonin to carry out its pleiotrophic actions. Till now, only few studies [Luboshitzky *et al.*, 2001; 2003; Prata Lima *et al.*, 2004; Tamura *et al.*; 2009; 2012] have been carried out to show association between melatonin and PCOS in human population. Since no study of such type has been done on Indian population, we, therefore, have designed this study in an effort to investigate the role of melatonin and its correlation with testosterone in PCOS patients.

MATERIALS AND METHODS

A prospective case-control study was designed taking 50 PCOS patients and 50 age- and weight-matched healthy controls, attending outpatient department of Department of Obstetrics and Gynecology, Sir Sunderlal Hospital, Banaras Hindu University, Varanasi from September 2011 to December 2012. Sample size was calculated and it came out to be 50 by taking the level of significance 1%, power of study 80% and combined standard deviation 10.

Inclusion criteria for selection of cases

The Rotterdam European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine-sponsored PCOS consensus criteria was used to diagnose PCOS and women with presence of any two of the following three features were included in the study:

1. Oligomenorrhea and/or amenorrhea (oligoamenorrhoea >45 days or <8 cycles per year and amenorrhea >3 months in a women with previous periodic menses) for a period of 6 months
2. Clinical and/or biochemical hyperandrogenemia, presence of acne, hirsutism (FG score >8), and alopecia
3. Polycystic ovaries on sonography (>12 follicles in one

or both ovaries, 2-9 mm in diameter and/or increased ovarian volume >10 mL).

Inclusion criteria for selection of controls

1. Regular menstrual cycle
2. Absence of hirsutism, alopecia, and acne
3. Absence of polycystic ovary on sonography
4. Normal hormonal parameters including thyroid-stimulating hormone (TSH), testosterone, prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), LH: FSH ratio.

Exclusion criteria

All patients with diabetes mellitus, hypertension, hyperprolactinaemia, thyroid disorder, cushing's syndrome, acromegaly, premature ovarian failure, virilising adrenal or ovarian tumors, and history of using oral contraceptive pill within last 6 months were excluded from the study. None of the subjects were alcoholic or smoker.

A written and informed consent was taken from all the participants.

Biochemical and hormonal analysis

Blood samples were drawn on day 2 of menstrual cycle or progesterone-induced bleeding after an overnight fast. Plasma LH, FSH, prolactin, total testosterone, progesterone and insulin were measured by chemiluminescent enzyme immunoassay using commercially available kits (Immuli 1000 systems, Siemens). Plasma Glucose was measured by glucose oxidase peroxidase method (selectra XL analyzer, Vital Scientifics, Holland). Serum cholesterol, triglycerides, low-density lipoprotein, and low-density lipoprotein levels were measured using kits by ERBA diagnostic, Mannheim, Germany. TSH levels were measured using IRMA kit (BARC, Mumbai, India). Cut off points for diagnosis of hyperandrogenemia was set at ≥ 118 ng/dL (according to chemiluminescent enzyme immunoassay), for insulin resistance it was set at a fasting glucose/insulin (G: I) ratio ≤ 4.5 and for hypersecretion of LH, LH: FSH ratio ≥ 2 was considered to be a cut-off point.

Sonography

Pelvic sonography (Nermio 30, Toshiba, Japan) was carried out on day 2 of menstrual cycle in both cases and controls.

Melatonin estimation

Blood samples for melatonin estimation were collected between 12:00 am and 04:00 am on day 2nd of menstrual cycle. A total of 5 mL of heparinized blood was taken and samples centrifuged for 15 min at 2500 RPM within 30 min of collection. Plasma was separated and stored samples in aliquot at -20°C or -80°C. Plasma melatonin concentration was measured using a commercially available enzyme-linked immunosorbent assay kit for melatonin

(Manufacturers: USCN Life Science Inc, USA). This assay employs the competitive inhibition enzyme immunoassay technique.

Statistical analysis

SPSS 16.0 version for Windows was used for statistical analysis. All quantitative variables were expressed as mean \pm standard deviation, while qualitative data were shown in the form of number and percentage. Student's t-test was used to compare the significant difference in mean values between cases and control groups. Chi-square test was used to test the significant association between the qualitative variables. Linear correlation coefficient and regression analysis were done to see the amount and direction of relationship between quantitative variables. A P value less than 5% ($P < 0.05$) was considered statistically significant.

RESULTS

The demographic, anthropometric, biochemical, and hormonal parameters of the study population (cases and controls) were compared [Table 1].

Melatonin concentration in PCOS patients varied from 47.9 pg/mL to 87.6 pg/mL, whereas in controls it ranged from 20.0 pg/mL to 44.04 pg/mL. Mean melatonin level was 63.27 ± 10.97 pg/mL in PCOS cases as compared with 32.51 ± 7.55 pg/mL in controls. Cut off level of melatonin was found to be 45 pg/mL. We found that all PCOS patients had significantly elevated serum melatonin levels (above cut-off value of 45 pg/mL, $P < 0.001$ and $t = 16.33$).

The mean melatonin level was shown in relation to demographic, anthropometric, biochemical, and hormonal profile of PCOS patient [Table 2].

Mean melatonin level in PCOS patients having regular menstrual cycle was 68.31 ± 11.18 pg/mL and in patients with oligomenorrhea, it was 61.84 ± 10.62 pg/mL. The difference in mean levels of melatonin between the groups was not statistically significant ($P = 0.84$ and $t = 1.76$) [Table 2].

We observed a significant positive correlation of serum melatonin with serum total testosterone levels in PCOS patients. Mean Melatonin level was 74.53 ± 10.99 pg/mL in patients with serum total testosterone level 128-140 ng/dL, whereas it was 53.28 ± 3.78 pg/mL in patients with total testosterone levels of ≤ 118 ng/dL. Thus, significant difference has been observed in mean melatonin level among different testosterone categories ($P < 0.001$, Chi-square = 20.97 and df = 2). Melatonin level was also correlated with serum LH: FSH ratio and fasting glucose: insulin ratio (G: I). Mean melatonin level in patients with LH:

FSH ratio ≥ 2 was 59.35 ± 10.02 pg/mL, whereas it was 71.24 ± 8.89 pg/mL in patients with LH: FSH ratio < 2 . These two variables seem to be inversely correlated ($P = 0.013$). We did not find any significant correlation between serum melatonin level and fasting glucose: Insulin ratio ($P = 0.290$) [Table 2].

Figure 1 represents the linear correlation coefficient (R) (cases: 0.85; controls: 0.06), percent variation explained ($R^2 \times 100$) (cases: 72.1%; controls: 3%), regression constant (cases: -101.0; controls: 29.57) and regression coefficient (cases: $\times 1.337$; controls: $\times 0.034$) for melatonin as dependent

Table 1: Demographic, anthropometric, biochemical, and hormonal parameters of the study population (polycystic ovarian syndrome cases and controls)

Parameters	Study population		<i>P</i> value
	PCOS (n=50)	Control (n=50)	
Age (years)	24.87 \pm 4.43	22.60 \pm 4.033	0.161
BMI (kg/m ²)	28.19 \pm 2.31	27.38 \pm 2.46	0.352
Waist: hip ratio	1.63 \pm 0.49	1.00 \pm 0.00	<0.001*
LH (mIU/mL)	16.13 \pm 7.95	7.18 \pm 1.97	<0.001*
FSH (mIU/mL)	5.43 \pm 1.53	6.60 \pm 2.86	0.106
LH/FSH ratio	3.10 \pm 1.69	1.15 \pm 0.25	<0.001*
TSH (IU/mL)	2.45 \pm 0.97	2.66 \pm 1.09	0.563
Prolactin (ng/mL)	14.7 \pm 4.48	13.35 \pm 3.26	0.380
Total testosterone (ng/dL)	122.84 \pm 6.96	84.71 \pm 12.75	<0.001*
Melatonin (pg/mL)	63.27 \pm 10.97	32.51 \pm 7.55	<0.001*
Progesterone (ng/mL)	2.58 \pm 2.83	16.87 \pm 4.29	<0.001*
Fasting glucose (mg/dL)	113.01 \pm 11.25	93.68 \pm 7.53	<0.001*
Fasting insulin (mU/mL)	26.06 \pm 4.44	16.48 \pm 3.54	<0.001*
Glucose insulin ratio	4.38 \pm 0.43	5.91 \pm 1.37	<0.001*

*P<0.05 was considered statistically significant. BMI=Body mass index, FSH=Follicle-stimulating hormone, LH=Luteinizing hormone, PCOS=Polycystic ovarian syndrome, TSH=Thyroid-stimulating hormone

Table 2: Distribution of melatonin in relation to demographic, anthropometric, biochemical, and hormonal profile of polycystic ovarian syndrome patient

Parameters	Melatonin (pg/mL)		<i>P</i> value
	Mean \pm SD		
Regular menstrual cycle	68.31 \pm 11.18	1.761	0.84
Oligomenorrhea	61.84 \pm 10.62		
Primary infertility	66.33 \pm 11.83	1.481	0.162
Secondary infertility	56.74 \pm 8.12		
Obese (>30 kg/m ²)	60.89 \pm 10.45	0.319	0.752
Overweight (25-<30 kg/m ²)	62.21 \pm 11.25		
LH: FSH ratio <2	71.24 \pm 8.89	2.649	0.013*
LH: FSH ratio ≥ 2	59.35 \pm 10.02		
Glucose insulin ratio ≤ 4.5	63.71 \pm 12.66	1.078	0.290
Glucose insulin ratio ≥ 4.5	59.46 \pm 8.07		
Testosterone (ng/dL) <118	53.28 \pm 3.78	12.68	0.001*
Testosterone (ng/dL) 118-128	62.45 \pm 6.74		
Testosterone (ng/dL) 128-140	74.53 \pm 10.99		

*P<0.05 was considered statistically significant. FSH=Follicle-stimulating hormone, LH=Luteinizing hormone, SD=Standard deviation

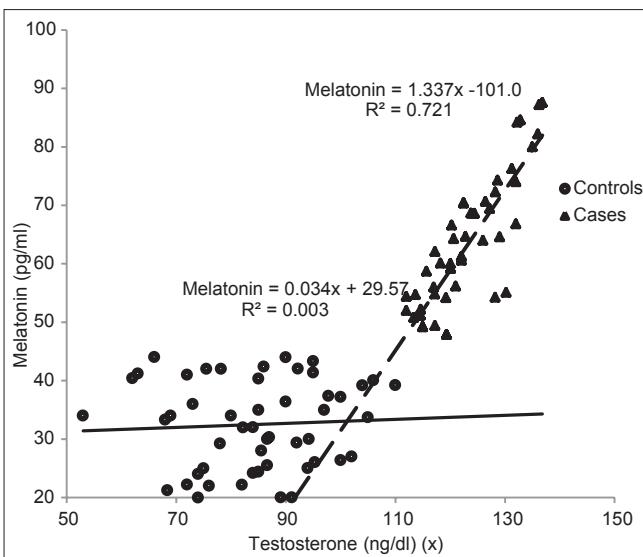


Figure 1: Linear regression of melatonin with testosterone

variable and testosterone as independent variable in both cases and controls. Testosterone explained 72.1% of total variability of melatonin in PCOS cases.

DISCUSSION

In present study, we found that patients with PCOS had significantly raised plasma melatonin levels ($>$ cut off value of 45 pg/mL) as compared with age- and weight-matched controls ($P < 0.001$). Melatonin is normally synthesized in the ovary, as both melatonin synthesizing enzymes AANAT (arylalkylamine N-acetyltransferase) and HIOMT (hydroxyindole-O-methyl transferase) are present in ovarian tissue.^[14] Melatonin, synthesized by the ovary, may be released into the follicular fluid. However, the bulk of melatonin detected in the ovary and preovulatory follicular fluid is derived from the circulation.^[10] There may be a reduction in the uptake of melatonin from circulation into the ovarian follicles of PCOS cases due to anovulation and increased number of atretic follicles and consequently serum melatonin concentration may increase in PCOS as a feedback response to decreased follicular concentration.^[10] Studies done by Luboshitzky *et al.*,^[9,15] gave the consistent results of raised plasma melatonin production in PCOS. They found that mean level of urinary 6-sulfatoxymelatonin (α MT6s), a major enzymatic metabolite of melatonin, in their study was $54.0 \pm 20.3 \mu\text{g}/24\text{ h}$ ($P = <0.001$). The study carried out by Lima *et al.*,^[16] confirmed the development of ovarian cysts in rats similarly to that observed in human PCOS under conditions of melatonin deficiency caused due to pinealectomy or continuous light in female rats.^[16]

Melatonin is a documented powerful free radical scavenger and a broad-spectrum antioxidant.^[11,12] Atresia is an apoptotic process that is highly regulated by proapoptotic

and antiapoptotic factors. In PCOS, ROS generation from mononuclear cells and serum lipid peroxidation products are significantly elevated,^[17,18] and levels of antioxidants superoxide dismutase, glutathione peroxidase, catalase get reduced, which ultimately may contribute to oxidative stress mediated apoptosis in atretic follicles.^[19] Melatonin has also been shown to regulate the gene expression of antioxidant enzymes superoxide dismutase, glutathione peroxidase, catalase and antiapoptotic/proapoptotic protein Bcl2 and Casp3. Melatonin prevents apoptosis by inducing Bcl2 expression and reducing Casp3 activity.^[10] Melatonin also acts as antioxidant by increasing insulin-like growth factor-1^[20] and transforming growth factor - beta (TGF- β) production.^[21] Normally, insulin-like growth factors act as mitogenic and antiapoptotic peptides. Thus, normally the increase in follicular melatonin concentration in the growing follicle could be an important factor in avoiding atresia. The follicle may be rescued by melatonin and this would allow a preovulatory follicle to fully develop and provide an oocyte for fertilization.^[10]

Melatonin influences sex steroid production at different stages of ovarian follicular maturation.^[10] It (100 mM) has been shown to increase progesterone and androgen production in mouse preantral follicles after incubation for 12 days.^[22] and melatonin (100 ng/mL) also stimulates progesterone and androgen production in 30-h cultures of porcine antral follicles without having any effect on estrogen levels.^[23] Similarly, the raised serum melatonin level seen in our PCOS cases was then found to be positively associated with serum testosterone level ($P < 0.001$). However, it has been seen that melatonin gets decreased in ovarian follicular fluid of PCOS patients and this intrafollicular decrease in melatonin is responsible for follicular atresia because of increased oxidative stress and consequent follicular damage in PCOS.^[10] These atretic follicles, escape full maturation and lead to formation of multiple small follicular cysts, surrounded by hyperplastic theca cells. Atretic follicles ultimately contribute to an expanding stroma that increases in volume over time, further increasing the cellular mass producing androgens, sets in another self-propagating cycle that predisposes to chronic anovulation and leads to increased concentration of androgens.^[24] Thus, melatonin correlates with hyperandrogenemia and anovulation in PCOS as found in our study ($R^2 = 0.721$). Women with ovarian hyperandrogenism have increased melatonin production only, which remains normal in women with hyperandrogenemia due to idiopathic hirsutism.^[9]

Hyperandrogenism is the key feature of PCOS, resulting primarily from excess androgen production in the ovaries and, to a lesser extent, in the adrenals. The primary mechanisms driving increased ovarian androgen production in PCOS include hypersecretion of LH and increased LH

bioactivity, hyperinsulinemia due to insulin resistance and increased volume of theca cells in an expanded ovarian stroma.^[24] In our study, serum melatonin was found to be positively associated with serum total testosterone levels, whereas it was inversely correlated with LH: FSH ratio and no correlation has been seen with fasting glucose: insulin ratio. This can be explained by diverse mode of action of melatonin, first by a direct action at receptors MT1 and MT2 leading to alteration in ovarian steroidogenesis and secondly by an action at follicular level as antioxidant.^[25]

High level of melatonin in the follicular fluid is essential for follicle growth, ovulation, and oocyte quality, whereas reduced follicular melatonin concentration may be responsible for anovulation and poor oocyte quality in PCOS. Follicles fail to mature fully and become atretic. Small follicles respond poorly to gonadotropins and undergo atresia.^[10]

Infertility is a major concern in PCOS patients and important causes of infertility in PCOS are follicular atresia, anovulation, and consequent hyperandrogenemia. Thus, melatonin can be used as a therapeutic agent to treat infertile patients undergoing *in vitro* fertilization in whom infertility occurs due to poor oocyte quality and anovulation and can create a new ray of hope for infertile patients. Melatonin may become the medicine of choice for improving oocyte quality for women who are unable to become pregnant because of poor oocyte quality.^[10,26] Melatonin works as a potent radical scavenger and antioxidant and thus may increase oocyte yield. In future, this may translate into improved oocyte quality as well. However, this needs further research and validation from larger studies.

Lacunae

Being the first study of its kind in India, we did not measure melatonin level in follicular fluid of PCOS patients. Correlation with midnight levels of melatonin was another hindrance in the study.

Scope of study

Future field of research would be to find out correlation between serum melatonin level and the level of antioxidants in PCOS patients. Determination of the quality of oocytes in relation to melatonin would be another area of exploration in patients of PCOS suffering from infertility.

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Review Article

Adolescent Obesity

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Correspondence: Aysel Özdemir, Lecturer in Public Health Nursing, Uludağ University, Shcool of Health Sciences, 16059 Bursa, Turkey e-mail: ayozdemir@uludag.edu.tr**Abstract**

Obesity is public health burden and affects all age groups, including children and adolescents. For children aged between 2 and 19 years having a BMI $\geq 85^{\text{th}}$ percentile but $< 95^{\text{th}}$ percentile is defined as being overweight. Being obese is defined as having a BMI $\geq 95^{\text{th}}$ percentile. Nutrition during early development is directly associated with future obesity. In case of having an obese mother; offspring's obesity onset occurs earlier regardless of race or ethnic groups. Obesity brings psychosocial problems with itself. Obese children may have difficulties in interacting socially with environment; may have problems particularly with their age groups. Withdrawal from the society may be a major problem. Preventive measures focusing parents, family and environment should begin at preconception. Maternal factors of childhood obesity can be eliminated, and risk factors for developing adolescent and adult obesity may be avoided. These measures may help us first to decrease the rate of obesity and achieve a downward trend in prevalence. This in turn; may decrease the number of people with obesity and obesity related diseases.

Keywords: Adolescent; Obesity**Adolescent Obesity****Definition of Adolescent Obesity**

Obesity can be defined as having excessive body fat. Williams et al. in their study that involved 3320 children aged between 5 and 18 years stated that; risk factors for cardiovascular disease was more common in case of having at or above 25% fat in males and at or above 30% fat in females even after adjusting for age, race, fasting status, and trunkal fat pattern (D. P. Williams et al., 1992). For children aged between 2 and 19 years having a BMI $\geq 85^{\text{th}}$ percentile but $< 95^{\text{th}}$ percentile is defined as being overweight. Being obese is defined as having a BMI $\geq 95^{\text{th}}$ percentile (Barlow, 2007).

Epidemiology

Obesity is a global pandemic (WHO, 1998). It a matter of public health burden and spreading to all the age groups, including children and adolescents. A global epidemic of obesity occurred in recent years among adolescents, and prevalence of obesity is continuing to rise in this population (Reilly, 2006). Given the high prevalence and chronic nature of obesity, coordinated models of care for health-service delivery for the management of paediatric obesity are needed (Baur et al., 2011). In a study conducted by Freedman et al. (1999) the rate of being overweight was 10.8% in examined school children, while a 10.5% obesity prevalence was

found in more recently studied school population in Greece (Jelastopulu et al., 2012).

Age-standardized prevalence of overweight was 17.8% among boys and 15.8% among girls in a study conducted in India (Ramachandran et al., 2002). Though obesity prevalence increases as a global problem; a study based on data from 1998 through 2011 conducted in Denmark, showed that the prevalence rates of overweight and obesity in infants, children and adolescents were largely still on a plateau with tendencies for a decline among children and adolescents (Schmidt Morgen et al., 2013). But this may be far from representing the global picture.

In the Jelastopulu et. al (2012) study which was conducted in Greece, it was found that the prevalence of overweight and obesity in the studied population of 10–13 year old children it was 32% and 10.5%, respectively, while in children with parents of lower educational level, the odds of being overweight/obese was higher.

In all paediatric age groups there is an increasing prevalence of being overweight and obese. National Health and Examination Surveys (NHANES) in the US showed constant increases in the prevalence of overweight among children and adolescents at age 2 to 18 years. According to the data approximately 14% of children aged 2 to 5 years and 19% of

children aged 6 to 11 years were overweight (Ogden et al., 2006).

Nutrition during early development is directly associated with future obesity. The monthly family income, self-attitude toward obesity, taking extra salt and spending time with computer all are part of a vicious cycle that lead children and adolescents toward obesity (Ghosh, 2007). In a study, it was reported that breakfast skipping was associated with BMI strongly compared to other factors. Missing breakfast increased consumption of snacks and fast foods (Ghosh, 2014). In case of having an obese mother; offspring's obesity onset occurs earlier regardless of race or ethnic groups. And the combination of having an obese mother and an earlier onset of obesity affects young adulthood causing higher BMI and weight (Gordon-Larsen et al., 2007). The environmental factors are very effective in children. The proximity of fast food restaurants to the schools clearly causes bad eating habits and being overweight (Davis and Carpenter, 2009). For development of obesity many factors are described like intrauterine conditions, diabetes mellitus, smoking of the mother, breast-feeding duration, feeding during early life, weight gain in early childhood and at puberty (Fisberg et al., 2004).

Both genetic and environmental factors are effective in body mass index and waist circumference in children as a result of a study carried out in twin pairs at age of 8 to 11 years (Wardle et al., 2008).

An interesting result was the finding of decrease in the prevalence of obesity among adolescents with high-socioeconomic status, where among the low-socioeconomic status adolescents' obesity prevalence was continuing to increase (Frederick et al., 2014). This may be due to the fact that obesity is highly influenced from environment. Probably the social environment is better in adolescents with high socio-economic status. This in turn may be supported with the finding that obesity in school-aged children is associated with parental factors like parental obesity and health literacy (Chari et al., 2014).

Related clinical problems

Adolescent obesity is associated with increased mortality and morbidity related to a variety of chronic diseases later in life (Must et al., 1992). Obesity brings up many problems which affect the whole life span of the youngster and has adverse effects on the lipid, insulin, and blood pressure levels (Berenson et al., 1993; Freedman et al., 1985; D P Williams et al., 1992). Adiposity causes fatty streaks, raised lesions, and calcifications in the aorta

and coronary arteries in adolescents and young adults (Berenson et al., 1998; Mahoney et al., 1996; McGill et al., 1995). Overweight children are also at increased risk for various chronic diseases in later life and some evidence suggests that this association may exist independently of obesity status in adulthood (Must et al., 1992; Power et al., 1997). Also in a study that enrolled 1076 adolescents aged 14-16 years, birth weight and attained size at 20th and 43rd months were related to being overweight and having obesity during adolescence period. However; four of five obese adolescents were normal weight during childhood and that makes us to focus on normal weight children with bad eating habits or environmental conditions that are prone to become obese in adolescence (Monteiro et al., 2003).

Among 3,861 school children in the age group 5-15 years 292 (7.56%) were identified as obese in a study by Gupta. Further, 10 (3.4%) of the 292 obese subjects were detected to have sustained elevations in BP levels suggesting a close association between childhood obesity and essential hypertension (Gupta and Ahmad, 1990). Release of non-esterified fatty acids, cytokines and other factors from the adipose tissue in obese individuals causes development of insulin resistance. Addition of pancreatic islet beta cell dysfunction causes failure in blood glucose control (Kahn et al., 2006).

Being overweight during childhood is related to having type 2 diabetes mellitus, adult obesity, cardiac disease, low self-esteem and depressive disorders (Fisberg et al., 2004). Obesity brings psychosocial problems with itself. Obese children may have difficulties in interacting socially with environment; may have problems particularly with their age groups. Withdrawal from the society may be a major problem. They may have less self-confidence due to perception of their body shape. Obesity in adolescence is associated with depression or anxiety. In a study conducted in adolescents; obesity was a predictor of an increased risk for developing major depressive disorder in females but not males (Anderson et al., 2007). In adolescent females obesity but not being overweight was significantly associated with future depressive symptoms but not major depression in a study that was conducted in 2010. The authors said "these results suggest that weight status could be considered a factor along the pathway of development of depression in some adolescent females" (Boutelle et al., 2010). According to Goodman and Whitaker; having depression in adolescence, increases risk of obesity in adolescence and persistency of it. In conclusion

they said "understanding the shared biological and social determinants linking depressed mood and obesity may inform the prevention and treatment of both disorders" (Goodman and Whitaker, 2002).

Treatment

In adolescence obesity; the main approach should be prevention. We are now aware that Preconception maternal factors have much more influence on child obesity than prenatal factors (Ehrenthal et al., 2013). We must consider effect of social environment and friends on adolescent health. Adolescents develop certain behaviours probably to feel comfortable. This may be the explanation of overweight adolescents having twice as likely to have overweight friends as reported by Valente et al. (Valente et al., 2009). Interventions focusing behavioural changes must be a part of preventive therapy. Interventions may cause modest changes and modifying TV watching, physical activity, eating behaviours must be some of the goals. Of course not only the adolescent but parents, grandparents, sibling must also be targeted. The social environment, school has great effect and must be in scope. But this is a global burden and the governments must take serious preventive measures to prevent and treat the disease itself. Education of mother or woman of child-bearing age may provide control early at preconception. Maternal factors of childhood obesity can be eliminated, and risk factors for developing adolescent and adult obesity may be avoided. These measures may help us first to decrease the rate of obesity and achieve a downward trend in prevalence. This in turn; may decrease the number of people with obesity and obesity related diseases. Orlistat; a pancreatic lipase inhibitor, reduces fat absorption and used in treatment of obesity is used in adolescents in combination with diet, exercise and behavioural modification without safety issues but with more common gastrointestinal side effects (Chanoine et al., 2005). Sibutramine also was used in adolescents and caused significantly more weight loss compared to behavioural therapy and placebo (Berkowitz et al., 2003). Metformin; combination of caffeine and ephedrine all reduced body weight index in adolescents (Freemark and Bursey, 2001; Molnár et al., 2000). Surgical procedures are applied when more conservative treatment options fail (Kumar et al., 2012).

Conclusion

Adolescent obesity is a global health burden which will affect future generations' health. Treatment options are diverse but pharmacological and surgical

therapies posses' serious disadvantages in this age group. Preventive measures focusing parents, family and environment should begin at preconception. Interventional strategies should cover all population and the main objective should be eliminating causative factors.

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Article

Overnight Melatonin Concentration and Sleep Quality Are Associated with the Clinical Features of Polycystic Ovary Syndrome

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Abstract: Circulating melatonin is elevated in women with polycystic ovary syndrome (PCOS); whether circadian disruptions coincide with sleep disturbances in women with PCOS or their symptom severity is unclear. The objective of this observational pilot study was to determine whether altered patterns of melatonin excretion are associated with reduced sleep quality in women with versus without PCOS. Participants underwent a clinical assessment, transvaginal ultrasound, and reproductive hormone testing. Morning and evening urine samples were assayed for urinary 6-sulfatoxymelatonin (MEL) as a proxy for melatonin production. The night (morning MEL)-to-day (evening MEL) ratio, or N:D ratio, was determined to approximate the rhythm of MEL production. Sleep quality and duration were assessed using the Pittsburgh Sleep Quality Index (PSQI) and wrist actigraphy. No differences were detected in overnight MEL, daytime MEL, or the N:D ratio in participants with PCOS versus controls. The PCOS group experienced reduced weekend sleep efficiency vs. controls (81% vs. 88% $p < 0.05$). The number of follicles per ovary (FNPO) was positively associated with overnight MEL ($r = 0.359$, $p < 0.05$). Weekend sleep time and overnight MEL concentrations were dependent on PCOS status. Therefore, diagnostic features of PCOS were associated with MEL production and sleep disturbances, suggesting that women with a more severe clinical presentation of PCOS may be more likely to experience altered MEL production or sleep disturbances.

Keywords: polycystic ovary syndrome; melatonin; sleep; sleep quality; ovary; circadian rhythm



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1. Introduction

Polycystic ovary syndrome (PCOS) is a reproductive disorder characterized by oligo-anovulation, hyperandrogenism, and polycystic ovarian morphology that affects approximately 10% of reproductive-aged females [1]. PCOS is associated with significant metabolic and psychological sequelae [2]—both of which are factors that have been linked to impaired sleep [3,4]. Females with PCOS are more likely to experience sleep disorders such as obstructive sleep apnea, as well as abnormalities in sleep architecture (i.e., a reduction in the percentage of rapid eye movement sleep) when compared to those without PCOS [5]. Prior studies have also shown that those with PCOS experience lower sleep quality, reduced sleep efficiency, and greater daytime sleepiness relative to healthy controls [5–10]. In addition to negatively impacting quality of life, impaired sleep may have far-reaching health implications for those living with PCOS, as aberrant sleep patterns have been associated with a more severe metabolic profile, including obesity and insulin resistance [6]. Therefore, the relevance of sleep in the pathophysiology of PCOS and its associated comorbidities is of growing interest.

Melatonin is synthesized and secreted by the pineal gland and predominantly functions as a chronobiotic to synchronize and facilitate entrainment of behavioral and physiological rhythms [11,12]. Melatonin is primarily excreted in urine as 6-sulfatoxymelatonin (MEL), which closely reflects plasma concentrations [13]. Melatonin is also hypothesized to exhibit endocrinologic effects beyond its circadian role, with recent evidence demonstrating antioxidant activity within the ovary [5]. Specifically, melatonin has been implicated in the regulation of ovarian sex hormone production and in the reduction in local reactive oxygen species (ROS), thereby preventing follicular atresia [14]. Therefore, it is plausible that disruptions in melatonin secretion may impact not only circadian rhythms but also reproductive function. Indeed, there is evidence for disrupted melatonin secretion among women with reproductive dysfunction, including those with PCOS. Namely, elevated 24 h total [13], morning [6,15], and nighttime [8] melatonin concentrations have been documented in women with PCOS. Further, women with PCOS were shown to have a reduced night-to-day (N:D) ratio of MEL, driven by increased daytime MEL concentrations [16]. Given that the N:D ratio can serve as a proxy for the circadian rhythm of MEL production, a lower N:D ratio or dampened magnitude of the night-to-day shift of MEL implies that the physiological control of melatonin secretion by the circadian timing system may be altered in the context of PCOS. Factors impacting altered melatonin dynamics in PCOS are unclear, as are their alignment with the degree of disordered sleep common in this condition. The role of androgens is inconsistent, as both positive [6] and negative [13] associations between melatonin and hyperandrogenism have been reported. Evidence linking the degree of menstrual cycle dysfunction and/or ovarian dysmorphology to altered melatonin secretion is also largely unexplored. Interestingly, analysis of ovarian granulosa cells obtained from infertile women with PCOS has demonstrated blunting of the rhythmic expression of some circadian clock genes, highlighting the critical impact such disruptions may have on gonadal function [17]. Ultimately, more data are needed to corroborate that disrupted circadian rhythms may occur concurrently with and/or contribute to the pathophysiology of PCOS while simultaneously contributing to the appearance of marked sleep disturbances in these women.

To address this knowledge gap, the primary objective of this observational pilot study was to determine whether altered patterns of day and night MEL excretion coincided with reduced sleep quality among women with PCOS. A secondary objective was to determine whether disrupted MEL production was associated with the diagnostic features of PCOS.

2. Materials and Methods

2.1. Study Subjects

In this ancillary study, participants were prospectively recruited at the University of Rochester or Cornell University (ClinicalTrials.gov NCT01859663, NCT01927432, NCT01927471, NCT01785719) from 2015–2019. Existing study protocols already collecting relevant reproductive and metabolic endpoints were amended to include sleep and circadian endpoints uniquely for this study. Participants were phenotyped according to criteria supported by the 2018 International Guideline for PCOS [18]. Specifically, participants with PCOS met at least two out of the three criteria: menstrual irregularity, biochemical or clinical hyperandrogenism (HA), and/or polycystic ovarian morphology on ultrasound (PCOM). Menstrual irregularity was defined as <21 or >35 days between menses based on self-reporting during hormone-free intervals. Biochemical HA was defined as either Free Testosterone (T) > 0.815 ng/dL, bioavailable T > 19.06 ng/dL, or free androgen index (FAI) >6%; clinical HA was defined using a modified Ferriman Gallwey (mFG) score of ≥6. PCOM was defined as at least one ovary with an ovarian volume (OV) > 10mL or >9 follicles in a single cross-section of the ovary (FNPS)—the latter of which has been shown to have high diagnostic accuracy for PCOS on ultrasound [19]. Exclusionary criteria included the use of medications known or suspected to interfere with reproductive function within 2 months of enrollment, melatonin supplementation, elevated prolactin (PRL), thyroid stimulating hormone (TSH), or follicle-stimulating hormone (FSH),

current pregnancy or active breastfeeding. The non-PCOS reference group exhibited no more than one of the diagnostic criteria and is herein referred to as the control group.

2.2. Ethical Considerations

Written informed consent was obtained from the participants before any procedures were conducted. All parent protocols and study-specific amendments were approved by the Institutional Research Boards at Cornell University and the University of Rochester. Study procedures occurred at the Human Metabolic Research Unit (Cornell University, Ithaca, NY, USA) or Strong Fertility and Clinical Research Center (University of Rochester, Rochester, NY, USA).

2.3. Procedures

Participants attended a clinical research unit after an overnight fast for the following clinical assessments and procedures: (a) transvaginal ultrasound of the ovaries (b) reproductive and medical health history, (c) 75 g oral glucose tolerance test (OGTT), (d) physical exam and participant self-report to grade terminal hair growth using the modified Ferriman-Gallwey scoring system and (e) vitals and anthropometry assessment (waist and hip circumference, height, weight, blood pressure). Blood glucose was measured on-site using a glucometer (Accu-chek Aviva, Roche, Basel, Switzerland), and values were used to calculate the homeostatic model assessment for insulin resistance (HOMA-IR; $(\text{Insulin}_{0\text{hr}} * \text{Glucose}_{0\text{hr}})/22.5$) [20,21].

Participants with self-reported regular menstrual cycles were evaluated during the early follicular phase. Participants with self-reported irregular menstrual cycles were evaluated at random times. Participants were asked to reschedule their clinical assessments if investigators (1) observed the presence of a large follicle (>10 mm) or (2) had evidence of recent ovulation on the day of the ultrasound. Voluson ultrasound systems (GE, Milwaukee, WI, USA) using either a RIC5-9W-RS, RIC5-9A-RS, or RIC6-12-D endovaginal transducer were used to capture volumes of the ovaries. Images of the right and left ovaries were analyzed in 2D offline using a grid overlay [22] by trained members of the research team who achieved excellent agreement [intraclass correlation coefficient >0.9]. Follicle number per ovary (FNPO) represented the mean number of antral follicles 2–9 mm across both ovaries. Ovarian volume was determined using the following formula: $[\pi * (\text{average of all four linear measurements in orthogonal planes})]$ and reported as the mean of both ovaries, based on an internal study comparing different formulae to calculate ovarian volume in 2D versus 3D measures. If a dominant follicle was identified in one ovary, ovarian data from the other ovary were used in the event a follow-up ultrasound could not be scheduled. When poor image quality prevented reliable assessments in one of two ovaries, only the values of the ovary that could be visualized were analyzed by investigators.

2.4. Sleep-Related Endpoints

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), which is a valid and reliable 10-item questionnaire that reflects sleep habits for the most recent month based on self-report [23]. A score of less than or equal to 5 on the PSQI is associated with good sleep quality, whereas a score above 5 is associated with poor sleep quality.

Sleep measures were evaluated using a wrist-worn triaxial accelerometer. Participants were instructed to wear a triaxial accelerometer around their wrists at night and remove the device when out of bed for six consecutive nights. Participants recorded the dates and times the accelerometer was put on and taken off. The Sadeh Sleep Model [24] was used to compute overall, weekday night, and weekend night total sleep time and sleep efficiency. Sleep efficiency was reported as the percent of the time spent asleep divided by the time spent in bed. Participants were also instructed to obtain urine samples at home, collecting their first-morning void and evening (18:00–21:00) urine for two consecutive mornings and evenings during the week of wrist accelerometer wear. Participants were asked to record the dates and times of urine collection. Urine samples were stored in participants' home

freezers and were brought into their local clinical research unit on the ice. Urine samples were brought to room temperature for aliquoting and stored at -80°C until analysis.

2.5. Assays

Urinary 6-sulfatoxymelatonin (MEL) was measured using the Buhlmann ELISA kit in triplicate (inter- and intra-assay variability <10%). Urinary MEL concentrations were adjusted for urinary creatinine. The average of the replicates was computed for analysis. The N:D ratio was computed as mean overnight MEL divided by mean daytime MEL for each of the two 24 h periods of data collection, totaling two N:D ratios. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), sex hormone binding globulin (SHBG), prolactin (PRL), and thyroid stimulating hormone (TSH) were measured from serum using chemiluminescence immunoassay, Siemens Medical Solutions Diagnostics, Deerfield, IL (inter- and intra-assay variability <10%). Total testosterone was measured using LC/MS/MS by a laboratory associated with the Centers for Disease Control and Prevention's Hormone Standardization Project (CDC-HoST) (Brigham Research Assay Core, Boston, MA, USA). FAI was calculated as Total T/SHBG (%). Free T and bioavailable testosterone were computed as described previously [25].

2.6. Statistical Analyses

Data were evaluated for normality, and the log was transformed as needed to meet statistical assumptions. Group comparisons were conducted using independent *t*-tests for continuous variables and Fisher's exact tests for categorical variables. Associations between the diagnostic features of PCOS and sleep-related endpoints were evaluated using Pearson partial correlations after adjusting for BMI (Table A1). To test whether associations between sleep quality (i.e., PSQI) or accelerometer-defined sleep measures and MEL concentrations (day, night, or night-to-day ratio) differed between PCOS and control groups, multiple linear regression analyses were conducted. The dependent variables were MEL or N:D ratio, and the predictors included a sleep measure-by-PCOS interaction term. Data are presented as mean \pm standard deviation (SD). Analyses were conducted using JMP Pro 14 (Cary, NC, USA). Statistical significance was set at $p < 0.05$. If participants had incomplete data collection for certain variables, they were still utilized in the analyses for which they had data. The original observational pilot sample size was determined via a power calculation to detect a difference in the mean N:D MEL ratio, which showed that six participants per group gave a statistical power of greater than 95% [16]. This sample size was preliminary, assuming a three-fold difference across groups, and was intended to generate effect sizes to inform a larger study.

3. Results

A total of forty-two participants were enrolled, with seven excluded due to oral contraceptive use ($N = 6$) and melatonin supplementation ($N = 1$). Twenty-two individuals met the criteria for PCOS, and thirteen met the criteria for controls. The demographic and clinical features of each group are shown in Table 1. There were no differences between groups with respect to BMI or age. By design and compared to controls, women with PCOS had significantly longer mean menstrual cycle lengths ($p < 0.05$), larger ovaries ($p < 0.0001$), increased follicle counts (FNPO, $p = 0.0016$, FNPS, $p = 0.003$), and were hyperandrogenic, as defined by hirsutism ($p = 0.033$) and TT ($p = 0.03$). Furthermore, 2 h insulin following an OGTT was higher ($p = 0.01$), and 2 h glucose also tended to be greater ($p = 0.051$) in PCOS versus controls.

Table 1. Demographic and clinical features.

	Control		PCOS		<i>p</i> Value
	Mean	Std Dev	Mean	Std Dev	
N	13		22		
Age (y)	28.0	5.8	28.3	5.5	NS
Age at menarche (y)	12.2	0.9	13.1	1.1	0.018
Anthropometry and glucoregulation					
BMI (kg/m^2)	31.3	4.49	30.9	9.41	NS
WHR	0.83	0.08	0.82	0.08	NS
Body fat (%)	39.4	5.43	39.7	10.21	NS
Insulin (0 HR, mIU/mL)	7.6	2.77	13.9	12.47	NS
Glucose (0 HR, mg/dL)	90.5	5.83	93.3	11.96	NS
HOMA-IR	1.7	0.63	3.5	3.79	NS
Insulin (2 HR, mIU/mL)	28.5	12.70	73.2	64.67	0.010
Glucose (2 HR, mg/dL)	81.8	87.20	101.6	38.18	0.051
Systolic BP (mmHg)	117	17.6	115	15.6	NS
Diastolic BP (mmHg)	72	19.4	69	9.7	NS
Diagnostic features of PCOS					
MCL (days)	30	2.2	67	72.3	0.001
Hirsutism score	3	2.9	8	6.2	0.005
TT (ng/dL)	18.7	14.01	36.7	26.36	0.033
FAI (%)	1	1.0	4	3.6	0.071
FT (ng/dL)	0.25	0.18	0.58	0.52	0.075
BIOT (ng/dL)	5.9	4.42	13.6	12.11	0.072
Mean OV (cm^3)	5.4	1.31	9.7	2.90	<0.001
Mean FNPO	19	10	40	20	0.002
Mean FNPS	6	3	11	4	<0.001
Reproductive endocrinology					
LH (mIU/mL)	4.3	1.96	8.49	5.83	0.009
FSH (mIU/mL)	6.6	2.62	5.28	1.79	NS
SHBG (nmol/L)	54.6	31.90	57.77	35.65	NS

p-values reflect two-sided *t*-tests. Variables were transformed as needed (logarithmic or square root) to meet assumptions. Ovarian analyses reflect mean values, except when a dominant follicle (DF) or corpus luteum (CL) was present, then the ovarian data reflect the ovary that did not contain the DF or CL. Abbreviations: BMI, body mass index; WHR, waist-hip ratio; HOMA-IR, homeostasis model assessment for insulin resistance; MCL, mean cycle length; TT, total testosterone; FAI, free androgen index; FT, free testosterone; BIOT, bioavailable testosterone; Mean OV, mean ovarian volume; Mean FNPO, mean follicle number per ovary; Mean FNPS, mean follicle number per single cross-section; LH, luteinizing hormone; FSH, follicle stimulating hormone; SHBG, sex hormone binding globulin; Fasting glucose and insulin levels (0HR) prior to administration of a 75 g oral glucose tolerance test (OGTT) and 2 h afterward (2HR).

Differences in sleep-related endpoints between groups are presented in Table 2. No differences in MEL-related or PSQI-defined sleep variables were detected between PCOS and controls (*p* > 0.05). With respect to the accelerometer-defined sleep variables, women with PCOS had significantly reduced weekend sleep efficiency when compared to controls (81% vs. 88%, *p* = 0.01). Regression analyses with a sleep measure-by-PCOS interaction term revealed that the association between overnight MEL concentration and accelerometer-defined sleep time on the weekend differed between those with and without PCOS (Figure 1; *p*_{interaction} = 0.0416). Similarly, the association between N:D MEL ratio and weekend sleep efficiency varied by PCOS status (*p*_{interaction} = 0.0017, N:D MEL (1); *p*_{interaction} = 0.0028, N:D MEL (2)). There were no statistically significant interactions between PCOS status and PSQI or other accelerometer-defined sleep measures on any MEL outcomes (*p* > 0.05). With respect to data collection, 5 participants had incomplete MEL data sets, 1 participant did not complete the PSQI, and four did not have accelerometer-defined sleep data.

Table 2. Differences in sleep-related endpoints between PCOS and controls.

Urinary Melatonin Variables	Controls		PCOS		<i>p</i> Value	
	Mean	Std Dev	Mean	Std Dev		
Mean overnight MEL (ng MEL/mg CRE)	6213.07	4146.26	6972.42	3584.04	NS	
Mean daytime MEL (ng MEL/mg CRE)	865.93	643.20	1297.28	1122.41	NS	
Night/day ratio (1)	15.76	16.06	13.41	8.72	NS	
Night/day ratio (2)	13.60	13.01	11.49	8.57	NS	
PSQI-defined sleep variables						
PSQI total	5	2.7	7	4.0	NS	
Good sleep quality, N (%)	9 (69)		12 (55)		NS	
Poor sleep quality, N (%)	4 (31)		10 (45)			
Accelerometer-defined sleep variables						
Total sleep time (h/day)	6.5	0.80	6.5	0.94	NS	
Total weekday sleep time (h/day)	6.3	1.28	6.5	1.05	NS	
Total weekend sleep time (h/day)	7.1	1.16	6.5	1.46	NS	
Total sleep efficiency (%)	84	6.9	82	7.7	NS	
Weekday sleep efficiency (%)	82	10.1	81	7.6	NS	
Weekend sleep efficiency (%)	88	5.0	81	8.3	0.010	

Variables were transformed as needed (logarithmic or square root) to meet assumptions. Means and SD reflect raw data. Implausible values (sleep efficiency > 100%) were excluded from their endpoint-specific analyses. Categorical analyses were conducted using Fisher's Exact tests (two-sided). A PSQI score of >5 is categorized as poor sleep quality. MEL, 6-sulfatoxymelatonin; CRE, serum creatinine; PSQI, Pittsburgh Sleep Quality Index.

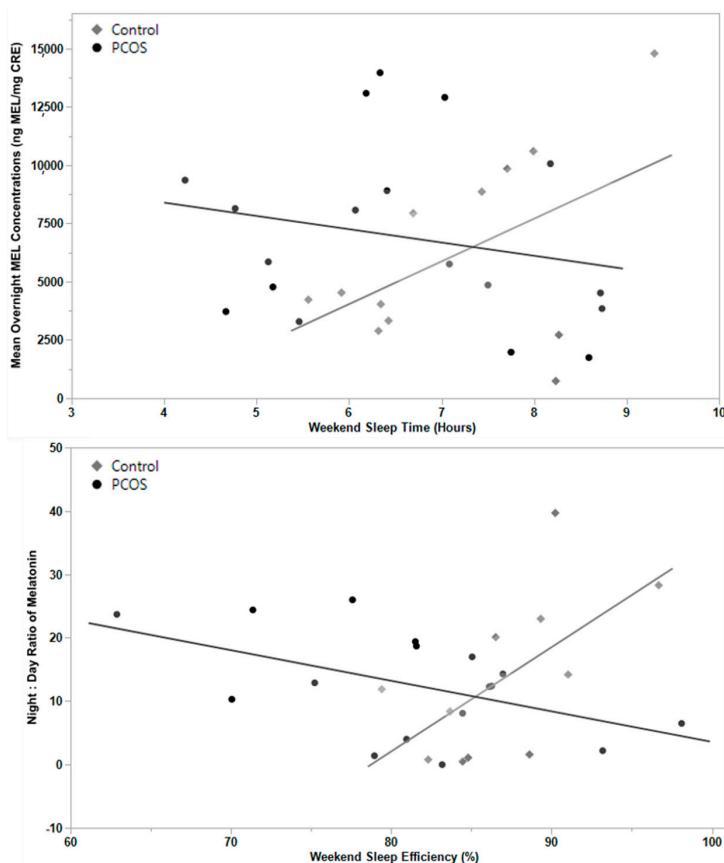


Figure 1. Associations between melatonin concentrations and weekend sleep quality are dependent on PCOS status. Associations between overnight melatonin production estimated using morning urinary MEL concentration and increasing weekend sleep time differ based on PCOS status (top panel; *p* < 0.05). Similarly, the association between N:D MEL ratios and weekend sleep efficiency differs based on PCOS status (bottom panel; *p* < 0.05).

Partial correlations were performed to assess the independent association between the diagnostic features of PCOS and urinary MEL endpoints, adjusting for BMI, which may have confounded the associations (Table A1). FNPO was positively associated with mean overnight MEL concentrations ($p < 0.05$; Table 3). No other significant associations between menstrual cyclicity, biochemical hyperandrogenism, or ovarian morphology and MEL endpoints were observed ($p > 0.05$).

Table 3. Associations between diagnostic features of PCOS and urinary melatonin.

	MCL	TT	FT	FAI	Bio T	OV	FNPS	FNPO
Mean overnight MEL (ng MEL/mg CRE)	−0.016	0.082	0.131	0.137	0.127	0.120	0.298	0.359 *
Mean daytime MEL (ng MEL/mg CRE)	0.177	0.074	0.093	0.087	0.092	0.215	0.137	0.206
N:D ratio (1)	0.134	0.136	0.208	0.218	0.204	0.123	0.299	0.246
N:D ratio (2)	−0.215	−0.001	−0.069	−0.076	−0.070	−0.114	0.047	0.074

Partial correlations between urinary melatonin concentrations and diagnostic features of PCOS. Partial correlations were adjusted for any potential confounding effects of BMI (Table A1). In the cases of women with dominant follicles, ovarian data from the other ovary were reported ($N = 6$) or excluded if in the luteal phase ($N = 1$). In this case, ovarian endpoints from the other ovary are presented. One participant was excluded from all ovarian analyses because both ovaries had DFs. Abbreviations: MEL, melatonin; CRE, creatinine; MCL, mean menstrual cycle length; TT, total testosterone; FT, free testosterone; FAI, free androgen index; Bio T, bioavailable testosterone; OV, ovarian volume; FNPS, follicle number per single cross-section; FNPO, follicle number per ovary; CRE, serum creatinine. *, $p < 0.05$.

4. Discussion

In this observational pilot study, we examined sleep quality in women with and without PCOS and tested whether an altered circadian rhythm output (i.e., urinary melatonin) is uniquely associated with poor sleep quality in individuals with PCOS. We also determined whether the degree of urinary melatonin excretion was associated with the severity of the diagnostic features of PCOS. Our data demonstrate that weekend sleep efficiency was lower in women with PCOS and that the association between weekend sleep time and overnight MEL concentrations is dependent on PCOS status. Furthermore, we report that FNPO is positively associated with mean overnight MEL concentration, which, to our knowledge, has not been previously reported.

Among all participants, mean overnight MEL was positively associated with FNPO but not hyperandrogenism, which was somewhat unexpected. The precise relationship between MEL and hyperandrogenism remains controversial, with previous studies reporting positive [6,26] or negative [13] associations between circulating androgens and MEL in PCOS. The relationship between MEL and ovarian morphology is also poorly established. We note two possible explanations for the associations between FNPO and MEL. First, it is plausible that in the present study, the degree of follicle excess (FNPO) may serve as a proxy for the phenotypic severity of PCOS [27] and that the severity of PCOS is associated with the magnitude of circadian rhythm disruption [15]. The severity of a PCOS phenotype may be related to the degree of circadian disruption as prior studies have demonstrated associations between melatonin and increased cardiovascular risk [16] and the degree of hyperandrogenism [6]—albeit not consistently. Second, increased MEL excretion may reflect ovarian inflammation and not hyperandrogenism. PCOS is characterized by a state of high oxidative stress [8], and melatonin has an antioxidant role as a free radical scavenger within the ovary [14]. Therefore, higher serum melatonin concentrations reported in PCOS may be a consequence of reduced intra-follicular melatonin concentrations via a negative feedback mechanism [14]. Furthermore, low intrafollicular melatonin has been associated with chronic anovulation and poor oocyte quality secondary to oxidative stress and a pro-inflammatory state [14]. A prior study examining human ovarian follicular fluid following in vitro fertilization cycles found that women with PCOS have lower intrafollicular melatonin levels than controls [28]. We posit that an increased FNPO in these patients may be indicative of pronounced ovarian dysfunction secondary to greater ovarian oxidative stress from a lower intrafollicular concentration of melatonin. The combination of

these features, therefore, may contribute to aberrant folliculogenesis. However, the degree to which MEL (the urinary metabolite of melatonin) reflects the intra-ovarian melatonin milieu is not well established and was not measured in this study; therefore, additional research is needed to corroborate this hypothesis. To contextualize this argument, PCOS has been described as a pro-inflammatory state, with prior studies demonstrating elevated C-reactive protein levels in addition to markers of oxidative stress [29]. Furthermore, a study examining the impact of 12 weeks of oral supplementation with melatonin in patients with PCOS demonstrated a reduction in serum inflammatory markers [29]. With respect to possible clinical implications of these findings, a future exploration of whether oral melatonin supplementation impacts intrafollicular melatonin levels and whether this correlates with a decrease in FNPO and/or an improvement in menstrual cyclicity would allow elucidation of a possible therapeutic pathway.

We also observed a misalignment between overnight MEL and sleep efficiency in participants with PCOS. In women without PCOS, overnight MEL increased as anticipated alongside increased sleep duration relative to the time spent in bed (sleep efficiency). However, in participants with PCOS, as sleep efficiency increased, the magnitude of the overnight MEL rise relative to the daytime was significantly blunted. This observation supports previous reports of circadian misalignment in this population. An increased MEL [13,26], increased morning MEL [15], and a delayed MEL offset after wakening [6] have all been observed in women and adolescents with PCOS. We should note that not all studies report concomitant sleep disruptions in women with PCOS, which we posit may be attributed to heterogeneity in how circadian rhythms and sleep patterns are assessed across studies. With that said, our study contributes to a growing body of evidence that sleep quality, assessed quantitatively, and MEL may be misaligned in women with PCOS. Whether disrupted melatonin production and MEL excretion are a cause or a consequence of poor sleep quality in PCOS (in our case, reduced sleep efficiency) remains unclear and warrants further investigation.

In a departure from previous studies, we did not detect group differences in PSQI-defined measures of sleep quality [8]. Similarly, we did not detect differences between PCOS and non-PCOS groups with respect to measures of circadian rhythm (as represented by overnight MEL, daytime MEL, or the N:D ratio), which contrasts previous studies reporting such findings [6,16]. However, our finding that weekend sleep efficiency is significantly reduced in the PCOS group is consistent with other studies [6,8,30]. Our null findings were unexpected, as co-morbid sleep disorders are known to be common in women with PCOS [7,9]. Likewise, insulin resistance is associated with both obstructive sleep apnea [7,31] and PCOS. Indeed, women in the PCOS group had higher insulin levels following an OGTT. However, as a group, they did not exhibit worse sleep quality. It is plausible that our participant pool—both the PCOS and control groups—may have blunted any effects of PCOS status. On average, neither group met the nightly sleep recommendation defined by the American Academy of Sleep Medicine (7–9 h per night) during the period of data collection, which is likely to have diluted any possible effect attributed to PCOS status [32]. It is also plausible that our definition of controls may have reduced the effect size attributed to PCOS status. Controls were defined as having no more than 1 of the diagnostic features of PCOS; therefore, they may have exhibited some mild evidence of reproductive dysfunction. As an observational pilot study, direct clinical correlations cannot be drawn from our results; however, our findings of a misalignment between MEL and sleep efficiency in participants with PCOS, as well as reduced weekend sleep efficiency, highlight the importance of discussing sleep and sleep hygiene during routine clinical evaluation. This is especially relevant, given the association between abnormal sleep, metabolic derangements, and insulin resistance—factors with well-established links to PCOS [6].

The study had several strengths. Participants were prospectively recruited and well-phenotyped by the research team using detailed reproductive health histories, standardized testosterone assays, and rigorous ovarian imaging. We conducted a comprehensive assessment of metrics to assess sleep quality and circadian rhythm, which enabled comprehensive

assessments of qualitative and quantitative sleep quality alongside MEL. The study also had limitations. Although we provided instructions for week-long accelerometer wear, participant compliance represented a significant challenge in capturing sleep and circadian shifts, and therefore, wrist-worn accelerometer wear was varied (total number of weekday nights data obtained: 3 to 5; total number of weekend nights data obtained: 1 to 2). Moreover, because the timing of urine can greatly reflect the degree to which overnight MEL production is captured or missed [33], it is plausible that the null findings may be partially attributed to inconsistent timing of urine collection (first morning voids among participants ranged from 04:00–12:00). We acknowledge that measurement of urinary 6-sulfatoxymelatonin in urine using ELISA may significantly overestimate circulating MEL levels [34] and that our approach abrogates any definitive conclusions regarding the exact timing and amplitude of MEL secretion. Future studies would benefit from the assessment of dim light onset MEL (DLMO) in plasma or salivary samples collected every 30 min to 1 h during a constant dim light protocol and assayed using mass spectrophotometry. Reduced compliance also resulted in missing values, which may further reduce the ability to detect differences across groups. The nature of this observational pilot study did not allow for subdivision by PCOS phenotype; therefore, the impact of phenotypic severity per se, on circadian disruption could not be elucidated. With respect to sample size, our analysis determined that we were sufficiently powered to detect a statistically significant difference when investigating the mean N:D MEL ratio as an outcome. However, future research should include larger sample sizes to establish clinically meaningful differences (i.e., threshold of clinical significance) to investigate among the different PCOS phenotypes. Finally, one participant reported a history of obstructive sleep apnea during study participation, which may lower sleep quality due to nighttime awakening. Although it is unlikely that one participant could drive an effect size, future studies should carefully screen participants for sleep-disordered breathing at the time of enrollment, given the increased risk of OSA in women with PCOS, even after controlling for BMI [5].

5. Conclusions

In summary, we report reduced weekend sleep efficiency and evidence of misalignment between circadian rhythms and sleep quality in participants with PCOS. We also report that the degree of overnight MEL is positively associated with increasing follicle number, suggesting that the severity of a PCOS phenotype may be linked to circadian disruption. Due to the heterogeneity in sample collection, additional research is needed to corroborate these findings. However, these data provide formative evidence that the pathophysiology of PCOS may be closely related to circadian disruption, and there is fertile ground for further clinical investigation.

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Institutional Review Board Statement: To conduct this observational pilot investigation, the study team designed an auxiliary study, which was amended onto four prospective ongoing studies (NCT01927432, NCT01927471, NCT01859663, NCT01785719) to obtain sleep-specific endpoints uniquely for this study. Written informed consent was obtained from the participants before any procedures were conducted. Both parent protocols and study-specific amendments were approved by the Institutional Research Boards at Cornell University and the University of Rochester. Study procedures occurred at the Human Metabolic Research Unit (Cornell University, Ithaca, NY, USA) or Strong Fertility and Clinical Research Center (University of Rochester, Rochester, NY, USA).

Informed Consent Statement: Written informed consent was obtained from the participants before any procedures were conducted.

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Appendix A

Table A1. Parametric Associations Between Potential Metabolic Confounders and Covariates.

	BMI (kg/m^2)	Fasting Insulin	2HR Insulin	HOMA-IR	% Fat
Overnight MEL (ng MEL/mg CRE)	-0.387 *	-0.306	-0.304	-0.298	-0.531 ***
Daytime MEL (ng MEL/mg CRE)	0.087	0.137	0.309	0.172	0.164
Night/Day Ratio (1)	-0.097	-0.003	-0.060	-0.038	-0.220
Night/Day Ratio (2)	-0.262	-0.248	-0.367 *	-0.269	-0.346 *
MCL (days)	0.285	0.376 *	0.391 *	0.409 *	0.260
TT (ng/dL)	0.092	0.338 *	0.364 *	0.312	0.049
FT (ng/dL)	0.365 *	0.510 **	0.530 ***	0.498 **	0.258
FAI (%)	0.442 **	0.560 ***	0.567 ***	0.556 ***	0.313
Bio T (ng/dL)	0.364 *	0.508 **	0.529 ***	0.497 **	0.255
OV (mL)	0.077	0.119	0.367 *	0.118	0.033
FNPS	0.118	0.307	0.538 **	0.290	0.091
FNPO 2–9 mm	0.214	0.336	0.535 **	0.326	0.105

Variables were log-transformed as needed to meet assumptions. In the cases of women with DFs, ovarian data from the other ovary were reported ($N = 6$) or were excluded if in the luteal phase ($N = 1$). In this case, ovarian endpoints from the other ovary are presented. One participant was excluded from all ovarian analyses because both ovaries had DFs. Abbreviations: MEL, melatonin; MCL, mean menstrual cycle length; TT, total testosterone; FT, free testosterone; FAI, free androgen index; Bio T, bioavailable testosterone; OV, ovarian volume; FNPS, follicle number per cross-section; FNPO, follicle number per ovary. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

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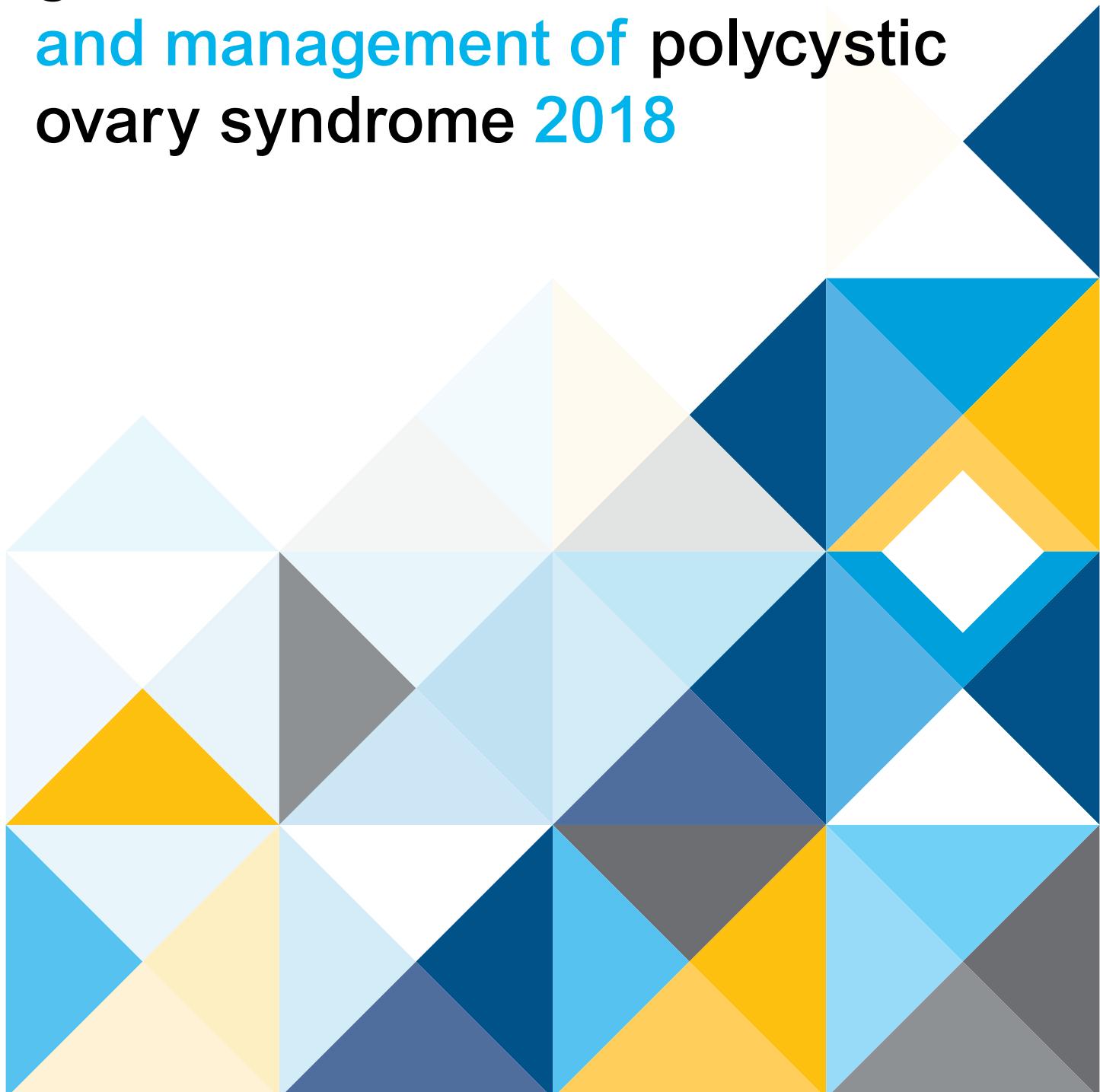
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International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018



Publication approval



Australian Government

National Health and Medical Research Council

The guideline recommendations on pages 16 to 34 of this document were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 2 July 2018 under section 14A of the *National Health and Medical Research Council Act 1992*. In approving the guideline recommendations, NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years.

NHMRC is satisfied that the guideline recommendations are systematically derived, based on the identification and synthesis of the best available scientific evidence, and developed for health professionals practising in an Australian health care setting.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

Disclaimer

The Centre for Research Excellence in Polycystic Ovary Syndrome (CREPCOS) research in partnership with the European Society of Human Reproduction and Embryology (ESHRE) and American Society of Reproductive Medicine (ASRM), and in collaboration with professional societies and consumer advocacy groups internationally, developed the evidence-based guideline to provide evidence-based recommendations to improve the quality of healthcare, health outcomes and quality of life of women with PCOS. The guideline represents the integration of the best evidence available at the time of preparation, multidisciplinary, international clinical perspectives and patient preferences. In the absence of scientific evidence in PCOS, evidence from the general population was considered and a consensus between the engaged stakeholders was obtained.

The aim of evidenced-based guideline is to aid healthcare professionals and consumers in decisions about appropriate and effective care, although recommendations are generalised and application requires consideration of individual patient characteristics and preferences. All recommendations and practice points need to be considered in the context of regional regulations.

Adherence to the guideline does not guarantee a successful or specific outcome in an individual or override the healthcare professional's clinical judgment or patient preference in diagnosis and treatment of individual patients. Ultimately, healthcare professionals must make their own clinical decisions on a case-by-case basis, using their clinical judgment, knowledge, and expertise, and taking into account the condition, circumstances, and perspectives of the individual patient, in consultation with that patient and/or the guardian or carer.

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 - Endocrine Society Australia (ESA)
 - European Society of Endocrinology (ESE)
 - European Society for Paediatric Endocrinology (ESPE)
 - Exercise and Sports Science Australia (ESSA)
 - Federation of Obstetric and Gynaecological Societies of India (FOGSI)
 - Fertility Society Australia (FSA)
 - International Society of Endocrinology (ISE)
 - International Federation of Fertility Societies (IFFS)
 - International Federation of Gynaecology and Obstetrics (FIGO)
 - Italian Society of Gynaecology and Obstetrics (SIGO)
 - Japanese Society for Paediatric Endocrinology (JSPE)
 - Jean Hailes for Women's Health (Translation partner)
 - Latin American Society for Paediatric Endocrinology (SLEP)
 - Nordic Federation of Societies of Obstetrics and Gynaecology (NFOG)
 - PCOS Challenge Inc: The National Polycystic Ovary Syndrome Association
 - The PCOS Society (India)
 - Paediatric Endocrine Society (PES)
 - Polycystic Ovary Syndrome Association of Australia (POSAA)
 - Royal Australasian College of Physicians (RACP)
 - Royal Australian College of General Practitioners (RACGP)
 - Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
 - Royal College of Obstetricians and Gynaecologists (RCOG)
 - Society for Endocrinology (United Kingdom)
 - South African Society of Gynaecology and Obstetrics (SASOG)
 - Verity UK
 - Victorian Assisted Reproductive Technology Association (VARTA)

Other relevant organisations are welcome to partner in guideline translation once approved.

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Preface

This International evidence-based guideline for the assessment and management of Polycystic Ovary Syndrome (PCOS), designed to provide clear information to assist clinical decision making and support optimal patient care, is the culmination of the work of over 3000 health professionals and consumers internationally. The vast majority gave of their time and expertise voluntarily. We fully appreciate the considerable contributions of the guideline development group members and particularly of the project board ([Appendix I](#)), international advisory board ([Appendix II](#)) and most importantly to the chairs, co-chairs and members of the international, multidisciplinary guideline development groups ([Appendix III](#)).

Acknowledgement goes to the tireless efforts, commitment, dedication and drive of the Project Manager, Ms Linda Downes, Evidence lead Dr Marie Misso, Translation lead Dr Rhonda Garad, Project Board Chair, Professor Robert Norman, and the guideline evidence team for their contribution. We acknowledge the enthusiasm and engagement of the health professionals and women affected by PCOS, our partners European Society of Human Reproduction and Embryology and American Society for Reproductive Medicine and our collaborating and engaged professional societies and consumer advocacy and support organisations internationally. These stakeholders have guided scope, identification of gaps and needs, prioritisation of clinical questions and outcomes of importance, review of evidence, formulations of recommendations and the guideline, as well as development and implementation of the dissemination and translation program.



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Abstract

Objective: To develop and translate rigorous, comprehensive evidence-based diagnosis, assessment and treatment guidelines, to improve the lives of women with polycystic ovary syndrome (PCOS) worldwide.

Participants: Extensive health professional and patient engagement informed guideline priority areas. International Society-nominated panels included consumers, paediatrics, endocrinology, gynaecology, primary care, reproductive endocrinology, psychiatry, psychology, dietetics, exercise physiology, public health, project management, evidence synthesis and translation experts.

Evidence: Best practice evidence-based guideline development involved extensive evidence synthesis and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework covered evidence quality, feasibility, acceptability, cost, implementation and ultimately recommendation strength.

Process: Governance included an international advisory board from six continents, a project board, five guideline development groups with 63 members, consumer and translation committees. The Australian Centre for Research Excellence in PCOS, funded by the National Health and Medical Research Council (NHMRC), partnered with European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine. Thirty seven organisations across 71 countries collaborated with 23 face to face international meetings over 15 months. Sixty prioritised clinical questions involved 40 systematic and 20 narrative reviews, generating 166 recommendations and practice points. Convened Committees from partner and collaborating organisations provided peer review and the guideline was approved by the NHMRC.

Conclusions: We endorse the Rotterdam PCOS diagnostic criteria in adults (two of clinical or biochemical hyperandrogenism, ovulatory dysfunction, or polycystic ovaries on ultrasound) and where irregular menstrual cycles and hyperandrogenism are present, highlight that ultrasound is not necessary in diagnosis. Within eight years of menarche, both hyperandrogenism and ovulatory dysfunction are required, with ultrasound not recommended. Ultrasound criteria are tightened with advancing technology. Anti-Müllerian hormone levels are not yet adequate for diagnosis. Once diagnosed, assessment and management includes reproductive, metabolic and psychological features. Education, self-empowerment, multidisciplinary care and lifestyle intervention for prevention or management of excess weight are important. Depressive and anxiety symptoms should be screened, assessed and managed with the need for awareness of other impacts on emotional wellbeing. Combined oral contraceptive pills are first-line pharmacological management for menstrual irregularity and hyperandrogenism, with no specific recommended preparations and general preference for lower dose preparations. Metformin is recommended in addition or alone, primarily for metabolic features. Letrozole is first-line pharmacological infertility therapy; with clomiphene and metformin having a role alone and in combination. In women with PCOS and anovulatory infertility, gonadotrophins are second line. In the absence of an absolute indication for IVF, women with PCOS and anovulatory infertility, could be offered IVF third line where other ovulation induction therapies have failed. Overall evidence is low to moderate quality, requiring significant research expansion in this neglected, yet common condition. Guideline translation will be extensive including a multilingual patient mobile application and health professional training.

Executive Summary

This international guideline and translation program addresses health professional and consumer priorities. The guideline integrates the best available evidence with international, multidisciplinary clinical expertise and consumer preferences to provide health professionals, consumers and policy makers with guidance. The guideline and translation program promote accurate and timely diagnosis and optimal and consistent assessment and treatment of polycystic ovary syndrome (PCOS), with prevention of complications and improved patient experience and health outcomes for the one in ten women worldwide with PCOS.

Context and background

Polycystic ovary syndrome (PCOS) is a significant public health issue with reproductive, metabolic and psychological features. PCOS is one of the most common conditions in reproductive aged women affecting 8-13% of reproductive-aged women [1-4] with up to 70% of affected women remaining undiagnosed [3]. Presentation varies by ethnicity and in high-risk populations such as Indigenous women, prevalence and complications are higher [4, 5]. Women with PCOS present with diverse features including psychological (anxiety, depression, body image) [6-8], reproductive (irregular menstrual cycles, hirsutism, infertility and pregnancy complications) [9] and metabolic features (insulin resistance (IR), metabolic syndrome, prediabetes, type 2 diabetes (DM2) and cardiovascular risk factors) [10, 11].

Diagnosis and treatment of PCOS remain controversial with challenges defining individual components within the diagnostic criteria, significant clinical heterogeneity generating a range of phenotypes with or without obesity, ethnic differences and variation in clinical features across the life course. These factors contribute to variation in diagnosis and care across geographical regions and health professional groups [12]. This culminates in delayed diagnosis, poor diagnosis experience and dissatisfaction with care reported by women internationally [13]. These challenges are exacerbated by a lack of recognition of the diverse features of PCOS, inadequate funding for quality research and a lack of comprehensive international evidence-based guidelines [14]. In this context, there was a compelling need for development and translation of an international evidence-based guideline for assessment and management of PCOS, addressing psychological, metabolic and reproductive features of PCOS, promoting consistent evidence-based care and guiding and encouraging research in PCOS.

The extensive international guideline network across our partners and collaborators engaged in prioritisation of clinical questions and outcomes, identification of gaps in knowledge and care and into translation preferences and information needs for health professionals and consumers. This stakeholder engagement directly informed the guideline and translation program and involved over 3000 health professionals and consumers with PCOS. Our partners and collaborators contributed members to the guideline governance, development and translation committees. They formed special interest groups with considerable expertise in PCOS to provide feedback during the public consultation process and are engaged in translation and evaluation. Partners and collaborators have agreed that the National Health and Medical Research Council (NHMRC) is the single approving body for the guideline.

Governance included international representation across the Advisory Committee, Project Board, Consumer Reference Group, Translation Committee and five multidisciplinary Guideline Development Groups comprising partner and collaborator nominated experts, practising clinicians and consumers ([Figure 1](#), [Figure 2](#) and [Appendix I-III](#)). Guideline development groups and special interest groups/experts were nominated by the partner and collaborator organisations. The Australian Centre for Research Excellence in PCOS (CREPCOS), funded by the National Health and Medical Research Council (NHMRC), led and primarily funded the guideline development. In this endeavour, we partnered with the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) to fund and complete the guideline.

Guideline development engagement and processes were extensive and followed best practice. Four project board and 15 guideline development group face to face meetings occurred across Europe, USA and Australia over 15 months, and enabled training, guideline development and informed translation. Sixty prioritised clinical questions were addressed with 40 systematic and 20 narrative reviews, generating 166 recommendations and practice points.

International best practice comprehensive methods for evidence review and guideline development were applied, aligned with the NHMRC and ESHRE requirements. A highly experienced team undertook evidence synthesis with a focus on study designs least susceptible to bias; *a priori* criteria for inclusion and appraisal of studies, stakeholder prioritised clinical questions and outcome measures, extraction of study data; quality appraisal and meta-analysis where appropriate. Recommendations were formulated using the considered judgement process in the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework [15] across the quality of available evidence, integrating clinical expertise and consumer preference, and considering the applicability, feasibility, equity, cost effectiveness, implementation and value for consumers and health professionals through the GRADE framework. Implementation issues and international health systems and settings were also considered. Special interest groups of world experts and affected women were formulated to review and provide feedback on the guideline, with subsequent refinement and guideline development group approval. The guideline was then appraised independently by independent evidence synthesis experts and submitted to NHMRC for consideration of approval.

Guideline purpose and aims

The purpose of this international evidence-based guideline is to integrate the best available evidence with multidisciplinary expertise and consumer preferences to provide health professionals, consumers and policy makers with transparent evidence-based guidance on timely diagnosis, accurate assessment and optimal treatment of PCOS, to reduce variation in care, optimise prevention of complications and improve health outcomes.

The guideline aims to ensure that women with PCOS receive optimal, evidence-based care by:

- engaging multidisciplinary international expert representation in PCOS care nominated by partner and collaborator societies;
- including international consumer and primary care representatives;
- following rigorous Appraisal of Guidelines for Research and Evaluation (AGREE) II-compliant evidence-based guideline processes;
- developing an international comprehensive guideline on diagnosis, assessment and management of PCOS;
- providing a single source of international evidence-based recommendations to guide clinical practice and reduce variation worldwide, with the opportunity for adaptation in relevant health systems as needed;
- providing a basis for improving patient outcomes;
- identifying knowledge gaps and promoting research and translation into practice and policy;
- co-developing resources to upskill health professionals and empower consumers, including a mobile app and online resources; and
- delivering an international translation program with in-depth evaluation.

Key principles

Principles that underpinned the development and interpretation of all evidence-based guidelines are:

- the need for consumers and health professionals to recognise the life course implications of PCOS;
- partnership between health professionals and women in managing PCOS;
- individual differences, preferences and modulating or exacerbating factors are understood;
- metabolic, reproductive and psychological features of PCOS are all considered;
- education, optimal lifestyle and emotional wellbeing are important in PCOS; and
- Indigenous and high-risk ethnic populations are considered.

Patient population

This guideline is relevant to the assessment and management of adolescents, reproductive age and postmenopausal women who have PCOS, including women with PCOS who are infertile.

Setting and audience

The guideline is designed to apply in a broad range of health care settings and to a broad audience including:

- Patients
- General practitioners/primary care physicians
- Obstetricians and gynaecologists
- Endocrinologists
- Dermatologists
- Allied health professionals - psychologists, dietitians, exercise physiologists, physiotherapists
- Community care practitioners
- Indigenous health care workers
- Nurses
- Policy makers
- Community support groups (i.e. POSAA)
- General public
- Students

When translating the guideline into practice, issues such as cost, accessibility, availability and ethnic considerations are required.

Governance

A formal international governance process was established as outlined in [Figure 1](#).

Figure 1: Governance

Evidence-based guideline for assessment and management of PCOS update project governance

International Strategic Advisors Group

(Chair Prof Bart Fauser)

CRE Co-Director (Prof Rob Norman), CALD Advisor, international consumer representative(s), Evidence-based guidelines lead, international society representatives including ESHRE and ASRM and geographical representation

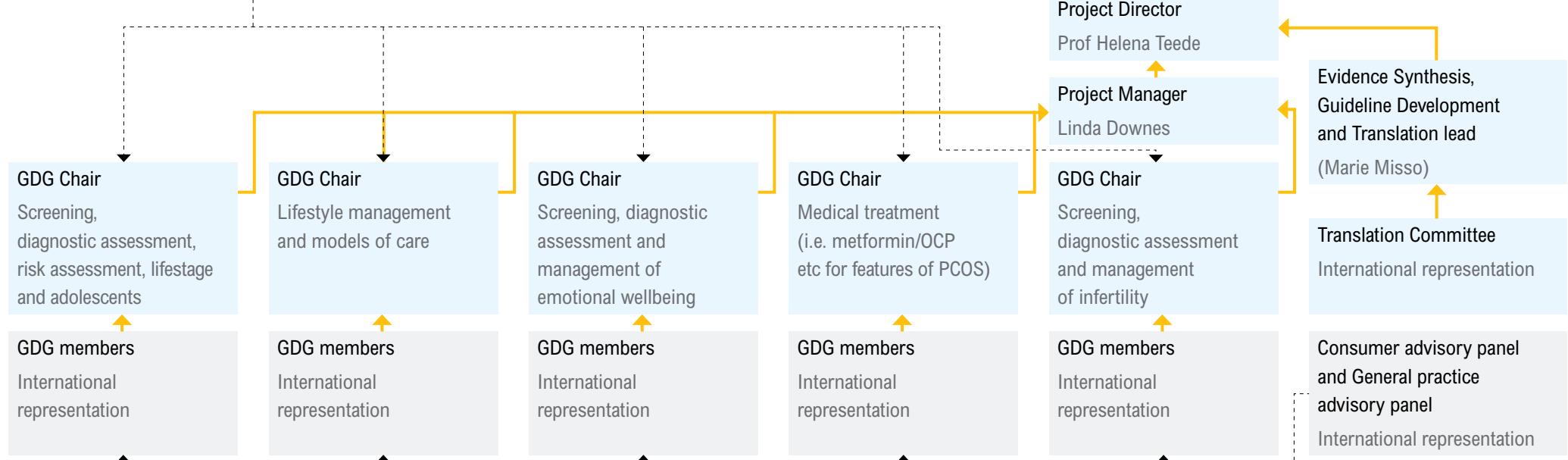
CRE in PCOS Steering Committee / Monash University (Chair Rob Norman)

Project Board

Project Owner and Project Director CRE Co-Director of CRE (Prof Helena Teede)

Senior User – PCOS consumer; GP; representation from clinical specialties and allied health, Chair – International Strategic Advisors Group

Senior Suppliers – GDG Chairs; Guideline Development Lead; representatives from international organisations **contributing at least 10% project funding** (ESHRE X 2 and ASRM X 1 included)



Definitions:

Project Owner:

Person ultimately accountable for the success of the project and owns the business case. Has the final say in decision making process.

Senior User:

Represents end users of the delivered service. Chairs Project User Group if there is one.

Senior Supplier:

Senior representative of project's suppliers. There may be more than one.

Project Director:

Project Owner's eyes and ears on the job. Undertakes day to day management and decisions on behalf of the Project Owner.

Strategic Advisors Group:

Represents key stakeholders with valid interest, but not sufficiently central to project success to warrant a seat on the Project Board.

Concerns and issues in this group have a direct conduit to the Project Board.

Decision making path

Advisory and feedback path

Guideline Development Groups

Guideline development groups (GDGs) were formed based on skills (clinical and academic interests), expertise, geographical spread **and were nominated by partner or collaborator organisations**. The GDGs encompassed the broad range of clinical expertise involved in the care of women with PCOS as well as consumers. Over 100 members were engaged across the governance, guideline development and translation committee. Whilst this does not encompass all leaders internationally with expertise in PCOS, these were engaged in the consultation process through online surveys and in providing feedback into the guideline through special interest groups formed across the partner and collaborator organisations. Representatives from all continents engaged in the process, however given primary funding was from the Australian Government, diverse Australian organisations engaged.

Prioritised clinical questions

Prioritisation of guideline clinical questions was informed by an International Delphi exercise and by the multidisciplinary GDGs, with final questions (detailed in the methods section) addressed across:

GDG 1 Screening, diagnostic assessment, risk assessment and life-stage

GDG 2 Prevalence, screening, diagnostic assessment and management of emotional wellbeing

GDG 3 Lifestyle management and models of care

GDG 4 Medical treatment

GDG 5 Screening, diagnostic assessment and management of infertility

What the guideline does not address

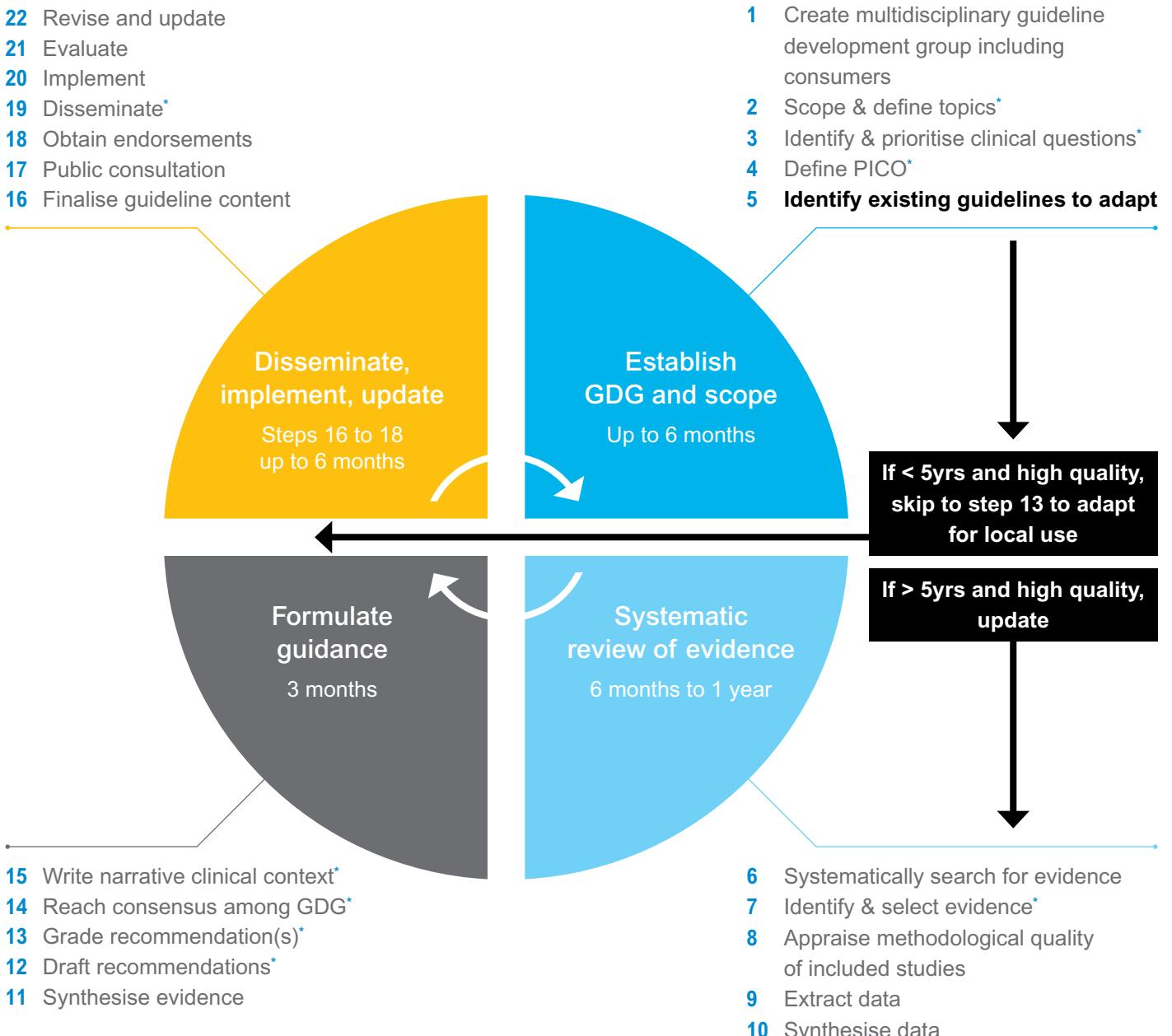
This guideline does not seek to provide full safety and usage information on pharmacological and surgical interventions. The pharmacological and surgical interventions recommended in the guideline should not be applied without consideration of the patient's clinical profile and preferences. We recommend that the reader consults relevant regional bodies for prescribing information including indications, drug dosage, method and route of administration, contraindications, supervision and monitoring, product characteristics and adverse effects. All recommendations and practice points need to be considered in the context of regional regulations. This guideline does not include a formal analysis of cost effectiveness or economic feasibility, however the potential impact of cost on recommendations was considered in GRADE process.

Guideline development methods

Methods used to develop this guideline align with international best practice, and follow comprehensive evidence-based guideline development processes and criteria including the Appraisal of Guidelines for REsearch & Evaluation (AGREE II), the Australian National Health and Medical Research Council (NHMRC) and ESHRE criteria. The steps are summarised in Figure 2, with details found in [Chapter 6: Guideline Development Methods](#).

Figure 2: Guideline development process

(adapted from Misso and Teede, Knowledge Transfer: Practice, Types and Challenges 2012, Nova Publishers)



* Time points and tasks where prioritisation of engagement from GDG is required.

Community and consumer engagement

Extensive engagement and formative research on unmet needs of women with PCOS was a key driver for this work. Far-reaching engagement included focus groups and then surveys of over 1500 women with PCOS. We adopted the International Association for Public Participation (IPA), Public Participation Spectrum framework, in which consumer's capacity to participate was built and enhanced throughout the process. Consumers were engaged in all phases as active contributors within a distributed decision making environment, ensuring that the lived experiences of women with PCOS were prioritised. Consumer representatives were informed about the process of participation and at GDG meetings were present to embed consumer perspectives within the GRADE decision-making process. Consumers were empowered to ensure that all decisions optimised participation in care. Consumer organisations proactively participated in feedback and public consultation processes and have co-designed and will continue to guide and influence the implementation, translation and dissemination program.

Funding

The Australian NHMRC funded guideline development through the NHMRC Centre for Research Excellence in Polycystic Ovary Syndrome (APP1078444), administered through Monash University and University of Adelaide, Australia. Guideline partners, European Society of Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) provided additional funding and assisted in guideline development activities.

Editorial independence and disclosures of interest

This guideline is editorially independent. The primary funders, NHMRC, were not involved in the development of the guideline and have not influenced the scope. They set standards for guideline development and based on independent peer review approved the guideline process. ESHRE and ASRM nominated experts in PCOS who participated in the project board and GDGs. ESHRE and ASRM formed special interest groups to provide feedback on the guideline during public consultation and all feedback was reviewed by the project board and GDGs, blinded by the organisation providing the feedback. All members of committees and GDGs publicly disclosed all relevant interests and these were reviewed at each meeting and considered when making recommendations.

Guideline translation

A comprehensive, international translation program will disseminate, translate and amplify the impact of the international evidence-based guideline on the assessment and management of PCOS (see [Dissemination and implementation](#)).

The aims of the translation program are to:

- build capability of health professionals to deliver high-quality, evidence-based assessment and management of PCOS;
- augment the health literacy of PCOS health consumers, optimising diagnosis and improving health outcomes; and
- promote best-practice evidence-based PCOS care.

The guiding principles of the comprehensive international translation and dissemination program are:

- components are informed by the needs and preferences of women with PCOS;
- resources are co-created with, and attuned to, the needs of end-users; and
- dissemination strategies are multi-faceted, multi-modal and refined to the communication channels of end-users.

Central to the translation and dissemination program is active engagement of 37 partner and collaborator organisations ([see acknowledgements](#)) and leading engaged health experts who will leverage their extensive reach and influence to promote guideline uptake. Leading consumer groups internationally and translation organisations are strongly engaged and committed to translation and impact. The program is supported by a comprehensive evaluation framework, measuring international impacts and outcomes.

Context statement on diagnosis: Prelude to the guideline

In the international evidence-based guideline for the assessment, diagnosis and management of PCOS, we endorse the Rotterdam diagnostic criteria in adults and recommend tighter criteria requiring both hyperandrogenism and irregular cycles, with ultrasound not indicated in adolescents, due to overlap with normal reproductive physiology. Exclusion of thyroid disease (thyroid stimulating hormone), hyperprolactinemia (prolactin), and non-classic congenital adrenal hyperplasia (17-hydroxy progesterone) is recommended with further evaluation recommended in those with amenorrhea and more severe clinical features including consideration of hypogonadotropic hypogonadism, Cushing's disease, or androgen producing tumours.

We acknowledge the challenges in defining specific diagnostic features, including around menarche and menopause, where diagnostic features naturally evolve.

The guideline aims to facilitate timely and appropriate diagnosis for women with PCOS, whilst avoiding over diagnosis, especially in adolescents. Specific recommendations of relevance here include:

- ultrasound is now not recommended in diagnosis in those within 8 years of menarche;
- young women "at risk" can be identified, where diagnosis is unclear, with follow-up reassessment
- diagnostic features are refined to limit overlap with those without PCOS to improve diagnostic accuracy

Resource use in diagnosis will also be reduced with a stronger focus on clinical features in diagnosis, more limited indications for ultrasound and simpler tests for biochemical hyperandrogenism.

We endorse the recommendation of the National Institutes of Health (NIH) evidence-based methodology workshop of PCOS 2012 that specific phenotypes should be reported explicitly in all research [16]. The natural history and clinical implications of the phenotypes remain unclear at this stage:

- Androgen excess + ovulatory dysfunction + polycystic ovarian morphology (Phenotype A)
- Androgen excess + ovulatory dysfunction (Phenotype B)
- Androgen excess + polycystic ovarian morphology (Phenotype C)
- Ovulatory dysfunction + polycystic ovarian morphology (Phenotype D)

We recognise that PCOS is an insulin resistant and metabolic disorder; tests for insulin resistance, however, lack accuracy and should not be incorporated into the diagnostic criteria for PCOS at this time.

We recognise PCOS has psychological features and poorer quality of life and whilst assessment is vital, these are not currently included in PCOS diagnostic criteria.

The value and optimal timing of assessment and diagnosis of PCOS should be discussed with the individual patient, taking into account psychosocial and cultural factors and patient preferences. Education is vitally important to women at the time of diagnosis, including reassurance about the potential for prevention of complications and about good general reproductive potential and family size, acknowledging some medical assistance may be required. As a general guiding principle, in partnering with women with PCOS in their diagnosis and care, self-empowerment is a priority and personal characteristics, preferences, culture and values should be considered when undertaking assessment, providing information or recommending intervention or treatments.

Interpreting the recommendations

Detailed methods for stakeholder engagement and guideline development can be found in [Chapter six: Guideline development methods](#). In developing and interpreting the guideline, evidence has been evaluated alongside multidisciplinary health professional expertise and consumer perspectives throughout all stages from conceptualisation, prioritisation, development, review and translation. Variability in resources, health systems and access to health professionals, investigations and therapies were considered across international settings and consistent with best practice, adaptation may be required in translation. The process for adaptation is available at [website link to be inserted here](#).

To assist in interpreting guideline recommendations, these are presented by **category, terms used, GRADE and quality of evidence**. The **category of the recommendations** includes evidence-based or consensus recommendations and have accompanying relevant clinical practice points as described in table 1. When sufficient evidence was available in PCOS, an evidence-based recommendation was made, where there was insufficient evidence in PCOS, evidence in general or other relevant populations was also considered and if appropriate and there was consensus, the GDG made clinical consensus recommendations. Clinical practice points highlighted important clinical and implementation issues arising from GDG consideration of evidence-based or clinical consensus recommendations and from peer review.

Table 1: Categories of the PCOS guideline recommendations

EBR	Evidence based recommendations: Evidence sufficient to inform a recommendation made by the guideline development group.
CCR	Clinical Consensus Recommendations: In the absence of evidence, a clinical consensus recommendation has been made by the guideline development group.
CPP	Clinical Practice Points: Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or clinical consensus recommendations.

The **recommendation terms** include “should”, “could” and “should not”. These terms are informed by the nature of the recommendation (evidence or consensus), the GRADE framework and evidence quality and are independent descriptors reflecting the judgement of multidisciplinary GDG including consumers. They refer to overall interpretation and practical application of the recommendation, balancing benefits and harms. “Should” is used where benefits of the recommendation exceed harms, and where the recommendation can be trusted to guide practice. “Could” is used where either the quality of evidence was limited or the available studies demonstrate little clear advantage of one approach over another, or the balance of benefits to harm was unclear. “Should not” is used where there is either a lack of appropriate evidence, or the harms may outweigh the benefits.

The **GRADE of the recommendation** is determined by the GDG from structured consideration of the GRADE framework [15] including desirable effects, undesirable effects, balance of effects, resource requirements and cost effectiveness, equity, acceptability and feasibility and includes:

-
- ❖ Conditional recommendation against the option;
 - ❖❖ Conditional recommendation for either the option or the comparison;
 - ❖❖❖ Conditional recommendation for the option;
 - ❖❖❖❖ Strong recommendation for the option.
-

Quality of the evidence is categorised (see table 2) according to:

- information about the number and design of studies addressing the outcome;
- judgments about the quality of the studies and/or synthesised evidence, such as risk of bias, inconsistency, indirectness, imprecision and any other considerations that may influence the quality of the evidence: key statistical data;
- and classification of the importance of the outcomes.

The quality of evidence reflects the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation [15] and was largely determined by the expert evidence synthesis team.

Table 2: Quality (certainty) of evidence categories (adapted from GRADE [15]):

High	⊕⊕⊕⊕	Very confident that the true effect lies close to that of the estimate of the effect
Moderate	⊕⊕⊕○	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	⊕⊕○○	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very Low	⊕○○○	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GRADE note that quality of evidence is a continuum; any discrete categorisation involves a degree of arbitrariness. Nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations [15].

The recommendations summary table below applies the **category, descriptive terms, GRADE of the recommendations and the quality of the evidence**. Within the body of the guideline, we outline the clinical need for the question, the clinical question, the evidence summary, the recommendation and practice points and a summary of the justification developed by the GDG and modified by extensive international peer review. The comprehensive evidence reviews, profiles and GRADE frameworks supporting each recommendation, can be found in the supplementary Technical report.

Recommendations Summary

Table notes:

The recommendation number reflects the corresponding evidence section.

Clinical consensus recommendations (CCR) and clinical practice points (CPP) do not have a 'GRADE' rating.

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
1		Screening, diagnostic assessment, risk assessment and life-stage	
1.1		Irregular cycles and ovulatory dysfunction	
1.1.1	CCR	<p>Irregular menstrual cycles are defined as:</p> <ul style="list-style-type: none"> • normal in the first year post menarche as part of the pubertal transition • > 1 to < 3 years post menarche: < 21 or > 45 days • > 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year • > 1 year post menarche > 90 days for any one cycle • Primary amenorrhea by age 15 or > 3 years post thelarche (breast development) <p>When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to the guidelines.</p>	❖❖❖❖
1.1.2	CCR	In an adolescent with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient, taking into account diagnostic challenges at this life stage and psychosocial and cultural factors.	❖❖❖❖
1.1.3	CPP	For adolescents who have features of PCOS but do not meet diagnostic criteria, an "increased risk" could be considered and reassessment advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before combined oral contraceptive pill (COCP) commencement, those with persisting features and those with significant weight gain in adolescence.	
1.1.4	CPP	Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.	
1.2		Biochemical hyperandrogenism	
1.2.1	EBR	Calculated free testosterone, free androgen index or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS.	❖❖❖❖ ⊕⊕○○
1.2.2	EBR	High quality assays such as liquid chromatography–mass spectrometry (LCMS)/mass spectrometry and extraction/chromatography immunoassays, should be used for the most accurate assessment of total or free testosterone in PCOS.	❖❖❖ ⊕⊕○○

CATE- NO.	CATE- GORY	RECOMMENDATION	QUALITY## AND GRADE
1.2.3	EBR	Androstenedione and dehydroepiandrosterone sulfate (DHEAS) could be considered if total or free testosterone are not elevated; however, these provide limited additional information in the diagnosis of PCOS.	❖❖❖ ⊕⊕○○
1.2.4	CCR	Direct free testosterone assays, such as radiometric or enzyme-linked assays, preferably should not be used in assessment of biochemical hyperandrogenism in PCOS, as they demonstrate poor sensitivity, accuracy and precision.	❖❖❖❖
1.2.5	CPP	Reliable assessment of biochemical hyperandrogenism is not possible in women on hormonal contraception, due to effects on sex hormone-binding globulin and altered gonadotrophin-dependent androgen production.	
1.2.6	CPP	Where assessment of biochemical hyperandrogenism is important in women on hormonal contraception, drug withdrawal is recommended for three months or longer before measurement, and contraception management with a non-hormonal alternative is needed during this time.	
1.2.7	CPP	Assessment of biochemical hyperandrogenism is most useful in establishing the diagnosis of PCOS and/or phenotype where clinical signs of hyperandrogenism (in particular hirsutism) are unclear or absent.	
1.2.8	CPP	Interpretation of androgen levels needs to be guided by the reference ranges of the laboratory used, acknowledging that ranges for different methods and laboratories vary widely. Normal values are ideally based on levels from a well phenotyped healthy control population or by cluster analysis of a large general population considering age and pubertal specific stages.	
1.2.9	CPP	Where androgen levels are markedly above laboratory reference ranges, other causes of biochemical hyperandrogenism need to be considered. History of symptom onset and progression is critical in assessing for neoplasia, however, some androgen-secreting neoplasms may only induce mild to moderate increases in biochemical hyperandrogenism.	
1.3		Clinical hyperandrogenism	
1.3.1	CCR	A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, alopecia and hirsutism and, in adolescents, severe acne and hirsutism	❖❖❖❖
1.3.2	CCR	Health professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism. Reported unwanted excess hair growth and/or alopecia should be considered important, regardless of apparent clinical severity.	❖❖❖❖
1.3.3	CCR	Standardised visual scales are preferred when assessing hirsutism, such as the modified Ferriman Gallwey score (mFG) with a level $\geq 4 - 6$ indicating hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment. (See recommendations on ethnic variation)	❖❖❖❖
1.3.4	CCR	The Ludwig visual score is preferred for assessing the degree and distribution of alopecia.	❖❖❖❖

NO.	CATE-	GORY RECOMMENDATION	QUALITY## AND GRADE	
1.3.5	CPP	There are no universally accepted visual assessments for evaluating acne.		
1.3.6	CPP	The prevalence of hirsutism is the same across ethnicities, yet the mFG cut-off scores for defining hirsutism and the severity of hirsutism varies by ethnicity.		
1.3.7	CPP	As ethnic variation in vellus hair density is notable, over-estimation of hirsutism may occur if vellus hair is confused with terminal hair; only terminal hairs need to be considered in pathological hirsutism, with terminal hairs clinically growing > 5mm in length if untreated, varying in shape and texture and generally being pigmented.		
1.4		Ultrasound and polycystic ovarian morphology (PCOM)		
1.4.1	CCR	Ultrasound should not be used for the diagnosis of PCOS in those with a gynaecological age of < 8 years (< 8 years after menarche), due to the high incidence of multi-follicular ovaries in this life stage.		
1.4.2	CCR	The threshold for PCOM should be revised regularly with advancing ultrasound technology, and age-specific cut off values for PCOM should be defined.		
1.4.3	CCR	The transvaginal ultrasound approach is preferred in the diagnosis of PCOS, if sexually active and if acceptable to the individual being assessed.		
1.4.4	CCR	Using endovaginal ultrasound transducers with a frequency bandwidth that includes 8MHz, the threshold for PCOM should be on either ovary, a follicle number per ovary of > 20 and/or an ovarian volume ≥ 10ml, ensuring no corpora lutea, cysts or dominant follicles are present.		
1.4.5	CPP	If using older technology, the threshold for PCOM could be an ovarian volume ≥ 10ml on either ovary.		
1.4.6	CPP	In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis; however, ultrasound will identify the complete PCOS phenotype.		
1.4.7	CPP	In transabdominal ultrasound reporting is best focused on ovarian volume with a threshold of ≥ 10ml, given the difficulty of reliably assessing follicle number with this approach.		
1.4.8	CPP	Clear protocols are recommended for reporting follicle number per ovary and ovarian volume on ultrasound. Recommended minimum reporting standards include: <ul style="list-style-type: none"> ● last menstrual period ● transducer bandwidth frequency ● approach/route assessed ● total follicle number per ovary measuring 2-9mm ● three dimensions and volume of each ovary ● reporting of endometrial thickness and appearance is preferred – 3-layer endometrial assessment may be useful to screen for endometrial pathology ● other ovarian and uterine pathology, as well as ovarian cysts, corpus luteum, dominant follicles ≥ equal 10mm 		
1.4.9	CPP	There is a need for training in careful and meticulous follicle counting per ovary, to improve reporting.		

NO.	CATE-	GORY RECOMMENDATION	QUALITY## AND GRADE
1.5		Anti-müllerian hormone (AMH)	
1.5.1	EBR	Serum AMH levels should not yet be used as an alternative for the detection of PCOM or as a single test for the diagnosis of PCOS.	❖❖❖ ⊕⊕○○
1.5.2	CPP	There is emerging evidence that with improved standardisation of assays and established cut off levels or thresholds based on large scale validation in populations of different ages and ethnicities, AMH assays will be more accurate in the detection of PCOM.	
1.6		Ethnic variation	
1.6.1	CCR	Health professionals should consider ethnic variation in the presentation and manifestations of PCOS, including:	❖❖❖❖
		<ul style="list-style-type: none"> ● a relatively mild phenotype in Caucasians ● higher body mass index (BMI) in Caucasian women, especially in North America and Australia ● more severe hirsutism in Middle Eastern, Hispanic and Mediterranean women ● increased central adiposity, insulin resistance, diabetes, metabolic risks and acanthosis nigricans in South East Asians and Indigenous Australians ● lower BMI and milder hirsutism in East Asians ● higher BMI and metabolic features in Africans 	
1.7		Menopause life stage	
1.7.1	CCR	Postmenopausal persistence of PCOS could be considered likely with continuing evidence of hyperandrogenism.	❖❖❖
1.7.2	CCR	A diagnosis of PCOS postmenopause could be considered if there is a past diagnosis of PCOS, a long-term history of irregular menstrual cycles and hyperandrogenism and/or PCOM, during the reproductive years.	❖❖❖
1.7.3	CPP	Postmenopausal women presenting with new-onset, severe or worsening hyperandrogenism including hirsutism, require further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis.	
1.8		Cardiovascular disease risk (CVD)	
1.8.1	CCR	All those with PCOS should be offered regular monitoring for weight changes and excess weight, in consultation with and where acceptable to the individual woman. Monitoring could be at each visit or at a minimum 6-12 monthly, with frequency planned and agreed between the health professional and the individual (see 3.5).	❖❖❖❖
1.8.2	CCR	Weight, height and ideally waist circumference should be measured and BMI calculated with the following considered:	❖❖❖❖
		<ul style="list-style-type: none"> ● BMI categories and waist circumference should follow World Health Organisation guidelines, also noting ethnic and adolescent ranges. ● Consideration should be given for Asian and high-risk ethnic groups including recommended monitoring of waist circumference. 	
1.8.3	CCR	All women with PCOS should be assessed for cardiovascular risk factors and global CVD risk	❖❖❖❖

NO.	CATE- GORY	RECOMMENDATION	QUALITY## AND GRADE
1.8.4	CCR	If screening reveals CVD risk factors including obesity, cigarette smoking, dyslipidemia, hypertension, impaired glucose tolerance and lack of physical activity, women with PCOS should be considered at increased risk of CVD.	♦♦♦♦
1.8.5	CCR	Overweight and obese women with PCOS, regardless of age, should have a fasting lipid profile (cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level at diagnosis). Thereafter, frequency of measurement should be based on the presence of hyperlipidemia and global CVD risk.	♦♦♦♦
1.8.6	CCR	All women with PCOS should have blood pressure measured annually, or more frequently based on global CVD risk.	♦♦♦♦
1.8.7	CPP	Health professionals need to be aware that CVD risk in women with PCOS remains unclear pending high quality studies, however prevalence of CVD risk factors is increased, warranting consideration of screening.	
1.8.8	CPP	Consideration needs to be given to the significant differences in CVD risk across ethnicities (see 1.6.1) when determining frequency of risk assessment.	
1.9	Gestational diabetes, impaired glucose tolerance and type 2 diabetes		
1.9.1	CCR	Health professionals and women with PCOS should be aware that, regardless of age, the prevalence of gestational diabetes, impaired glucose tolerance and type 2 diabetes (5 fold in Asia, 4 fold in the Americas and 3 fold in Europe) are significantly increased in PCOS, with risk independent of, yet exacerbated by, obesity	♦♦♦♦
1.9.2	CCR	Glycaemic status should be assessed at baseline in all women with PCOS. Thereafter, assessment should be every one to three years, influenced by the presence of other diabetes risk factors	♦♦♦♦
1.9.3	CCR	An oral glucose tolerance test (OGTT), fasting plasma glucose or HbA1c should be performed to assess glycaemic status. In high-risk women with PCOS (including a BMI > 25kg/m ² or in Asians > 23kg/m ² , history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of diabetes mellitus type 2, hypertension or high-risk ethnicity), an OGTT is recommended.	♦♦♦♦
1.9.4	CCR	A 75-g OGTT should be offered in all women with PCOS preconception when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed preconception, an OGTT should be offered at < 20 weeks gestation, and all women with PCOS should be offered the test at 24-28 weeks gestation.	♦♦♦♦
1.10	Obstructive sleep apnea (OSA)		
1.10.1	CCR	Screening should only be considered for OSA in PCOS to identify and alleviate related symptoms, such as snoring, waking unrefreshed from sleep, daytime sleepiness, and the potential for fatigue to contribute to mood disorders. Screening should not be considered with the intention of improving cardiometabolic risk, with inadequate evidence for metabolic benefits of OSA treatment in PCOS and in general populations.	♦♦♦♦

CATE- NO.	GORY	RECOMMENDATION	QUALITY## AND GRADE
1.10.2	CCR	A simple screening questionnaire, preferably the Berlin tool, could be applied and if positive, referral to a specialist considered.	❖❖❖
1.10.3	CPP	A positive screen raises the likelihood of OSA, however it does not quantify symptom burden and alone does not justify treatment. If women with PCOS have OSA symptoms and a positive screen, consideration can be given to be referral to a specialist centre for further evaluation.	
1.11		Endometrial cancer	
1.11.1	CCR	Health professionals and women with PCOS should be aware of a two to six-fold increased risk of endometrial cancer, which often presents before menopause; however absolute risk of endometrial cancer remains relatively low.	❖❖❖
1.11.2	CPP	Health professionals require a low threshold for investigation of endometrial cancer in women with PCOS or a history of PCOS, with investigation by transvaginal ultrasound and/or endometrial biopsy recommended with persistent thickened endometrium and/or risk factors including prolonged amenorrhea, abnormal vaginal bleeding or excess weight. However, routine ultrasound screening of endometrial thickness in PCOS is not recommended.	
1.11.3	CPP	Optimal prevention for endometrial hyperplasia and endometrial cancer is not known. A pragmatic approach could include COCP or progestin therapy in those with cycles longer than 90 days.	
2		Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing	
2.1		Quality of life	
2.1.1	CCR	Health professionals and women should be aware of the adverse impact of PCOS on quality of life.	❖❖❖❖
2.1.2	CCR	Health professionals should capture and consider perceptions of symptoms, impact on quality of life and personal priorities for care to improve patient outcomes.	❖❖❖❖
2.1.3	CPP	The PCOS quality of life tool (PCOSQ), or the modified PCOSQ, may be useful clinically to highlight PCOS features causing greatest distress, and to evaluate treatment outcomes on women's subjective PCOS health concerns.	
2.2		Depressive and anxiety symptoms, screening and treatment	
2.2.1	CCR	Health professionals should be aware that in PCOS, there is a high prevalence of moderate to severe anxiety and depressive symptoms in adults; and a likely increased prevalence in adolescents.	❖❖❖❖
2.2.2	CCR	Anxiety and depressive symptoms should be routinely screened in all adolescents and women with PCOS at diagnosis. If the screen for these symptoms and/or other aspects of emotional wellbeing is positive, further assessment and/or referral for assessment and treatment should be completed by suitably qualified health professionals, informed by regional guidelines.	❖❖❖❖

NO.	CATE-	GORY RECOMMENDATION	QUALITY## AND GRADE	
2.2.3	CCR	If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered in PCOS, informed by regional clinical practice guidelines.	♦♦♦♦	
2.2.4	CPP	The optimal interval for anxiety and depressive symptom screening is not known. A pragmatic approach could include repeat screening using clinical judgment, considering risk factors, comorbidities and life events.		
2.2.5	CPP	Assessment of anxiety and or depressive symptoms involves assessment of risk factors, symptoms and severity. Symptoms can be screened according to regional guidelines, or by using the following stepped approach:		
Step 1: Initial questions could include:		Over the last 2 weeks, how often have you been bothered by the following problems?		
<ul style="list-style-type: none"> ● feeling down, depressed, or hopeless? ● little interest or pleasure in doing things? ● feeling nervous, anxious or on edge? ● not being able to stop or control worrying? 		Step 2: If any of the responses are positive, further screening should involve:		
<ul style="list-style-type: none"> ● assessment of risk factors and symptoms using age, culturally and regionally appropriate tools, such as the Patient Health Questionnaire (PHQ) or the Generalised Anxiety Disorder Scale (GAD7) and/or refer to an appropriate professional for further assessment. 				
2.2.6	CPP	Where pharmacological treatment for anxiety and depression is offered in PCOS, the following need consideration:	<ul style="list-style-type: none"> ● Caution is needed to avoid inappropriate treatment with antidepressants or anxiolytics. Where mental health disorders are clearly documented and persistent, or if suicidal symptoms are present, treatment of depression or anxiety need to be informed by clinical regional practice guidelines. ● Use of agents that exacerbate PCOS symptoms, including weight gain, need careful consideration. 	
2.2.7	CPP	Factors including obesity, infertility, hirsutism need consideration along with use of hormonal medications in PCOS, as they may independently exacerbate depressive and anxiety symptoms and other aspects of emotional wellbeing.		
2.3	Psychosexual function			
2.3.1	CCR	All health professionals should be aware of the increased prevalence of psychosexual dysfunction and should consider exploring how features of PCOS, including hirsutism and body image, impact on sex life and relationships in PCOS.	♦♦♦♦	
2.3.2	CCR	If psychosexual dysfunction is suspected, tools such as the Female Sexual Function Index can be considered.	♦♦♦♦	

NO.	CATE-GORY RECOMMENDATION	QUALITY## AND GRADE
2.4	Body image	
2.4.1	CCR Health professionals and women should be aware that features of PCOS can impact on body image.	♦♦♦
2.4.2	CPP Negative body image, can be screened according to regional guidelines or by using the following stepped approach:	
	Step 1: Initial questions could include:	
	<ul style="list-style-type: none"> ● Do you worry a lot about the way you look and wish you could think about it less? ● On a typical day, do you spend more than 1 hour per day worrying about your appearance? (More than 1 hour a day is considered excessive) ● What specific concerns do you have about your appearance? ● What effect does it have on your life? ● Does it make it hard to do your work or be with your friends and family? 	
	Step 2: If an issue is identified, health professionals could further assess by:	
	<ul style="list-style-type: none"> ● Identifying any focus of concern of the patient and respond appropriately ● Assessing the level of depression and/or anxiety ● Identifying distortion of body image or disordered eating 	
2.5	Eating disorders and disordered eating	
2.5.1	CCR All health professionals and women should be aware of the increased prevalence of eating disorders and disordered eating associated with PCOS.	♦♦
2.5.2	CCR If eating disorders and disordered eating are suspected, further assessment, referral and treatment, including psychological therapy, could be offered by appropriately trained health professionals, informed by regional clinical practice guidelines.	♦♦
2.5.3	CPP Eating disorders and disordered eating can be screened using the following stepped approach.	
	Step 1: The SCOFF (Sick, Control, One stone, Fat, Food) screening tool can be used or initial screening questions can include:	
	<ul style="list-style-type: none"> ● Does your weight affect the way you feel about yourself? ● Are you satisfied with your eating patterns? 	
	Step 2: If the SCOFF tool or any of these questions are positive, further screening should involve:	
	<ul style="list-style-type: none"> ● assessment of risk factors and symptoms using age, culturally and regionally appropriate tools; ● referral to an appropriate health professional for further mental health assessment and diagnostic interview. If this is not the patient's usual healthcare provider, inform the primary care physician. 	

CATE- NO.	GORY RECOMMENDATION	QUALITY## AND GRADE
2.6	Information resources, models of care, cultural and linguistic considerations	
2.6.1	CCR Information and education resources for women with PCOS should be culturally appropriate, tailored and high-quality, should use a respectful and empathetic approach, and promote self-care and highlight peer support groups.	❖❖❖❖
2.6.2	CCR Information and education resources for healthcare professionals should promote the recommended diagnostic criteria, appropriate screening for comorbidities and effective lifestyle and pharmacological management.	❖❖❖❖
2.6.3	CCR PCOS information should be comprehensive, evidence-based and inclusive of the biopsychosocial dimensions of PCOS across the life-span.	❖❖❖❖
2.6.4	CCR Women's needs, communication preferences, beliefs and culture should be considered and addressed through provision of culturally and linguistically appropriate co-designed resources and care.	❖❖❖❖
2.6.5	CCR Interdisciplinary care needs to be considered for those with PCOS where appropriate and available. Primary care is generally well placed to diagnose, screen and coordinate interdisciplinary care.	❖❖❖❖
2.6.6	CCR Care needs to be person centred, address women's priorities and be provided in partnership with those with PCOS and where appropriate, their families.	❖❖❖❖
2.6.7	CPP Guideline dissemination and translation including multimodal education tools and resources is important, with consultation and engagement with stakeholders internationally.	
3	Lifestyle	
3.1	Effectiveness of lifestyle interventions	
3.1.1	CCR Healthy lifestyle behaviours encompassing healthy eating and regular physical activity should be recommended in all those with PCOS to achieve and/or maintain healthy weight and to optimise hormonal outcomes, general health, and quality of life across the life course.	❖❖❖❖
3.1.2	EBR Lifestyle intervention (preferably multicomponent including diet, exercise and behavioural strategies) should be recommended in all those with PCOS and excess weight, for reductions in weight, central obesity and insulin resistance.	❖❖❖ ⊕⊕○○
3.1.3	CPP Achievable goals such as 5% to 10% weight loss in those with excess weight yields significant clinical improvements and is considered successful weight reduction within six months. Ongoing assessment and monitoring is important during weight loss and maintenance in all women with PCOS.	
3.1.4	CPP SMART (Specific Measurable, Achievable, Realistic and Timely), goal setting and self-monitoring can enable achievement of realistic lifestyle goals.	
3.1.5	CPP Psychological factors such as anxiety and depressive symptoms, body image concerns and disordered eating, need consideration and management to optimise engagement and adherence to lifestyle interventions.	

NO.	CATE- GORY	RECOMMENDATION	QUALITY## AND GRADE
3.1.6	CPP	Health professional interactions around healthy lifestyle, including diet and exercise, need to be respectful, patient-centred and to value women's individualised healthy lifestyle preferences and cultural, socioeconomic and ethnic differences. Health professionals need to also consider personal sensitivities, marginalisation and potential weight-related stigma.	
3.1.7	CPP	Adolescent and ethnic-specific BMI and waist circumference categories need to be considered when optimising lifestyle and weight.	
3.1.8	CPP	Healthy lifestyle may contribute to health and quality of life benefits in the absence of weight loss.	
3.1.9	CPP	Healthy lifestyle and optimal weight management appears equally effective in PCOS as in the general population and is the joint responsibility of all health professionals, partnering with women with PCOS. Where complex issues arise, referral to suitably trained allied health professionals needs to be considered.	
3.1.10	CPP	Ethnic groups with PCOS who are at high cardiometabolic risk as per 1.6.1 require greater consideration in terms of healthy lifestyle and lifestyle intervention.	
3.2	Behavioural strategies		
3.2.1	CCR	Lifestyle interventions could include behavioural strategies such as goal-setting, self-monitoring, stimulus control, problem solving, assertiveness training, slower eating, reinforcing changes and relapse prevention, to optimise weight management, healthy lifestyle and emotional wellbeing in women with PCOS.	♦♦♦♦
3.2.2	CPP	Comprehensive health behavioural or cognitive behavioural interventions could be considered to increase support, engagement, retention, adherence and maintenance of healthy lifestyle and improve health outcomes in women with PCOS.	
3.3	Dietary intervention		
3.3.1	CCR	A variety of balanced dietary approaches could be recommended to reduce dietary energy intake and induce weight loss in women with PCOS and overweight and obesity, as per general population recommendations.	♦♦♦♦
3.3.2	CCR	General healthy eating principles should be followed for all women with PCOS across the life course, as per general population recommendations.	♦♦♦♦
3.3.3	CPP	To achieve weight loss in those with excess weight, an energy deficit of 30% or 500 - 750 kcal/day (1,200 to 1,500 kcal/day) could be prescribed for women, also considering individual energy requirements, body weight and physical activity levels.	
3.3.4	CPP	In women with PCOS, there is no or limited evidence that any specific energy equivalent diet type is better than another, or that there is any differential response to weight management intervention, compared to women without PCOS.	
3.3.5	CPP	Tailoring of dietary changes to food preferences, allowing for a flexible and individual approach to reducing energy intake and avoiding unduly restrictive and nutritionally unbalanced diets, are important, as per general population recommendations.	

NO.	CATE-GORY RECOMMENDATION	QUALITY## AND GRADE
3.4	Exercise intervention	
3.4.1	CCR Health professionals should encourage and advise the following for prevention of weight gain and maintenance of health:	
	<ul style="list-style-type: none"> ● in adults from 18 – 64 years, a minimum of 150 min/week of moderate intensity physical activity or 75 min/week of vigorous intensities or an equivalent combination of both, including muscle strengthening activities on 2 non-consecutive days/week ● in adolescents, at least 60 minutes of moderate to vigorous intensity physical activity/day, including those that strengthen muscle and bone at least 3 times weekly ● activity be performed in at least 10-minute bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days. 	
3.4.2	CCR Health professionals should encourage and advise the following for modest weight-loss, prevention of weight-regain and greater health benefits:	
	<ul style="list-style-type: none"> ● a minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensity or an equivalent combination of both, and muscle strengthening activities involving major muscle groups on 2 non-consecutive days/ week ● minimised sedentary, screen or sitting time. 	
3.4.3	CPP Physical activity includes leisure time physical activity, transportation such as walking or cycling, occupational work, household chores, games, sports or planned exercise, in the context of daily, family and community activities. Daily, 10000 steps is ideal, including activities of daily living and 30 minutes of structured physical activity or around 3000 steps. Structuring of recommended activities need to consider women's and family routines as well as cultural preferences.	
3.4.4	CPP Realistic physical activity SMART (Specific, Measureable, Achievable, Relevant, Time limited) goals could include 10 minute bouts, progressively increasing physical activity 5% weekly, up to and above recommendations.	
3.4.5	CPP Self-monitoring including with fitness tracking devices and technologies for step count and exercise intensity, could be used as an adjunct to support and promote active lifestyles and minimise sedentary behaviours.	
3.5	Obesity and weight assessment	
3.5.1	CCR Health professionals and women should be aware that women with PCOS have a higher prevalence of weight gain and obesity, presenting significant concerns for women, impacting on health and emotional wellbeing, with a clear need for prevention.	
3.5.2	CCR All those with PCOS should be offered regular monitoring for weight changes and excess weight as per 1.8.1 and 1.8.2.	

NO.	CATE-	GORY RECOMMENDATION	QUALITY## AND GRADE
3.5.3	CPP	When assessing weight, related stigma, negative body image and/or low self-esteem need to be considered and assessment needs to be respectful and considerate. Beforehand, explanations on the purpose and how the information will be used and the opportunity for questions and preferences need to be provided, permission sought and scales and tape measures adequate. Implications of results need to be explained and where this impacts on emotional wellbeing, support provided.	
3.5.4	CPP	Prevention of weight gain, monitoring of weight and encouraging evidence-based and socio-culturally appropriate healthy lifestyle is important in PCOS, particularly from adolescence.	
4	Pharmacological treatment for non-fertility indications		
4.1	Pharmacological treatment principles in PCOS		
4.1.1	CPP	Consideration of the individual's personal characteristics, preferences and values is important in recommending pharmacological treatment.	
4.1.2	CPP	When prescribing pharmacological therapy in PCOS, benefits, adverse effects and contraindications in PCOS and general populations need to be considered and discussed before commencement.	
4.1.3	CPP	COCPs, metformin and other pharmacological treatments are generally off label [#] in PCOS. However off label use is predominantly evidence-based and is allowed in many countries. Where it is allowed, health professionals need to inform women and discuss the evidence, possible concerns and side effects of treatment.	
4.1.4	CPP	Holistic approaches are required and pharmacological therapy in PCOS needs to be considered alongside education, lifestyle and other options including cosmetic therapy and counselling.	
4.2	Combined oral contraceptive pills (COCPs)		
4.2.1	EBR	The COCP alone should be recommended in adult women with PCOS for management of hyperandrogenism and/or irregular menstrual cycles.	❖❖❖ ⊕⊕○○
4.2.2	EBR	The COCP alone should be considered in adolescents with a clear diagnosis of PCOS for management of clinical hyperandrogenism and/or irregular menstrual cycles.	❖❖❖ ⊕⊕○○
4.2.3	EBR	The COCP could be considered in adolescents who are deemed "at risk" but not yet diagnosed with PCOS, for management of clinical hyperandrogenism and irregular menstrual cycles.	❖❖❖ ⊕⊕○○
4.2.4	EBR	Specific types or dose of progestins, estrogens or combinations of COCP cannot currently be recommended in adults and adolescents with PCOS and practice should be informed by general population guidelines.	❖❖❖ ⊕⊕○○

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
4.2.5	CCR	The 35 microgram ethinyloestradiol plus cyproterone acetate preparations should not be considered first line in PCOS as per general population guidelines, due to adverse effects including venous thromboembolic risks.	❖
4.2.6	CPP	When prescribing COCPs in adults and adolescents with PCOS: <ul style="list-style-type: none"> various COCP preparations have similar efficacy in treating hirsutism the lowest effective estrogen doses (such as 20-30 micrograms of ethinyloestradiol or equivalent), and natural estrogen preparations need consideration, balancing efficacy, metabolic risk profile, side effects, cost and availability the generally limited evidence on effects of COCPs in PCOS needs to be appreciated with practice informed by general population guidelines (WHO Guidelines) the relative and absolute contraindications and side effects of COCPs need to be considered and be the subject of individualised discussion PCOS specific risk factors such as high BMI, hyperlipidemia and hypertension need to be considered. 	❖
4.3		Combined oral contraceptive pills in combination with metformin and/or anti-androgen pharmacological agents	
4.3.1	EBR	In combination with the COCP, metformin should be considered in women with PCOS for management of metabolic features where COCP and lifestyle changes do not achieve desired goals.	❖❖❖ ⊕⊕○○
4.3.2	EBR	In combination with the COCP, metformin could be considered in adolescents with PCOS and BMI $\geq 25\text{kg/m}^2$ where COCP and lifestyle changes do not achieve desired goals.	❖❖❖ ⊕⊕○○
4.3.3	CPP	In combination with the COCP, metformin may be most beneficial in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.	
4.3.4	EBR	In combination with the COCP, antiandrogens should only be considered in PCOS to treat hirsutism, after six months or more of COCP and cosmetic therapy have failed to adequately improve symptoms.	❖❖ ⊕⊕○○
4.3.5	CCR	In combination with the COCP, antiandrogens could be considered for the treatment of androgen-related alopecia in PCOS.	❖❖
4.3.6	CPP	In PCOS, antiandrogens must be used with effective contraception, to avoid male foetal undervirilisation. Variable availability and regulatory status of these agents is notable and for some agents, potential liver toxicity requires caution.	
4.4		Metformin	
4.4.1	EBR	Metformin in addition to lifestyle, could be recommended in adult women with PCOS, for the treatment of weight, hormonal and metabolic outcomes.	❖❖❖ ⊕⊕○○
4.4.2	EBR	Metformin in addition to lifestyle, should be considered in adult women with PCOS with BMI $\geq 25\text{kg/m}^2$ for management of weight and metabolic outcomes.	❖❖❖ ⊕⊕○○

CATE- NO.	GORY	RECOMMENDATION	QUALITY## AND GRADE
4.4.3	EBR	Metformin in addition to lifestyle, could be considered in adolescents with a clear diagnosis of PCOS or with symptoms of PCOS before the diagnosis is made.	❖❖❖ ⊕⊕○○
4.4.4	CPP	Metformin may offer greater benefit in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups (see 1.6.1).	
4.4.5	CPP	Where metformin is prescribed the following need to be considered: <ul style="list-style-type: none"> ● adverse effects, including gastrointestinal side-effects that are generally dose dependent and self-limiting, need to be the subject of individualised discussion ● starting at a low dose, with 500mg increments 1-2 weekly and extended release preparations may minimise side effects ● metformin use appears safe long-term, based on use in other populations, however ongoing requirement needs to be considered and use may be associated with low vitamin B12 levels ● use is generally off label and health professionals need to inform women and discuss the evidence, possible concerns and side effects. 	
4.5 Anti-obesity pharmacological agents			
4.5.1	CCR	Anti-obesity medications in addition to lifestyle, could be considered for the management of obesity in adults with PCOS after lifestyle intervention, as per general population recommendations.	❖❖
4.5.2	CPP	For anti-obesity medications, cost, contraindications, side effects, variable availability and regulatory status need to be considered and pregnancy needs to be avoided whilst taking these medications.	
4.6 Anti-androgen pharmacological agents			
4.6.1	EBR	Where COCPs are contraindicated or poorly tolerated, in the presence of other effective forms of contraception, anti-androgens could be considered to treat hirsutism and androgen-related alopecia.	❖❖❖ ⊕○○○
4.6.2	CPP	Specific types or doses of antiandrogens cannot currently be recommended with inadequate evidence in PCOS.	
4.7 Inositol			
4.7.1	EBR	Inositol (in any form) should currently be considered an experimental therapy in PCOS, with emerging evidence on efficacy highlighting the need for further research.	❖ ⊕○○○
4.7.2	CPP	Women taking inositol and other complementary therapies are encouraged to advise their health professional.	

NO.	CATE-GORY RECOMMENDATION	QUALITY## AND GRADE
5	Assessment and treatment of infertility	
5.1	Assessment of factors that may affect fertility, treatment response or pregnancy outcomes	
5.1.1	CPP Factors such as blood glucose, weight, blood pressure, smoking, alcohol, diet, exercise, sleep and mental, emotional and sexual health need to be optimised in women with PCOS, to improve reproductive and obstetric outcomes, aligned with recommendations in the general population.	
	Refer to Lifestyle , Emotional Wellbeing and Diabetes risk sections	
5.1.2	CPP Monitoring during pregnancy is important in women with PCOS, given increased risk of adverse maternal and offspring outcomes.	
5.1.3	CCR In women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing of tubal patency testing should be discussed on an individual basis.	♦♦♦
5.1.4	CCR Tubal patency testing should be considered prior to ovulation induction in women with PCOS where there is suspected tubal infertility.	♦♦♦
5.2	Ovulation induction principles	
5.2.1	CPP The use of ovulation induction agents, including letrozole, metformin and clomiphene citrate is off label in many countries. Where off label use of ovulation induction agents is allowed, health professionals need to inform women and discuss the evidence, possible concerns and side effects.	
5.2.2	CPP Pregnancy needs to be excluded prior to ovulation induction.	
5.2.3	CPP Unsuccessful, prolonged use of ovulation induction agents needs to be avoided, due to poor success rates.	
5.3	Letrozole	
5.3.1	EBR Letrozole should be considered first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates.	♦♦♦♦
⊕⊕○○		
5.3.2	CPP Where letrozole is not available or use is not permitted or cost is prohibitive, health professionals can use other ovulation induction agents.	
5.3.3	CPP Health professionals and women need to be aware that the risk of multiple pregnancy appears to be less with letrozole, compared to clomiphene citrate.	

CATE- NO.	GORY RECOMMENDATION	QUALITY## AND GRADE
5.4	Clomiphene citrate and metformin	
5.4.1	EBR Clomiphene citrate could be used alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and pregnancy rates.	❖❖❖ ⊕○○○
5.4.2	EBR Metformin could be used alone in women with PCOS, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates, although women should be informed that there are more effective ovulation induction agents.	❖❖❖ ⊕⊕⊕○
5.4.3	EBR Clomiphene citrate could be used in preference, when considering clomiphene citrate or metformin for ovulation induction in women with PCOS who are obese (BMI is $\geq 30 \text{ kg/m}^2$) with anovulatory infertility and no other infertility factors.	❖❖❖ ⊕⊕○○
5.4.4	EBR If metformin is being used for ovulation induction in women with PCOS who are obese (BMI $\geq 30\text{kg/m}^2$) with anovulatory infertility and no other infertility factors, clomiphene citrate could be added to improve ovulation, pregnancy and live birth rates.	❖❖❖ ⊕⊕○○
5.4.5	EBR Clomiphene citrate could be combined with metformin, rather than persisting with clomiphene citrate alone, in women with PCOS who are clomiphene citrate-resistant, with anovulatory infertility and no other infertility factors, to improve ovulation and pregnancy rates.	❖❖❖ ⊕⊕○○
5.4.6	CPP The risk of multiple pregnancy is increased with clomiphene citrate use and therefore monitoring needs to be considered.	
5.5	Gonadotrophins	
5.5.1	EBR Gonadotrophins could be used as second line pharmacological agents in women with PCOS who have failed first line oral ovulation induction therapy and are anovulatory and infertile, with no other infertility factors.	❖❖❖ ⊕⊕○○
5.5.2	EBR Gonadotrophins could be considered as first line treatment, in the presence of ultrasound monitoring, following counselling on cost and potential risk of multiple pregnancy, in women with PCOS with anovulatory infertility and no other infertility factors.	❖❖❖ ⊕⊕○○
5.5.3	EBR Gonadotrophins, where available and affordable, should be used in preference to clomiphene citrate combined with metformin therapy for ovulation induction, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates.	❖❖❖❖ ⊕⊕⊕○
5.5.4	EBR Gonadotrophins with the addition of metformin, could be used rather than gonadotrophin alone, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates.	❖❖❖ ⊕⊕⊕○
5.5.5	EBR Either gonadotrophins or laparoscopic ovarian surgery could be used in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, following counselling on benefits and risks of each therapy.	❖❖❖❖ ⊕⊕⊕○

NO.	CATE-	GORY RECOMMENDATION	QUALITY## AND GRADE
5.5.6	CPP	Where gonadotrophins are prescribed, considerations include:	
		<ul style="list-style-type: none"> ● cost and availability ● expertise required for use in ovulation induction ● degree of intensive ultrasound monitoring required ● lack of difference in clinical efficacy of available gonadotrophin preparations ● low dose gonadotrophin protocols optimise monofollicular development ● risk and implications of potential multiple pregnancy 	
5.5.7	CPP	Gonadotrophin induced ovulation is only triggered when there are fewer than three mature follicles and needs to be cancelled if there are more than two mature follicles with the patient advised to avoid unprotected intercourse.	
5.6	Anti-obesity agents		
5.6.1	CCR	Pharmacological anti-obesity agents should be considered an experimental therapy in women with PCOS for the purpose of improving fertility, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy.	❖
5.7	Laparoscopic surgery		
5.7.1	EBR	Laparoscopic ovarian surgery could be second line therapy for women with PCOS, who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors.	❖❖❖ ⊕⊕○○
5.7.2	CCR	Laparoscopic ovarian surgery could potentially be offered as first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors.	❖❖❖
5.7.3	CPP	Risks need to be explained to all women with PCOS considering laparoscopic ovarian surgery.	
5.7.4	CPP	Where laparoscopic ovarian surgery is to be recommended, the following need to be considered:	
		<ul style="list-style-type: none"> ● comparative cost ● expertise required for use in ovulation induction ● intra-operative and post-operative risks are higher in women who are overweight and obese ● there may be a small associated risk of lower ovarian reserve or loss of ovarian function ● periadnexal adhesion formation may be an associated risk. 	

CATE- NO.	GORY RECOMMENDATION	QUALITY## AND GRADE
5.8	Bariatric surgery	
5.8.1 CCR	Bariatric surgery should be considered an experimental therapy in women with PCOS, for the purpose of having a healthy baby, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy.	❖
5.8.2 CPP	<p>If bariatric surgery is to be prescribed, the following need to be considered:</p> <ul style="list-style-type: none"> ● comparative cost ● the need for a structured weight management program involving diet, physical activity and interventions to improve psychological, musculoskeletal and cardiovascular health to continue post-operatively ● perinatal risks such as small for gestational age, premature delivery, possibly increased infant mortality ● potential benefits such as reduced incidence of large for gestational age fetus and gestational diabetes ● recommendations for pregnancy avoidance during periods of rapid weight loss and for at least 12 months after bariatric surgery with appropriate contraception. <p>If pregnancy occurs, the following need to be considered:</p> <ul style="list-style-type: none"> ● awareness and preventative management of pre-and post-operative nutritional deficiencies is important, ideally in a specialist interdisciplinary care setting ● monitoring of fetal growth during pregnancy. 	
5.9	In-vitro fertilisation (IVF)	
5.9.1 CCR	In the absence of an absolute indication for IVF ± intracytoplasmic sperm injection (ICSI), women with PCOS and anovulatory infertility could be offered IVF as third line therapy where first or second line ovulation induction therapies have failed.	❖❖❖
5.9.2 CPP	In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used multiple pregnancies can be minimised.	
5.9.3 CPP	Women with PCOS undergoing IVF ± ICSI therapy need to be counselled prior to starting treatment including on:	
	<ul style="list-style-type: none"> ● availability, cost and convenience ● increased risk of ovarian hyperstimulation syndrome ● options to reduce the risk of ovarian hyperstimulation. 	
5.9.4 CCR	Urinary or recombinant follicle stimulation hormone can be used in women with PCOS undergoing controlled ovarian hyperstimulation for IVF ± ICSI, with insufficient evidence to recommend specific follicle stimulating hormone (FSH) preparations.	❖❖❖
5.9.5 CCR	Exogenous recombinant luteinising hormone treatment should not be routinely used in combination with follicle stimulating hormone therapy in women with PCOS undergoing controlled ovarian hyperstimulation for IVF ± ICSI.	❖❖❖

CATE- NO.	GORY	RECOMMENDATION	QUALITY## AND GRADE
5.9.6	EBR	A gonadotrophin releasing hormone antagonist protocol is preferred in women with PCOS undergoing an IVF ± ICSI cycle, over a gonadotrophin releasing hormone agonist long protocol, to reduce the duration of stimulation, total gonadotrophin dose and incidence of ovarian hyperstimulation syndrome (OHSS).	❖❖❖ ⊕⊕○○
5.9.7	CPP	Human chorionic gonadotrophins is best used at the lowest doses to trigger final oocyte maturation in women with PCOS undergoing an IVF ± ICSI cycle to reduce the incidence of OHSS.	
5.9.8	CPP	Triggering final oocyte maturation with a gonadotropin-releasing hormone (GnRH) agonist and freezing all suitable embryos could be considered in women with PCOS having an IVF/ICSI cycle with a GnRH antagonist protocol and at an increased risk of developing OHSS or where fresh embryo transfer is not planned.	
5.9.9	CPP	In IVF ± ICSI cycles in women with PCOS, consideration needs to be given to an elective freeze of all embryos.	
5.9.10	EBR	Adjunct metformin therapy could be used before and/or during follicle stimulating hormone ovarian stimulation in women with PCOS undergoing a IVF ± ICSI therapy with a GnRH agonist protocol, to improve the clinical pregnancy rate and reduce the risk of OHSS.	❖❖❖ ⊕⊕○○
5.9.11	CCR	In a GnRH agonist protocol with adjunct metformin therapy, in women with PCOS undergoing IVF ± ICSI treatment, the following could be considered: <ul style="list-style-type: none"> ● metformin commencement at the start of GnRH agonist treatment ● metformin use at a dose of between 1000mg to 2550mg daily ● metformin cessation at the time of the pregnancy test or menses (unless the metformin therapy is otherwise indicated) ● metformin side-effects (see above metformin section) 	❖❖❖
5.9.12	CPP	In IVF ± ICSI cycles, women with PCOS could be counselled on potential benefits of adjunct metformin in a GnRH antagonist protocol to reduce risk of ovarian hyperstimulation syndrome (see above for metformin therapy considerations).	
5.9.13	CPP	The term in vitro maturation (IVM) treatment cycle is applied to “the maturation in vitro of immature cumulus oocyte complexes collected from antral follicles” (encompassing both stimulated and unstimulated cycles, but without the use of a human gonadotrophin trigger).	
5.9.14	CCR	In units with sufficient expertise, IVM could be offered to achieve pregnancy and livebirth rates approaching those of standard IVF ± ICSI treatment without the risk of OHSS for women with PCOS, where an embryo is generated, then vitrified and thawed and transferred in a subsequent cycle.	❖❖❖

Off-label' prescribing occurs when a drug is prescribed for an indication, a route of administration, or a patient group that is not included in the approved product information document for that drug by the regulatory body. Prescribing off label is often unavoidable and common and does not mean that the regulatory body has rejected the indication, more commonly there has not been a submission to request evaluation of the indication or that patient group for any given drug.

Chapter One

Screening, diagnostic assessment, risk assessment and life-stage

Diagnosis and treatment of polycystic ovary syndrome (PCOS) remain controversial with challenges defining individual components within the diagnostic criteria and significant clinical heterogeneity across the phenotypes, which is further varied by ethnic differences and changes in clinical features across the life course. The guideline addresses issues for all those affected with PCOS across the lifespan. Where recommendations differ by life stages or body mass index (BMI) status, this is clarified.



1.1 Irregular cycles and ovulatory dysfunction

In adolescents, at what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction?

Clinical need for the question

Ovulatory dysfunction is a key diagnostic feature of PCOS with irregular menstrual cycles reflecting ovulatory dysfunction, as reflected in the Rotterdam criteria. Ovulatory dysfunction can occur with regular cycles. When anovulation needs to be confirmed, hormonal assessment is relevant if PCOS is clinically suspected and cycles are regular.

Irregular cycles and ovulatory dysfunction are also a normal component of the pubertal and menopausal transitions and defining abnormality at these life stages remains challenging. Indeed, the greatest controversy in this diagnostic criteria is during the pubertal transition. Physiological maturation of the hypothalamic, pituitary ovarian axis occurs over years and ovulation and cycles in adolescents do not match those of reproductive-aged women. When irregular cycles reflect reproductive maturity and when they may indicate PCOS is unclear, challenging accurate diagnosis with potential concerns about over-diagnosis. Likewise, women internationally report under diagnosis and delayed diagnosis, dissatisfaction in diagnosis experience, with related anxiety and limited opportunity for education, prevention of complications and treatment of symptoms [13]. Young women may also be commenced on the combined oral contraceptive pill (COPC) prior to assessment and diagnosis, potentially delaying diagnosis. Hence this clinical question was prioritised.

Summary of systematic review evidence

We did not identify any evidence in our patient population to answer the question.

Summary of narrative review evidence

Given the limited evidence identified on systematic review, a narrative review was completed (see supplementary Technical report) and is summarised here. Physiologically, during the first year post-menarche, hormonal responses do not match adult patterns. During the second year about one half of the menstrual cycles range from 21 - 45 days in length, however progesterone levels are low [17]. The average adult menstrual cycle is 28 days, ranging from 24 - 35 days [18]. The majority of irregular cycles may be ovulatory two years post-menarche [18-21], with 80% of cycles being within 21 - 45 days [19, 21-23]. By the third post-menarcheal year, 95% of cycles fall into this range, however cycles can remain irregular until the fifth year [24, 25]. Regular ovulatory cycle onset is also related to age at menarche [26]. In those who begin menses before 12 years, between 12 - 13 years, and after 13 years of age, 50% of cycles are ovulatory by one year, three years, and 4.5 years, respectively [26]. At age 15, more than 50% of girls who are oligo-amenorrhoeic remain so at age 18 [27]. Overall, irregular cycles (> 35 or < 21 days) that continue for more than two years post-menarche are likely to have oligo-anovulation, based on general population data, with consideration needed for age of menarche. With increasing gynaecologic age, fewer females experience cycles exceeding 45 days [28].

It is recognised that irregular menstrual cycles and other features of PCOS can overlap with those observed in the normal pubertal transition and it is important to define where these features are more likely to reflect PCOS. Overall the greatest controversy here relates to the past approaches of identifying the 95th centile of cycle duration as abnormal. If this percentile is used to define a single diagnostic feature (e.g. menstrual cycles) in a condition with a prevalence of around 10%, this is a simplistic and poorly informed approach. In fields such as diabetes and other conditions where diagnostic features represent a continuum, considerable refinement has occurred with alignment with other clinical features and health outcomes. This approach was applied here and the body of literature on normal menstrual cycles reviewed to identify the 85th to 90th percentile, pending more appropriate cluster analysis and longitudinal follow-up data.

This approach was approved by the Paediatric guideline development group (GDG) panel ([Appendix III](#)).

Recommendations

1.1.1 CCR Irregular menstrual cycles are defined as:



- normal in the first year post menarche as part of the pubertal transition
- > 1 to < 3 years post menarche: < 21 or > 45 days
- > 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year
- > 1 year post menarche > 90 days for any one cycle
- Primary amenorrhea by age 15 or > 3 years post thelarche (breast development)

When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to the guidelines.

1.1.2 CCR In an adolescent with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient, taking into account diagnostic challenges at this life stage and psychosocial and cultural factors.



1.1.3 CPP For adolescents who have features of PCOS but do not meet diagnostic criteria, an “increased risk” could be considered and reassessment advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before combined oral contraceptive pill (COCP) commencement, those with persisting features and those with significant weight gain in adolescence.

1.1.4 CPP Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.

Justification

Whilst limited evidence was found to specifically address this question in PCOS, recommendations are informed by the best available evidence on normal adolescent menstrual patterns and ovulatory function and by previous available guidelines, multidisciplinary expertise and consumer perspectives. The GDG and the paediatric endocrine and gynecology expert panel from across the GDGs, carefully considered the available literature, the international feedback and the potential for both over diagnosis and delayed diagnosis when assessing this diagnostic feature in PCOS. They also considered the need for individual consideration around timing and value of diagnosis and the potential desirable and undesirable impacts of making a diagnosis. It was also recognised that many adolescents may be commenced on pharmacological therapy for irregular cycles without a diagnostic assessment for PCOS and this was addressed in the recommendations and practice points highlighting the need to identify those “at risk” and to emphasise reassessment. It is recognised these recommendations will change practice and deviate from past guidelines stipulating > 45 days for all adolescents. Here more specific cut-offs were provided aligned with gynaecological maturity.

1.2 Biochemical hyperandrogenism

In women with suspected PCOS, what is the most effective measure to diagnose PCOS-related biochemical hyperandrogenism?

Clinical need for the question

Hyperandrogenism is a key diagnostic feature of PCOS affecting between 60% - 100% with the condition with both clinical (hirsutism, alopecia and acne) and biochemical hyperandrogenism. Both features of hyperandrogenism are challenging to assess and vary by methods of assessment, ethnicity and confounding factors including excess weight and life stage. Assessment of biochemical hyperandrogenism is hampered by a lack of clarity on which androgens to measure, what assays to use, how to define normal ranges, overlaps between values obtained in controls and PCOS, and access and cost issues for high quality assays. Calculated bioavailable testosterone and calculated free testosterone using the formula of Vermeulen et al is commonly used [29], as is free androgen index (FAI = 100 x (total testosterone/SHBG)). Direct testosterone assays are widely used, however deficiencies in the accuracy of these assays limit their use. Moving forward standardised testosterone measurements that are accurate, reliable and comparable over time are essential [30, 31]. Given the controversy, methodological challenges, options, uncertainty in clinical practice and role of biochemical hyperandrogenism in the diagnosis of PCOS, this question was prioritised.

Summary of systematic review evidence

Seven studies of moderate to high risk of bias reported the diagnostic accuracy of different hormone markers to detect PCOS [32-38]; and another study of moderate risk of bias compared the diagnostic accuracy of different types of assays to detect PCOS [39]. There was insufficient evidence to make definitive recommendations on the optimal hormone and method to measure biochemical diagnosis hyperandrogenism in PCOS, although data indicates that, as a single measure, free testosterone measures provide the most optimal accuracy to detect biochemical hyperandrogenism followed, in no specific order by total testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione.

Summary of narrative review evidence

Given the limited evidence identified on systematic review, a narrative review was completed (see supplementary Technical Report). In summary, with few exceptions, methods for directly assessing total circulating testosterone levels (e.g. direct radioimmunoassays or chemiluminescence immunoassays) are of insufficient precision, sensitivity and specificity to be used for the accurate assessment of total testosterone levels in women and female adolescents, including those with PCOS. There are also currently no reliable direct assays for total or free testosterone. However, laboratories can provide calculated bioavailable testosterone, calculated free testosterone, or free androgen index (FAI). Androstenedione and DHEAS have a more limited role and can increase the probability of detecting hyperandrogenemia, yet they are arguably more useful in exclusion of other causes of hyperandrogenism. DHEAS is predominantly an adrenal androgen and mild elevation may be seen with PCOS, with significant elevations and/or virilisation requiring investigation for possible androgen secreting adrenal tumour. Androstenedione, is elevated in 21-hydroxylase deficient non-classical congenital adrenal hyperplasia. Testosterone secretion may be increased during mid-cycle and assessment of androgen status should preferably be during the early follicular phase in cycling women, whilst diurnal variation means morning levels may be most predictive. Current studies focus on different assays in women already diagnosed with PCOS. This approach has inherent bias as the diagnosis includes hyperandrogenism and further studies are needed to explore relationships between androgen levels and the various immediate and long term clinical features of PCOS.

Recommendations

1.2.1	EBR	Calculated free testosterone, free androgen index or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS.	❖❖❖ ⊕⊕○○
1.2.2	EBR	High quality assays such as liquid chromatography–mass spectrometry (LCMS)/mass spectrometry and extraction/chromatography immunoassays, should be used for the most accurate assessment of total or free testosterone in PCOS.	❖❖❖ ⊕⊕○○
1.2.3	EBR	Androstenedione and dehydroepiandrosterone sulfate (DHEAS) could be considered if total or free testosterone are not elevated; however, these provide limited additional information in the diagnosis of PCOS.	❖❖❖ ⊕⊕○○
1.2.4	CCR	Direct free testosterone assays, such as radiometric or enzyme-linked assays, preferably should not be used in assessment of biochemical hyperandrogenism in PCOS, as they demonstrate poor sensitivity, accuracy and precision.	❖❖❖
1.2.5	CPP	Reliable assessment of biochemical hyperandrogenism is not possible in women on hormonal contraception, due to effects on sex hormone-binding globulin and altered gonadotrophin-dependent androgen production.	
1.2.6	CPP	Where assessment of biochemical hyperandrogenism is important in women on hormonal contraception, drug withdrawal is recommended for three months or longer before measurement, and contraception management with a non-hormonal alternative is needed during this time.	
1.2.7	CPP	Assessment of biochemical hyperandrogenism is most useful in establishing the diagnosis of PCOS and/or phenotype where clinical signs of hyperandrogenism (in particular hirsutism) are unclear or absent.	
1.2.8	CPP	Interpretation of androgen levels needs to be guided by the reference ranges of the laboratory used, acknowledging that ranges for different methods and laboratories vary widely. Normal values are ideally based on levels from a well phenotyped healthy control population or by cluster analysis of a large general population considering age and pubertal specific stages.	
1.2.9	CPP	Where androgen levels are markedly above laboratory reference ranges, other causes of biochemical hyperandrogenism need to be considered. History of symptom onset and progression is critical in assessing for neoplasia, however, some androgen-secreting neoplasms may only induce mild to moderate increases in biochemical hyperandrogenism.	

Justification

Total testosterone alone can identify 20 - 30% of women with PCOS as having biochemical hyperandrogenism, while measures of unbound or free testosterone will identify 50 - 60%. Laboratory calculated values are recommended. High quality assays provide a more accurate diagnosis and the additional associated cost was deemed important and justified after considering all elements of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. Access issues were also acknowledged. Given the challenges in assessing biochemical hyperandrogenism, whilst androgen measures are useful to detect biochemical hyperandrogenism where PCOS is suspected, these are likely to be most useful in diagnosis of PCOS in adolescents and women who demonstrate minimal to no features of clinical hyperandrogenism (e.g. hirsutism). Clarity around standardised assessment for biochemical hyperandrogenism provided by the guideline is likely to be valued.

1.3 Clinical hyperandrogenism

In women with suspected PCOS, what is the most effective measure to clinically diagnose PCOS-related hyperandrogenism?

Clinical need for the question

Signs and symptoms of severe androgen excess can result in virilisation (e.g. male pattern balding, severe hirsutism, and clitoromegaly) and masculinisation. Virilisation is rare. Clinical evidence of mild to moderate androgen excess is more common including hirsutism, acne, and androgen-related alopecia. The interrelationships of these clinical features remains unclear, varies by ethnicity, and requires clinician training, vigilance and skill to assess. These features impact considerably on quality of life in women with PCOS and treatment burden including cosmetic therapies can be significant. Given the fundamental role of hyperandrogenism in diagnosis, and the adverse impact on quality of life, this question was prioritised.

Summary of systematic review evidence

We did not identify any evidence in our patient population to answer the question.

Summary of narrative review evidence

A narrative review provided in the technical report, notes the most recognisable clinical sign of hyperandrogenism as terminal hairs in a male-like pattern in women or “hirsutism”. Elevated androgens are detected in the vast majority (> 70%) of women with hirsutism and few do not demonstrate other features of PCOS (< 5%) [40]. The most common visual assessment tool is the modified Ferriman-Gallwey (mFG) [41, 42] to assess terminal hairs (hairs that would grow > 5mm in length if left unmolested, are usually pigmented, and are medullated). mFG assesses nine primarily masculine body areas for terminal hair: upper lip, chin and neck, upper chest (excluding the nipples), upper abdomen (above the umbilicus), lower abdomen (also known as male escutcheon), thighs (front and/or back), upper back, lower back, and upper arms [42, 43]. Each area is visually scored from zero (no terminal hair visible) to four (terminal hair consistent with a well-developed male). A photographic atlas assists scoring [42].

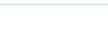
Comedonal acne is common in adolescent girls, moderate or severe comedonal acne (i.e. 10 or more facial lesions) in early puberty or moderate inflammatory acne through the perimenarcheal years is uncommon (< 5% prevalence) [44, 45]. There are no studies evaluating alopecia in adolescents. For these reasons, mild acne and alopecia are not recommended as considerations in the diagnostic criteria for adolescents.

Defining ‘abnormal’ in hirsutism is controversial. The mFG cut-off score can be based on percentile with a score > 6 - 8 consistent with the 95th percentile of unselected women [41, 43, 46]. It can also be defined by a lower percentile 85 - 90th percentile or by cluster analysis where the score is analysed in relation to other features of PCOS. These approaches suggest that an mFG scores of > 3 in White and Black women [47], and > 5 in Mongoloid Asian (Han Chinese) women [48] represents true abnormality. As outlined above under irregular menstrual cycles, a simplistic cut off at the 95th centile is not appropriate and for this reason the GDG, after reviewing all available evidence, recommended the cut offs of $\geq 4 - 6$ on mFG.

The prevalence of hirsutism is the same across ethnicities, yet the mFG cut-off scores for defining hirsutism and the severity of hirsutism varies by ethnicity. Overall, >50% of women with mFG scores of 3-5 have elevated androgens and/or PCOS [49], and >70-90% of women with scores >5 [42, 46]. Referral bias needs to be considered in reported populations [50, 51]. Hirsutism adversely impacts quality of life [52] and most women readily treat hirsutism complicating assessment, hence health professionals should be prepared to assess any woman who complains of excess hair [49, 53].

Acne is associated with biochemical hyperandrogenism [54, 55], yet the predictive value of acne alone is unclear [40, 54] and there is no accepted assessment tool [40]. Most studies of women with alopecia reveal a relatively low prevalence of hyperandrogenemia [40, 56] and the predictive value of alopecia alone remains unclear, in part as there are many causes that can contribute to alopecia aside from hyperandrogenism. Hair loss on the scalp is usually assessed visually using the Ludwig scale [40].

Recommendations

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- 1.3.1 CCR A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, alopecia and hirsutism and, in adolescents, severe acne and hirsutism. 
- 1.3.2 CCR Health professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism. Reported unwanted excess hair growth and/or alopecia should be considered important, regardless of apparent clinical severity. 
- 1.3.3 CCR Standardised visual scales are preferred when assessing hirsutism, such as the modified Ferriman Gallwey score (mFG) with a level ≥ 4 - 6 indicating hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment. (See recommendations on ethnic variation). 
- 1.3.4 CCR The Ludwig visual score is preferred for assessing the degree and distribution of alopecia. 
- 1.3.5 CPP There are no universally accepted visual assessments for evaluating acne.
- 1.3.6 CPP The prevalence of hirsutism is the same across ethnicities, yet the mFG cut-off scores for defining hirsutism and the severity of hirsutism varies by ethnicity.
- 1.3.7 CPP As ethnic variation in vellus hair density is notable, over-estimation of hirsutism may occur if vellus hair is confused with terminal hair; only terminal hairs need to be considered in pathological hirsutism, with terminal hairs clinically growing $> 5\text{mm}$ in length if untreated, varying in shape and texture and generally being pigmented.
-

Justification

Both patients and clinicians value an accurate diagnosis of PCOS, clinical hyperandrogenism is an important determinant of quality of life and simple treatments are readily available. While subjective and visual, the mFG score for facial and terminal hair growth is the principal instrument for clinical assessment of hirsutism. Hirsutism can be over-estimated if vellus and terminal hairs are not distinguished. The desirable effects (an accurate and sensitive diagnosis) outweigh the undesirable effects (over-estimation of hirsutism). Assessing for clinical hyperandrogenism is low cost, relative to biochemical assessments for hyperandrogenism, and a standardised assessment for clinical hyperandrogenism is likely to be valued.

1.4 Ultrasound and polycystic ovarian morphology

When is ultrasound indicated to diagnose PCOS?

What are the most effective ultrasound criteria to diagnose PCOS?

Clinical need for the questions

Polycystic ovarian morphology (PCOM) was incorporated into the diagnosis of PCOS in 2003 in the Rotterdam criteria, as a common feature associated with clinical and endocrine features of the condition [57]. This introduced arguably milder phenotypes into PCOS with limited data on natural history, prompting calls for phenotype identification and more research [16]. The definition of PCOM in the Rotterdam criteria is 12 or more follicles measuring 2 - 9mm throughout the entire ovary or an ovarian volume $\geq 10\text{cm}^3$. This was based on a single report on sensitivity and specificity in PCOS compared to controls. Factors that mandate revision of this diagnostic criteria include inadequate initial evidence, advances in ultrasound technology with greater resolution, variable operator skill level, lack of standard reporting, ill-defined cut-offs between normal ovaries and PCOM, the impact of approach (e.g. transvaginal), body habits and age. Natural changes occur in antral follicle count during the pubertal and menopausal transitions and up to 70% of adolescents have PCOM on original criteria [58]. The term "cystic" is a misnomer referring to arrested follicles (not cysts) and identification of PCOM alone can lead to over diagnosis. Diagnosis of PCOS mandates not only PCOM, but associated features of hyperandrogenism and/or ovulatory dysfunction. Independent of diagnosis, if clinically indicated, ultrasound is useful to screen for other pathology. This clinical question was prioritised, with recognition that a reproducible technique and standard reporting to reliably estimate follicle number per ovary and define PCOM, is critical in the accurate diagnosis of PCOS.

Summary of systematic review evidence

A systematic review was completed to address the second clinical question on the most effective ultrasound criteria to diagnose PCOS. Fifteen studies of moderate to high risk of bias, reported the diagnostic accuracy of different ovarian morphology parameters to detect PCOS [32, 37, 59-71]. Two of the fifteen studies were in adolescents [64, 71]. The index tests addressed in these studies included various measures and thresholds of ovarian volume and follicle number. None of the studies pre-specified thresholds. Some studies have reported diagnostic accuracy data using multiple thresholds. Due to the heterogeneity in threshold/cut off values for each index test, meta-analyses (for pooled sensitivity and specificity estimates) could not be performed. However, forest plots were created and imputation of sensitivity and specificity data performed to derive true and false positives and true and false negatives to provide greater detail on accuracy outlined in the technical report. This approach enabled a rigorous evaluation of available evidence, acknowledging the overall poor quality of the studies. For follicle number per ovary (FNPO) there were 11 studies with 2961 adult participants suggesting optimal sensitivity and specificity at > 19 per ovary. Other key challenges with the literature in this area included the variable populations (with and without women with PCOS) used to define cut off values and the use of the 95th percentile cut offs to define abnormality. For ovarian volume, 12 studies with 2096 participants showed significant heterogeneity with a lack of clarity on the optimal size with both 5 - 8 cm^3 and 9 - 10 cm^3 emerging. There is insufficient evidence to suggest use of other ultrasound parameters including ovarian area; maximum number follicles in a single sonographic plane (FSSP); peripheral distribution of ovarian follicles; bright ovarian stroma; combination of age, follicle number, log ovarian volume, and testosterone; or combination of follicular size and ovarian volume for diagnosis of PCOS.

Summary of narrative review evidence

A narrative review was completed to address the first question, supplemented with additional relevant evidence from the above systematic search. The ovary has a full complement of follicles and oocytes, arrested at meiosis, during fetal life. These mature in childhood with ovulation noted after puberty and continuing until menopause [72]. Ovarian volumes change over time with increased antral follicles and stroma. There are no large studies across the lifespan to validate normal ovarian development. Ovarian size increases from age 9 - 11 and maximum volume is reached at age 20 [73-77]. The correlation between menstrual function and ovarian morphology is not straightforward in adolescence with the majority of adolescents having PCOM consistent with Rotterdam criteria, and the few longitudinal studies suggest that 2 - 4 years postmenarche, PCOM is common and not associated with reproductive dysfunction [58, 78]. Therefore, adult PCOM criteria are likely inaccurate for ultrasound diagnosis of PCOS in adolescence with substantive overlap between follicle numbers per ovary in normal adolescents and those with other features of PCOS.

Recommendations

- | | | | |
|-------|-----|---|--|
| 1.4.1 | CCR | Ultrasound should not be used for the diagnosis of PCOS in those with a gynaecological age of < 8 years (< 8 years after menarche), due to the high incidence of multi-follicular ovaries in this life stage. |  |
| 1.4.2 | CCR | The threshold for PCOM should be revised regularly with advancing ultrasound technology, and age-specific cut off values for PCOM should be defined. |  |
| 1.4.3 | CCR | The transvaginal ultrasound approach is preferred in the diagnosis of PCOS, if sexually active and if acceptable to the individual being assessed. |  |
| 1.4.4 | CCR | Using endovaginal ultrasound transducers with a frequency bandwidth that includes 8MHz, the threshold for PCOM should be on either ovary, a follicle number per ovary of ≥ 20 and/or an ovarian volume $\geq 10\text{ml}$, ensuring no corpora lutea, cysts or dominant follicles are present. |  |
| 1.4.5 | CPP | If using older technology, the threshold for PCOM could be an ovarian volume $\geq 10\text{ml}$ on either ovary. | |
| 1.4.6 | CPP | In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis; however, ultrasound will identify the complete PCOS phenotype. | |
| 1.4.7 | CPP | In transabdominal ultrasound reporting is best focussed on ovarian volume with a threshold of $\geq 10\text{ml}$, given the difficulty of reliably assessing follicle number with this approach. | |
| 1.4.8 | CPP | Clear protocols are recommended for reporting follicle number per ovary and ovarian volume on ultrasound. Recommended minimum reporting standards include: <ul style="list-style-type: none">● last menstrual period● transducer bandwidth frequency● approach/route assessed● total follicle number per ovary measuring 2-9mm● three dimensions and volume of each ovary● Reporting of endometrial thickness and appearance is preferred – 3-layer endometrial assessment may be useful to screen for endometrial pathology● other ovarian and uterine pathology, as well as ovarian cysts, corpus luteum, dominant follicles \geq equal 10mm | |
| 1.4.9 | CPP | There is a need for training in careful and meticulous follicle counting per ovary, to improve reporting. | |

Justification

It was recognised that the data in young women with a gynaecological age of < 8 years (< 8 years after menarche) is inadequate, that peak ovarian maturity has not yet been reached and that defining PCOM at this life stage is not currently possible with the high incidence of multi-follicular ovaries. There was recognition of the risk of over diagnosis in adolescents if ultrasound criteria were included in this age group. Limitations in performing transvaginal ultrasounds in those not yet sexually active was also recognised. These factors were deemed to make the use of ultrasound inappropriate for diagnosis of PCOS in those with a gynaecological age < 8 years at this time. Ultrasound may be indicated for other reasons at this life stage, hence this recommendation is limited to the role of ultrasound in PCOS diagnosis.

Ultrasound is not required for diagnosis in adults with features of hyperandrogenism and ovulatory dysfunction, who already meet PCOS diagnostic criteria. It is recognised that omission of ultrasound does limit full phenotyping. The recommendation to use FNPO as the key diagnostic criteria for PCOM in adults was reconfirmed by the updated evidence review and expert deliberation. Technology advancements in the last decade support an increase in FNPO in diagnosis. Rigorous evaluation of the evidence and multidisciplinary expertise informed modified FNPO recommendations and reaffirmed secondary ovarian volume assessment in diagnosis. Limitations in the evidence were recognised, however significant advances were noted since the original Rotterdam recommendations. All relevant limitations of the evidence were considered by the GDG and co-opted experts, especially the limited relevance of the 95th centile cut offs in determining abnormal FNPO. These factors resulted in a FNPO recommendation between the original Rotterdam and more recent Androgen Excess and PCOS Society (AEPCOS) recommendations. These recommendations also recognise the optimal ultrasound approach, technological ultrasound advances and variability in availability of newer technologies and aim to improve training and standardise reporting. They are likely to improve the reliability of assessing and reporting FNPO, provide for more accurate reporting of PCOM in the diagnosis of PCOS. Importantly, they also limit use and costs of a somewhat invasive test, where it is not appropriate.

1.5 Anti-Müllerian Hormone (AMH)

Is Anti-Müllerian Hormone effective for diagnosis of PCOS?

Is Anti-Müllerian Hormone effective for diagnosis of PCOM?

Clinical need for the questions

Given the challenges with ultrasound in diagnosis of PCOS, including in the years after menarche, serum Anti-Müllerian Hormone (AMH) has been proposed as an alternative marker of ovulatory dysfunction in PCOS. AMH is a polypeptide of the transforming growth factor beta (TGF- β) family solely secreted by granulosa cells of the preantral and small antral ovarian follicles. Serum AMH levels are significantly higher in women with PCOS compared with normal ovulatory women [79, 80]. Strong correlations have been demonstrated between circulating AMH levels and antral follicle count on ultrasound in PCOS. AMH may also provide insight into the pathogenesis of PCOS and the different phenotypes. However, current literature reveals significant heterogeneity and the diagnostic value of serum AMH remains far from clear.

Summary of systematic review evidence

Twenty-nine studies of moderate to high risk of bias were identified by our search to address diagnostic accuracy of AMH for PCOS and/or PCOM [62, 65, 81-107]. One of these was a systematic review [88] and included nine of the studies identified here, however it also included studies that did not meet the inclusion criteria for this evidence review and it was missing additional more recently studies identified by the search: therefore it cannot be used. Four of the 28 primary studies addressed the diagnostic accuracy of AMH for PCOS and PCOM [85, 86, 92, 98]; and one for PCOM only [103]. Six studies included adolescents and one of these addressed PCOS and PCOM [86]. The remaining 21 studies included adult participants for diagnosis of PCOS, with three addressing PCOS and PCOM [85, 92, 98], and the remaining 18 addressing PCOS [62, 65, 81-84, 87, 91, 93-97, 99, 102, 104, 105, 107]. In adolescents, one was in overweight and obese participants [89] and one had unclear BMI [106]. In adults, one [82] included lean and obese participants; and five [62, 81, 85, 91, 107] included overweight and obese participants. Here we generated receiver operating characteristic (ROC) curves by plotting the true positive rate against the false positive rate at various threshold settings, based on published literature. The area under the ROC curve in adolescents for PCOS was around 0.5 - 0.88 and the threshold from 25 - 44pmol/L. In adults, the area under the ROC curve was about 0.66 - 0.994 and the threshold from 10-57pmol/L. In PCOM detection, in adolescents, one study showed an area under the ROC curve of about 0.87 and the threshold 50pmol/L. In adults, the ROC was about 0.67 - 0.92 and the threshold 20 - 30pmol/L.

Although serum AMH levels in adolescent and adult women with both PCOM and PCOS are significantly higher than those without these features in all studies, there is considerable overlap. A specific threshold of AMH in PCOS and PCOM is therefore very challenging. Heterogeneity between studies relates to assays, life stage and phenotypes studied. Another key contributor is the lack of well-defined populations including variable ultrasound criteria to establish PCOM and the criteria used to define controls.

Recommendations

1.5.1 EBR Serum AMH levels should not yet be used as an alternative for the detection of PCOM or as a single test for the diagnosis of PCOS.



1.5.2 CPP There is emerging evidence that with improved standardisation of assays and established cut off levels or thresholds based on large scale validation in populations of different ages and ethnicities, AMH may become a more accurate assay in the detection of PCOM.

Justification

Whilst an AMH assay to reflect ovarian morphology and diagnose PCOS offers convenience and lower costs, current assays and available evidence do not adequately support these roles for AMH at the current time. It is acknowledged that both ultrasound and AMH levels present challenges in PCOS diagnosis. It is also acknowledged that assays are improving and this recommendation may evolve over time.

1.6 Ethnic variation

In women with suspected PCOS is there evidence of ethnic and geographic variations in prevalence and presentation?

Clinical need for the question

PCOS was originally described in Caucasians and subsequently has shown to be prevalent across the world. Whilst there are many studies that explore PCOS within different ethnic groups, few compare across groups. Some studies consider within country populations by ethnicity, yet do not consider differences in diet, lifestyle and occupation. None the less, studies suggest differences in prevalence and clinical features across ethnic groups and greater clarity is needed to inform considerations and adaptation of guideline recommendations in the diagnosis and treatment of PCOS.

Summary of narrative review evidence

A systematic review was not conducted to answer this question which was reviewed narratively based on clinical expertise. In summary, an identified systematic review on prevalence and phenotypic features revealed some differences internationally [4] between ethnic and geographic regions. The highest prevalence has been reported among Australian Aboriginal women and South Asians migrating to developed countries, both populations with increased BMI [4, 108]. Ovulation appears not to differ, whilst androgen levels appear similar. Ultrasound ovarian features are difficult to compare, compromised by the differences in technology, diagnostic features and operator skill, yet no clear differences have emerged. For hirsutism there are clear ethnic differences in the cut off scores, with Middle Eastern and South Asian women having higher cut off scores for hirsutism than those of Eastern Asian origin. Acanthosis is more common in women of South East Asian background, reflecting increased insulin resistance. For metabolic features, BMI differs between ethnic groups, primarily dependent on lifestyle and environmental factors. Insulin resistance, diabetes risk and lipid profiles do appear to vary, potentially influenced by genetic factors and visceral adiposity. Genetic data shows both similarities and differences. Psychological features have not been well studied, however on quality of life studies, cultural rather than ethnic factors appear to impact, including cultural perspectives on infertility [109]. In terms of treatment responses, IVF may be less successful in women with of Asian ethnicity, but there is no similar data for ovulation induction.

Recommendations

- 1.6.1 CCR Health professionals should consider ethnic variation in the presentation and manifestations of PCOS, including:
- a relatively mild phenotype in Caucasians
 - higher BMI in Caucasian women, especially in North America and Australia
 - more severe hirsutism in Middle Eastern, Hispanic and Mediterranean women
 - increased central adiposity, insulin resistance, diabetes, metabolic risks and acanthosis nigricans in South East Asians and Indigenous Australians
 - lower BMI and milder hirsutism in East Asians
 - higher BMI and metabolic features in Africans

Justification

Ethnic differences appear to relate primarily to skin manifestations and metabolic features of PCOS. These may affect interpretation and application of relevant guideline recommendations and need to be considered by health professionals when assessing the individual woman. In response to peer review feedback specific ethnic differences have been noted in the guideline to inform practice.

1.7 Menopause life-stage

What is the post-menopausal phenotype of PCOS and how elevated should androgens be to indicate PCOS?

Clinical need for the question

Menopause is a natural life stage occurring generally around the age of 51 years. The diagnosis of PCOS by Rotterdam criteria requires two of three criteria in women, including oligo- and/or anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries by ultrasound [57]. However, these three criteria for diagnosis change naturally with age impacting on phenotype and presenting challenges in diagnosis. Overall it is acknowledged that there is inadequate evidence of the natural history of PCOS and the concept of whether PCOS resolves and/or persists remains unclear pending better longitudinal studies. Postmenopausal phenotypes of PCOS are poorly defined, with limited longitudinal natural history studies. Uncertainty in assessment and diagnosis at this life stage leads to confusion for health professionals and women on long term health risks and screening recommendations.

Summary of narrative review evidence

A systematic review was not conducted to answer this question, which was reviewed narratively based on clinical expertise. With aging, changes occur in all three diagnostic criteria. Menstrual cycles become more regular in PCOS [110-112]. Ovarian volume and follicle number decrease longitudinally in PCOS and control women. Using cross-sectional data, ovarian volume and follicle number decrease in both groups, but the decrease in ovarian volume is less pronounced in women with PCOS than in controls. Age-based criteria to define PCOM have been proposed using a combination of age, log ovarian volume, follicle number, and testosterone to distinguish PCOS from non-PCOS [60]. Androgens decline with age in women generally including those with PCOS [113-115] in longitudinal and cross-sectional studies [116]. Testosterone free androgen index (FAI), and calculated free testosterone are higher in women with PCOS aged 18–44 years compared to controls [116]. Regarding menstrual cycles, the average age of menopause in PCOS is not known. A two-year delay in the age of menopause has been estimated using AMH levels [117] and PCOS has been independently associated with later menopause [118]. There is no established phenotype for PCOS after menopause. In postmenopausal women, ovulation ceases. Hirsutism is greater in PCOS than in controls in postmenopausal women [119] but little is known about acne and alopecia in these women. Postmenopausal women with PCOS have higher 17-hydroxyprogesterone, androstenedione, DHEAS, total Testosterone and FAI than women without PCOS [116, 119, 120]. However, androgen assays are unreliable in women especially with the lower levels generally observed postmenopause [121]. Postmenopausal women with PCOS have abnormal glucose metabolism [122] and higher triglycerides than controls [119]. Other methods to identify PCOS in postmenopausal women have been proposed. For PCOS diagnosis in menopause, previous history of oligo-ovulation, PCOM and current features of hyperandrogenism [123, 124] have been considered, as have insulin resistance [125].

Recommendations

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|-------|-----|--|---|
| 1.7.1 | CCR | Postmenopausal persistence of PCOS could be considered likely with continuing evidence of hyperandrogenism. |  |
| 1.7.2 | CCR | A diagnosis of PCOS postmenopause could be considered if there is a past diagnosis of PCOS, a long-term history of irregular menstrual cycles and hyperandrogenism and/or PCOM, during the reproductive years. |  |
| 1.7.3 | CPP | Postmenopausal women presenting with new-onset, severe or worsening hyperandrogenism including hirsutism, require further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis. | |

Justification

A consensus recommendation was made around assessment of persistence of PCOS in those with a past diagnosis of PCOS or the relevant diagnostic features, or in women with persistent hyperandrogenism. The importance of excluding other diagnoses in cases of significant hyperandrogenism was recognised. These recommendations align with past guidelines with a key emphasis placed on research to provide clarity on postmenopausal PCOS phenotypes and persistence of PCOS postmenopause. Undesirable effects are unclear and it is important to note that reliance on history may overestimate the presence of oligo/amenorrhoea. Labelling of patients with a diagnosis may also have adverse consequences (psychological etc), whilst making a diagnosis may prompt risk recognition and screening such as for glycaemic abnormalities.

1.8 Cardiovascular disease

Are women with PCOS at increased risk for cardiovascular disease?

In women with PCOS, what is the most effective tool/method to assess risk of cardiovascular disease?

Clinical need for the questions

Cardiovascular disease (CVD) remains one of the leading causes of death in women and any condition further increasing CVD risk, will have significant public health impact. CVD primarily affects postmenopausal women in the later decades of life, however CVD development and risk factors are present in early adulthood. Longitudinal studies of well-defined cohorts with and without PCOS are limited. Existing cohorts have poorly defined PCOS status and focus on younger women, or on CVD risk factors rather than clinical events. This makes the determination of CVD risk in PCOS very challenging. It is acknowledged that metabolic syndrome and CVD risk factors are clearly increased in PCOS and that cardiovascular health overall needs to be considered, however given the limited current data on clinical events, overall CVD risk and optimal screening for additional risk factors remains highly controversial.

Summary of systematic review evidence

Two systematic reviews [126, 127] and eight observational studies [128-135] were identified by the search to address risk of CVD in women with PCOS. Seven of the observational studies were addressed across the two systematic reviews, however the systematic reviews included studies in the analysis that do not meet the PICO for this evidence review, therefore the data from the systematic reviews cannot be used here. The risk of bias/methodological quality assessments from the systematic reviews have been used. Studies were retrospective (6) and prospective cohort (1) studies reporting CVD-related event rates in women with and without PCOS over time.

Meta-analysis was conducted for outcomes with two or more studies. There was no statistical difference between PCOS and non-PCOS groups in terms of myocardial infarction (3 studies, 1633 participants, I² 0%); stroke (4 studies, 3012 participants, I² 14%; CVD-related death (2 studies, 779 participants, I² 0%); and coronary artery/heart disease (2 studies, 2152 participants, I² 80%). One study each addressed angina (no difference), large vessel disease (p value not reported), coronary artery calcification (p value not reported). One study presented odds ratios and suggest that when a group of women with PCOS are compared to a UK-wide population, the risk of myocardial infarction (but not angina) was increased in women with PCOS over 45 years (stratified into 15 - 44, 45 - 54, 55 - 64 and > 65). When they compared the same women with PCOS to a local community population, the risk of myocardial infarction and angina was increased in women with PCOS. However, when all age groups were combined, there was no difference in risk between women with and without PCOS, for either myocardial infarction or angina, regardless of where the control population was sourced. Given the methodological and reporting limitations and small sample sizes of these observational studies, all findings should be interpreted with caution. Furthermore the relatively young age of women included in most studies limits the interpretation of the available data.

On screening tools/methods for CVD, we did not identify any evidence in women with PCOS to answer the question regarding the most effective method/tool to assess risk of CVD. The summary of the narrative review evidence is provided here including an international position statement on CVD risk assessment in PCOS [136] and existing guidelines on absolute or global CVD risk assessment [137], obesity [138], lipids [139, 140] and hypertension [141] for the general population. The concept of overall or global CVD risk was also considered important and relevant in women with PCOS.

Recommendations

- 1.8.1 CCR All those with PCOS should be offered regular monitoring for weight changes and excess weight, in consultation with and where acceptable to the individual woman. Monitoring could be at each visit or at a minimum 6 - 12 monthly, with frequency planned and agreed between the health professional and the individual (see 3.5). 
- 1.8.2 CCR Weight, height and ideally waist circumference should be measured and BMI calculated with the following considered:
- BMI categories and waist circumference should follow World Health Organisation guidelines, also noting ethnic and adolescent ranges.
 - Consideration should be given for Asian and high-risk ethnic groups including recommended monitoring of waist circumference.
- 1.8.3 CCR All women with PCOS should be assessed for cardiovascular risk factors and global CVD risk. 
- 1.8.4 CCR If screening reveals CVD risk factors including obesity, cigarette smoking, dyslipidemia, hypertension, impaired glucose tolerance and lack of physical activity, women with PCOS should be considered at increased risk of CVD. 
- 1.8.5 CCR Overweight and obese women with PCOS, regardless of age, should have a fasting lipid profile (cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level at diagnosis). Thereafter, frequency of measurement should be based on the presence of hyperlipidemia and global CVD risk. 
- 1.8.6 CCR All women with PCOS should have blood pressure measured annually, or more frequently based on global CVD risk. 
- 1.8.7 CPP Health professionals need to be aware that CVD risk in women with PCOS, remains unclear pending high quality studies, however prevalence of CVD risk factors is increased, warranting consideration of screening.
- 1.8.8 CPP Consideration needs to be given to the significant differences in CVD risk across ethnicities (see 1.6.1) when determining frequency of risk assessment.

Justification

Whilst it remains unclear as to whether women with PCOS have a higher risk of CVD, data remains limited and women have generally been studied at a relatively young age. The guidelines therefore emphasise the increase in CVD risk factors, rather than making a recommendation about CVD risk. Assessment of CVD risk in PCOS needs to encompass assessment of well-established risk factors, including those specifically increased in PCOS: weight, BMI, waist circumference, lipid profiles, blood pressure, glucose levels and physical activity. The presence of PCOS as an independent CVD risk factor is yet to be confirmed pending quality studies to determine whether these elevated CVD risk factors convert to the anticipated risk of CVD in the longer term. However, in the presence of well-established CVD risk factors and inadequate longitudinal CVD data, it was deemed that women with PCOS require screening.

1.9 Gestational diabetes, impaired glucose tolerance and type 2 diabetes

Are women with PCOS at increased risk for impaired glucose tolerance, gestational diabetes and type 2 diabetes mellitus?

In women with PCOS, what is the most effective tool/method to assess risk of type 2 diabetes?

Clinical need for the questions

Glucose is a continuous variable. Cut off levels for gestational diabetes (GDM), impaired glucose tolerance (IGT) and type II diabetes (DM2) remain controversial and somewhat arbitrary. Clinical sequelae inform the arbitrary cut offs for these conditions; in pregnancy any elevation of blood glucose increases morbidity for mother and baby; in IGT long-term health risks including CVD are increased and in DM2, both micro and macrovascular risks are increased. In the general population, optimal screening protocols for these conditions vary and the most reliable tests for screening and diagnosis [oral glucose tolerance tests (OGTT), fasting glucose or HbA1c] remain controversial. These controversies extend to PCOS, where increased risks of GDM, IGT and DM2 [9] and underlying insulin resistance [142] have been demonstrated on meta-analyses, independent of BMI. Controversy around the optimal screening test is significant in PCOS, with proposed benefits of identifying IGT on an OGTT, requiring balance with increased inconvenience, cost and poor implementation, despite recommendations in past guidelines. Ethnicity, BMI and other risk factors also influence risk of glycaemic abnormalities and as per the general populations, these need to be considered when determining screening type and frequency.

Hyperglycaemic conditions

Summary of narrative review evidence

A systematic review was not conducted to answer the first question and was reviewed narratively based on clinical expertise and prior systematic reviews and meta-analyses. In summary, meta-analyses indicate increased IGT, GDM and DM2 risks, independent of obesity. Women with PCOS had increased prevalence of IGT (OR 2.48, 95% CI 1.63, 3.77; BMI-matched studies OR 2.54, 95% CI 1.44, 4.47), DM2 (OR 4.43, 95% CI 4.06, 4.82; BMI-matched studies OR 4.00, 95% CI 1.97, 8.10) [143]. Consistently, DM2 was four times higher in a recent Danish registry study and was diagnosed four years earlier in PCOS [144]. The prevalence differs by ethnicity and is higher in more obese study populations [144]. HbA1c, fasting glucose, 2h glucose, measures of insulin resistance, triglycerides, sex hormone binding globulin and BMI at baseline may be the best predictors for development of DM2 [144]. When models were corrected for age and BMI, fasting glucose, 2h glucose on OGTT and triglycerides were the best predictors.

Screening

Summary of systematic review evidence

One low quality systematic review with high risk of bias was identified by our search [145] that asked the question: How can women with PCOS be identified for risk of DM2 screening? The authors of the systematic review found no studies addressing the question and in the absence of evidence, the authors suggest that oligomenorrhoea, along with clinical or biochemical hyperandrogenism, obesity or a family history of risk of DM2 may be indicators of risk of DM2. The systematic review was deemed insufficient evidence on which to base a recommendation. Therefore clinical consensus recommendations have been made based on the systematic review, an international position statement on CVD risk assessment in PCOS [136] and guidelines for case detection and diagnosis of DM2 [146].

Summary of narrative review evidence

Whilst guidelines consistently recommend screening for DM2 in PCOS, whether to target subgroups, which test to use (fasting glucose, OGTT or HbA1c) and optimal frequency, vary between guidelines [147] and remain controversial. Some recommend screening all women with PCOS [148], whereas others consider additional risk factors including ethnicity, BMI, previous GDM or a family history of DM2. Most recommend the OGTT, whilst frequency of testing is variable. The specific impact of ethnicity (65% of the world's population are of high-risk Asian ethnicity) and of excess weight on DM2 risk in PCOS, presents challenges. In a low risk northern European ethnic group, lean women did not develop DM2 by 46 years, with risk increased in the majority who were overweight or obese [149]. Yet, in a recent abstract, 47% of Asian women with PCOS had IGT or DM2 by 41 years, despite limited obesity. The concept of absolute versus relative risk is also important as in low risk populations (Caucasian, healthy weight), a four-fold increased risk from PCOS equates to a low incidence of DM2, yet in high-risk South East Asians or obese women, PCOS significantly impacts on DM2 incidence [150].

General guidelines recommend testing for prediabetes and DM2 in adolescents and adults at any age who are overweight or obese (BMI over 25 kg/m² or 23 kg/m² in Asians), with additional risk factors (e.g. PCOS) [151]. Given the increased risks associated with hyperglycaemia in reproductive aged women (outlined below), the high prevalence of additional risk factors in PCOS and the increased risks with PCOS, screening was considered in all adults with PCOS, and adolescents who are overweight or from a high-risk ethnic group.

The optimal screening test remains unclear in the general population and in PCOS, with fasting glucose, OGTT or HbA1c now acceptable for diagnosis of DM2. The OGTT has higher cost and greater inconvenience, yet can define IGT and influence practice around lifestyle intervention and metformin use, with clear evidence of DM2 prevention in general populations [152], not yet demonstrated based on fasting glucose or HbA1c criteria [151]. HbA1c also brings cost, interference with other conditions and variation across ethnicities. The GDG deemed that on balance, the type of screening should be influenced by clinical judgement on overall risk, resources, access, preference and consideration of where results for IGT will influence practice on prevention of DM2. The high background risk of GDM and the increase in PCOS were considered, along with morbidity in pregnancy based on OGTT (fasting, one hour and two hour levels are all independently associated with adverse outcomes) [153]. Population recommendations are to screen at antenatal booking and at 24 - 28 weeks in women with risk factors for DM2 [151], with many guidelines recommending universal screening at 24 - 28 weeks. In this context the GDG recommended an OGTT preconception or at booking and at 24 - 28 weeks, acknowledging the need for further research.

In terms of frequency of screening, a minimum of three yearly is recommended in the general population, considering other risk factors. This was considered reasonable in PCOS, with increased frequency with other risk factors.

Recommendations

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- 1.9.1 CCR Health professionals and women with PCOS should be aware that, regardless of age, the prevalence of gestational diabetes, impaired glucose tolerance and type 2 diabetes (5 fold in Asia, 4 fold in the Americas and 3 fold in Europe) are significantly increased in PCOS, with risk independent of, yet exacerbated by, obesity. 
- 1.9.2 CCR Glycaemic status should be assessed at baseline in all women with PCOS. Thereafter, assessment should be every one to three years, influenced by the presence of other diabetes risk factors. 
- 1.9.3 CCR An oral glucose tolerance test (OGTT), fasting plasma glucose or HbA1c should be performed to assess glycaemic status. In high-risk women with PCOS (including a BMI > 25kg/m² or in Asians > 23kg/m², history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of diabetes mellitus type 2, hypertension or high-risk ethnicity), an OGTT is recommended. 
- 1.9.4 CCR A 75-g OGTT should be offered in all women with PCOS preconception when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed preconception, an OGTT should be offered at < 20 weeks gestation, and all women with PCOS should be offered the test at 24-28 weeks gestation. 
-

Justification

DM2 risk factors significantly increase background population risk and prevalence of GDM and DM2, which are further increased in PCOS, independent of BMI, age and ethnicity, representing a significant health and cost burden. The GDG unanimously agreed that screening was warranted in all adults with PCOS and in adolescents with additional risk factors at baseline. Optimal tests remain unclear and fasting glucose, HbA1c or OGTT can be used. An OGTT brings higher cost and inconvenience, yet where background risk is high, or where diagnosis of IGT will change practice (lifestyle intervention or metformin use) an OGTT is recommended, at minimum at baseline. Frequency of testing should be a minimum of three yearly informed by additional risk factors. These recommendations are less intensive than many prior guidelines. Where past guidelines were followed costs and inconvenience may now be reduced. The majority of GDG members voted in favour of the final recommendations, however support for these recommendations were not unanimous (see supplementary Technical Report).

1.10 Obstructive sleep apnea

Are women with PCOS at increased risk for sleep apnea and what is the method/tool most effective to screen for sleep apnea in PCOS?

Clinical need for the question

Obstructive sleep apnea (OSA) is characterised by repetitive occlusions of the upper airway during sleep with futile ventilatory efforts, oxygen desaturations, sleep arousal and the resumption of ventilation, fragmenting sleep and causing daytime sleepiness. OSA appears more common in PCOS and in obesity, a common corollary of PCOS. OSA prevalence among general adult populations varies across cohorts and is between 9 - 38% [154], with half being minimally symptomatic. Unlike conditions such as hypertension and diabetes where clinical sequelae are measurable at a particular cut off point that inform treatment decisions, there is no established cut off point at which OSA warrants treatment. Treatment process describes a personalised care plan that factors in symptomatology and disruptive impact of associated snoring. Although not well quantified, the potential long term health sequelae still remain an important consideration in the treatment decision and treatment is usually offered routinely to severe cases [155]. Addressing the public health implications of OSA are challenged by the magnitude of its prevalence, the complexity of the diagnostic process as well as the suboptimal effectiveness of device-based treatments such as continuous positive airway pressure (CPAP).

Summary of narrative review evidence

A systematic review was not conducted to answer this question and this was reviewed narratively based on clinical expertise. Randomised controlled trials (RCTs) demonstrate benefits for symptoms, quality of life, mood and productivity [156]. Observational trials link OSA to adverse cardiovascular outcomes and death [157] and surrogate outcomes may improve with treatment [158]. Relationships to diabetes and glycaemic response to treatment remain controversial [159-163], whilst large RCTs have failed to show CVD benefits of OSA treatment [156, 164, 165]. Clinically, OSA screening is currently warranted in those with symptoms, where treatment benefit has been demonstrated in the general population [166]. In PCOS, several studies demonstrate high rates of OSA [167-170] and with matched controls [167], the high prevalence of OSA was not explained by obesity. Hyperandrogenism may contribute to OSA [171] and there are links to metabolic syndrome [172, 173], although treatment studies in PCOS are very limited [172].

Despite poor quality evidence and the current lack of rationale for screening and treatment of OSA based on metabolic risk, screening for OSA has been advocated in PCOS [174]. In the setting of current evidence, clinical screening for those women with symptoms is justified consistent with recommendations in the general population, with validated tools available [175, 176] including the **Berlin Questionnaire** which does not include age criteria and may be more applicable here (**Appendix IV**), although none of these are validated in young women with and without PCOS. A positive screen cannot guide treatment and further experiences assessment is required through a detailed history. Overall the most compelling case for treating OSA relates to the improving symptoms of non-restorative sleep, daytime fatigue and sleepiness.

Recommendations

- 1.10.1 CCR Screening should only be considered for OSA in PCOS to identify and alleviate related symptoms, such as snoring, waking unrefreshed from sleep, daytime sleepiness, and the potential for fatigue to contribute to mood disorders. Screening should not be considered with the intention of improving cardiometabolic risk, with inadequate evidence for metabolic benefits of OSA treatment in PCOS and in general populations. 
- 1.10.2 CCR A simple screening questionnaire, preferably the Berlin tool, could be applied and if positive, referral to a specialist considered. 
- 1.10.3 CPP A positive screen raises the likelihood of OSA, however it does not quantify symptom burden and alone does not justify treatment. If women with PCOS have OSA symptoms and a positive screen, consideration can be given to referral to a specialist centre for further evaluation.

Justification

Screening and identification of women with symptomatic OSA who may benefit from treatment appears warranted. Wide scale screening on the basis of unproven metabolic benefits of OSA treatment is not currently warranted. The resource implications of selective screening in symptomatic women may both reduce or increase resources (clinician time) depending on current practice. Availability of ambulatory or in laboratory polysomnography in conjunction with clinical follow-up of the results and treatment planning may not be universal.

1.11 Endometrial cancer

Are women with PCOS at increased risk of endometrial cancer and what is the method/tool most effective to screen for endometrial cancer in PCOS?

Clinical need for the question

PCOS has been associated with increased risk of endometrial cancer, yet the interplay is complex with inter-related comorbidities including obesity, and with potential influence from PCOS treatments. Pathophysiology is related to unopposed estrogen in the setting of anovulation and prevention is feasible. Overall given the prevalence and interrelated comorbidities between endometrial cancer and PCOS, this question was prioritised.

Summary of narrative review evidence

A systematic review was not conducted to answer this question and it was reviewed narratively based on clinical expertise and is summarised here. The risk of endometrial cancer has been shown to be between 2 - 6 times higher in women with PCOS [177], with most adenocarcinomas (> 95%) including Type I and Type II cancers [178, 179], with type I increased in PCOS [180, 181]. The increased prevalence of endometrial cancer in PCOS [182], is related to prolonged endometrial exposure to unopposed estrogen in anovulation. Additionally, endometrium in PCOS may exhibit progesterone resistance [183]. Associations between PCOS and endometrial cancer are complex and co-morbid conditions such as obesity, infertility, DM2 and metabolic syndrome are relevant, whilst PCOS treatment options may influence cancer risk [181, 183].

Three meta-analyses, with overlapping studies, report increased risk of endometrial cancer in PCOS [184-186]. All include estimates from analyses that did not take into account BMI, relevant in both PCOS and endometrial cancer [177] with studies limited by few exposed cases. Where BMI was considered, associations with PCOS and endometrial cancer are less consistent [181]. A cohort study reported an increased risk of endometrial cancer in PCOS compared to age-matched controls with OR of 5.3 (95% CI=?1.5–18.6) without adjustment for BMI and 6.1 (95% CI=?1.0–36.9) with adjustment [187], yet others report contrasting results on BMI [180]. Another group reported a higher OR in premenopausal women [188]. Differences relate to variable adjustment for confounders and study population [181], with endometrial thickness and age significant predictors [189, 190].

Regarding PCOS treatments, metformin has no association or a protective association with endometrial cancer [181]. Clomiphene studies are limited by power, but a small non-significant increased risk of endometrial cancer has been shown [191]. Letrozole, yet to be explored in relation to endometrial cancer, is used as an adjuvant treatment for hormone receptor positive postmenopausal breast cancer and may decrease hormonal related cancer risk [181]. Oral contraceptives reduce risk for endometrial cancer in general populations and effects may be enduring.

Routine screening for endometrial hyperplasia or cancer in PCOS is not warranted although endometrial surveillance by transvaginal ultrasound or endometrial biopsy is indicated for those women with PCOS who have thickened endometrium, prolonged amenorrhea, unopposed estrogen exposure or abnormal vaginal bleeding, based upon clinical suspicion [183].

Recommendations

- 1.11.1 CCR Health professionals and women with PCOS should be aware of a two to six-fold increased risk of endometrial cancer, which often presents before menopause; however absolute risk of endometrial cancer remains relatively low. 
- 1.11.2 CPP Health professionals require a low threshold for investigation of endometrial cancer in women with PCOS or a history of PCOS, with investigation by transvaginal ultrasound and/or endometrial biopsy recommended with persistent thickened endometrium and/or risk factors including prolonged amenorrhea, abnormal vaginal bleeding or excess weight. However, routine ultrasound screening of endometrial thickness in PCOS is not recommended.
- 1.11.3 CPP Optimal prevention for endometrial hyperplasia and endometrial cancer is not known. A pragmatic approach could include COCP or progestin therapy in those with cycles longer than 90 days.

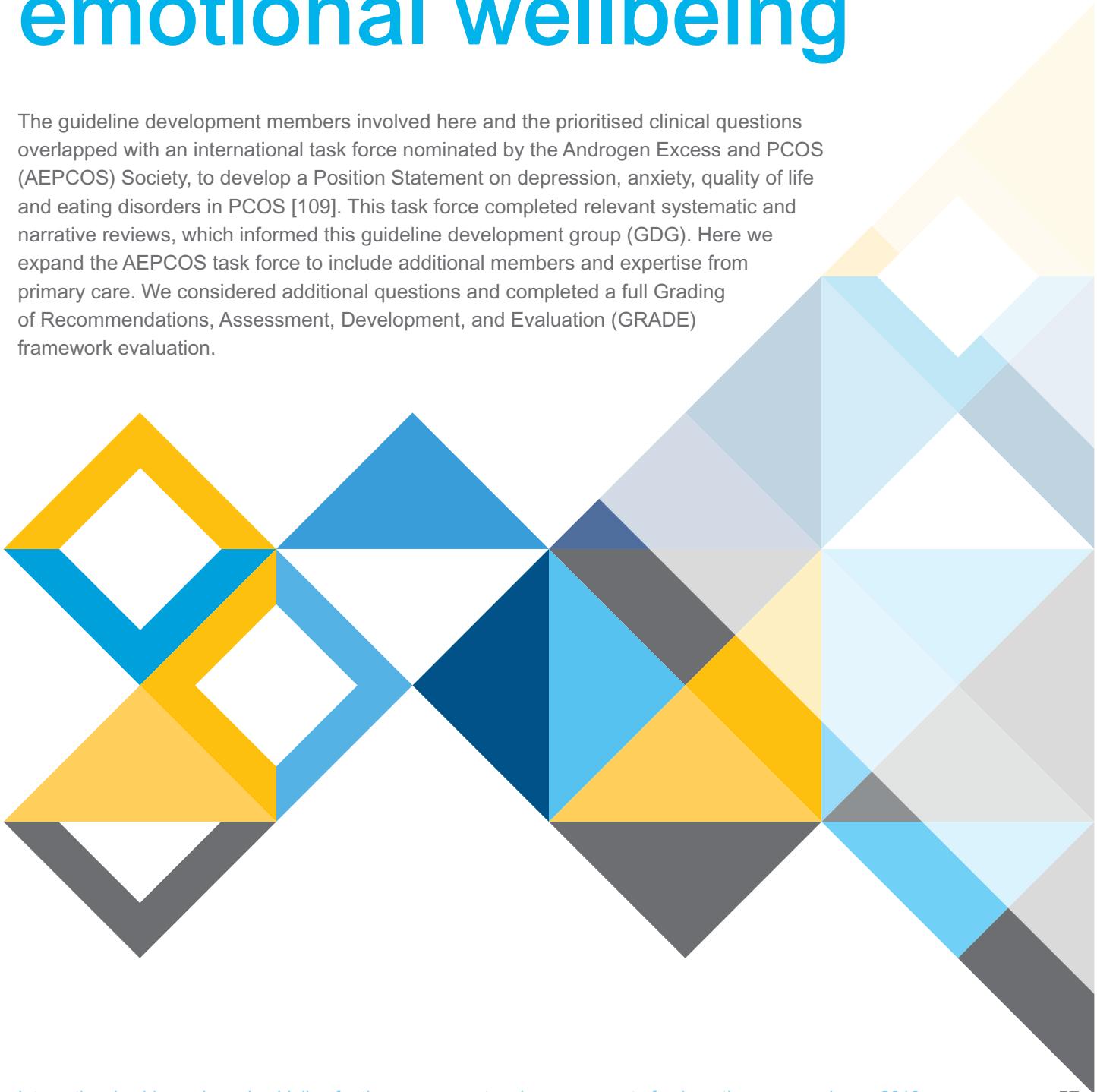
Justification

Associations between PCOS and endometrial cancer are complex, with many potential confounders. Women with PCOS appear to have an increased risk of endometrial cancer consistent with anovulation and increased prevalence of obesity. Routine screening for endometrial cancer in PCOS is not recommended, however vigilance and awareness of increased risk is important.

Chapter Two

Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing

The guideline development members involved here and the prioritised clinical questions overlapped with an international task force nominated by the Androgen Excess and PCOS (AEPCOS) Society, to develop a Position Statement on depression, anxiety, quality of life and eating disorders in PCOS [109]. This task force completed relevant systematic and narrative reviews, which informed this guideline development group (GDG). Here we expand the AEPCOS task force to include additional members and expertise from primary care. We considered additional questions and completed a full Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework evaluation.



2.1 Quality of life

In women with PCOS, what is the prevalence and severity of reduced quality of life and should quality of life be assessed as part of standard care?

In women with PCOS, what dimensions of quality of life are most affected?

In women with PCOS, what is the most effective tool/method to assess quality of life?

Clinical need for the questions

Health related quality of life (HRQoL) is a well-recognised and important health outcome, especially in chronic disease and relates to patient reported physical, social and emotional effects of a condition and its associated treatments [109]. Assessment is self-reported and can be measured through a variety of tools. Generic tools include the Short Form -36 (SF-36) and World Health Organisation (WHO) tools, yet these are not ideal for PCOS with a significant focus on mobility, impact on work, pain, environment and propensity to infective illnesses. They do not consider key dimensions of PCOS such as infertility and hirsutism and PCOS specific tools are now available. The polycystic ovary syndrome questionnaire (PCOSQ) has 26 items across emotions, body hair, weight, infertility and menstrual abnormalities and the modified polycystic ovary syndrome questionnaire (MPCOSQ) adds acne [109, 192]. These tools have been adapted and tested in different ethnic populations. The role of these tools in clinical care remains unclear and the key dimensions affecting quality of life (QoL) are controversial.

Summary of systematic review evidence

Meta-analysis of five studies using SF-36 and three studies using the WHO tool in adult women, all of which were low quality and low certainty, suggest that women with PCOS have lower quality of life compared to women without PCOS. Statistical heterogeneity was present in meta-analysis for six out of the ten domains in SF-36 and in one out of four domains in the WHO tool. These generic QoL tools are poorly tailored and include features unrelated to PCOS such as immobility, pain, risk of infections and environment with limited relevance in PCOS. However they are the only tools that can compare HRQoL across women with and without PCOS, with studies demonstrating reduced HRQoL scores in PCOS, compared to controls and normative population data, as summarised in the AEPCOS position statement [109].

Summary of narrative review evidence

PCOS specific tools have been developed, validated and applied across ethnic groups. The commonly used tools for screening women with PCOS are the PCOSQ scale with domains to assess emotions, body hair, weight, infertility difficulties and menstrual problems and the MPCOSQ which includes an acne domain [193, 194]. In PCOS, HRQoL occurs in the context of the multitude of clinical features and is affected by anxiety, poor body image and low self-esteem, depressive symptoms, delayed diagnosis and inadequate education and information provision by health professionals [7, 195]. A meta-analysis and recent update have showed that key domains were hirsutism, menstruation and infertility [196], yet this varied by population studied, life stage and cultural factors [109] and heterogeneity is to be expected.

In clinical care, the key consideration was determined by the GDG to be the self-reported priority of specific PCOS dimensions in an individual woman at a given life stage. Addressing patient-reported and prioritised outcomes is important in improving QoL and optimising health in chronic conditions. If patient-reported priorities and outcomes were recognised as fundamental in care, this was seen as a substantive step forward in addressing key gaps in care and dissatisfaction expressed by women with PCOS. It is important to consider QoL in PCOS research and may be useful to consider applying relevant tools in clinical care to highlight patient priorities, with the caveat that clinically meaningful differences in scores need to be determined.

Recommendations

- 2.1.1 CCR Health professionals and women should be aware of the adverse impact of PCOS on quality of life. 
- 2.1.2 CCR Health professionals should capture and consider perceptions of symptoms, impact on quality of life and personal priorities for care to improve patient outcomes. 
- 2.1.3 CPP The PCOS quality of life tool (PCOSQ), or the modified PCOSQ, may be useful clinically to highlight PCOS features causing greatest distress, and to evaluate treatment outcomes on women's subjective PCOS health concerns.
-

Justification

HRQoL is reduced in PCOS. This diverse condition varies across the lifespan, phenotypes and is influenced by cultural factors which all impact on HRQoL. Key gaps in patient satisfaction have been demonstrated along with limited capture of patient priorities to guide management. There is a need to determine clinical meaningful differences in QoL scores and to validate the tools for change over time, based on a range of evidence sources. However, the expert group including patient perspectives considered it important to formally measure QoL with condition-specific tools in research settings. In the clinical setting, the role of formal screening is less clear, however it may highlight clinical priorities for women. Primarily, health professionals should be armed with awareness of the impact of PCOS on QoL and should capture patient priorities to deliver meaningful outcomes when partnering with women with PCOS in their care.

2.2 Depressive and anxiety symptoms, screening and treatment

In women with PCOS, what is the prevalence and severity of depressive and anxiety symptoms and should they be screened?

In women with PCOS, what is the most effective tool/method to assess depression and/or anxiety?

Clinical need for the questions

The prevalence and severity of depressive and anxiety symptoms are increased in PCOS. Psychological conditions impact on QoL and are likely to influence engagement in lifestyle interventions and self-management in PCOS. Hormonal medications can influence mood in the general population, although literature in PCOS is limited [197]. Effective, readily available screening tools are available for clinical practice, yet uptake and recognition of psychological symptoms in PCOS appears limited internationally. A large international survey has shown that most women report psychological issues are under-recognised [13] and less than 5% are satisfied with emotional support and counselling. Given the prevalence and severity of depressive and anxiety symptoms and the dissatisfaction expressed by women in this area, these clinical questions were prioritised.

Summary of systematic review evidence

A systematic review was not completed for the first question and the review for the second question did not identify any evidence in women with PCOS to answer this question.

Summary of narrative review evidence

These areas were reviewed narratively, based on clinical expertise.

Depression: Depressive symptoms and depression are more common in PCOS [109], with daily fatigue, sleep disturbances and diminished interest prominent [195]. A meta-analysis of 10 studies reported increased depressive symptom scores in 44% with PCOS versus 17% in controls (OR: 4.03, 95% CI: 2.96-5.5, p<0.01) [198], which persisted in BMI matched studies. A meta-analysis of 910 women with PCOS and 1347 controls reported higher depression scores in PCOS [199], although these may not have been clinically significant. A meta-analysis of 26 studies including 4716 participants from 14 countries [200], noted scores were not in a clinically significant range in half of studies, and others were consistent with mild depression. A recent meta-analysis of 23 studies with rigorous inclusion criteria including physician diagnosis of PCOS [201], showed increased moderate/severe depressive symptoms (OR4.18, 95% CI: 2.68-6.52) with a prevalence of depression of 36.6% in PCOS (IQR: 22.3, 50.0%) and 14.2% in controls (IQR: 10.7, 22.2%), independent of obesity and seen in both clinic and community recruits. Limitations included relatively small sample sizes and limited formal diagnosis of depression on clinical assessment. Also, a large population-based registry study [202] showing an increased adjusted risk of depression in PCOS and a large hospital database study documented depression in PCOS (9.8%), compared to those without a recorded diagnosis of PCOS (4.6%) [203]. Overall, women with PCOS have a higher prevalence of depressive symptoms and depression, independent of obesity.

Anxiety: Anxiety symptoms are increased in PCOS [109]. Meta-analyses of six studies and another of eleven studies reported higher anxiety scores in PCOS compared to controls [199, 200]. Another of four studies reported a sevenfold increase in abnormal anxiety scores in PCOS [204], however, heterogeneity existed in all meta-analysis. A recent rigorous meta-analysis of ten studies [201] showed increased moderate/severe anxiety symptoms in PCOS (OR: 5.38; 95% CI: 2.28, 12.67), with a prevalence of 41.9% (IQR: 13.6, 52.0%) in PCOS and 8.5% (IQR: 3.3, 12.0%) in controls. A large population-based study of 24385 women with PCOS matched for sex, age and country of birth to ten controls, showed increased anxiety disorder (OR 1.37, CI: 1.32, 1.43) [202]. A large hospital database showed anxiety in PCOS at 14%, compared to 5.9% of those without a diagnosis of PCOS [203]. Collectively, these studies indicate increased anxiety symptoms and anxiety disorders in women with PCOS, across diverse ethnic groups.

The cause of depressive and anxiety symptoms in PCOS are not fully elucidated [109] as are the effects of PCOS treatments. While acne, hirsutism, infertility and increased BMI have been linked to increased mood and distress, the evidence is inconsistent [205-208]. Further potential contributors to depression and anxiety in PCOS include the chronic [209-213], complex and frustrating nature of PCOS [214, 215]. Chronic conditions can cause related emotional distress, and treatment of the underlying condition may improve these, although few PCOS studies have explored this. In PCOS, consideration should be given to the individual underlying concerns for each woman to optimise impact on emotional wellbeing.

Screening for depressive and anxiety symptoms:

Given the lack of evidence to address this question in PCOS on systematic review, key relevant sources of evidence-based information were sourced for the general population, and with multidisciplinary GDG expertise and consumer perspectives, informed the recommendations. These included:

- The treatment of depression in adults with chronic physical health problems, NICE, 2009 [216].
- Common mental health problems: identification and pathways to care, NICE, 2011 [217].
- Antenatal and postnatal mental health: clinical management and service guidance, NICE, 2014 [218].
- Screening for Depression in Adults: US Preventive Services Task Force Recommendations, 2016 [219].
- Screening for Depression in Children and Adolescents: US Preventive Services Task Force Recommendations 2016 [220].
- Screening for and Treatment of Suicide Risk Relevant to Primary Care: A Systematic Review for the US Preventive Services Task Force, 2014 [221].
- Royal Australian NZ College of Psychiatrists Clinical Practice Guidelines for Mood Disorders 2015 [222].
- Principles of Practice in Mental Health Assessment with Aboriginal Australians. In Working Together: Aboriginal and Torres Strait Islander mental health and wellbeing principles and practice, 2014 [223].

National US and UK guidelines recommend routine screening for common mental health disorders for all adults and adolescents, particularly with chronic physical health problems and in the perinatal period [216-220]. US guidelines conclude moderate benefit of depression screening in the general adult population [219]. Australian guidelines for the general population do not recommend routine screening, except during the perinatal period [222, 224].

Overall in PCOS, where prevalence and severity is higher, the GDG deemed that it was the responsibility of all health professionals partnering with women with PCOS to understand the increased prevalence of depressive and anxiety symptoms and the impact of PCOS on psychological health, and routine screening for depressive and anxiety symptoms was recommended. Reciprocally, screening may increase distress with another potentially stigmatising diagnosis. Evidence in diabetes suggests that depression and anxiety are over-estimated by screening questionnaires and that diabetes-specific distress explains considerable variance in these symptom scores. This would suggest a need to be sensitive to the distress associated with PCOS and emphasises the need to avoid over-diagnosis of anxiety and depression. While the optimal timing and interval for screening is unknown, a pragmatic approach may be to screen all women and adolescents at the time of PCOS diagnosis. Frequency of screening is unclear and some assessment at the time of regular physical health checks for PCOS may be warranted. Use of clinical judgement considering an individual woman's risk factors, can inform if additional screening appears warranted. Screening during the antenatal and postnatal periods in PCOS is aligned with recommendations in the general population.

Recommendations

2.2.1	CCR	Health professionals should be aware that in PCOS, there is a high prevalence of moderate to severe anxiety and depressive symptoms in adults; and a likely increased prevalence in adolescents.	
2.2.2	CCR	Anxiety and depressive symptoms should be routinely screened in all adolescents and women with PCOS at diagnosis. If the screen for these symptoms and/or other aspects of emotional wellbeing is positive, further assessment and/or referral for assessment and treatment should be completed by suitably qualified health professionals, informed by regional guidelines.	
2.2.3	CCR	If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered in PCOS, informed by regional clinical practice guidelines.	
2.2.4	CPP	The optimal interval for anxiety and depressive symptom screening is not known. A pragmatic approach could include repeat screening using clinical judgment, considering risk factors, comorbidities and life events.	
2.2.5	CPP	Assessment of anxiety and or depressive symptoms involves assessment of risk factors, symptoms and severity. Symptoms can be screened according to regional guidelines, or by using the following stepped approach: Step 1: Initial questions could include: <ul style="list-style-type: none">● Over the last 2 weeks, how often have you been bothered by the following problems?● feeling down, depressed, or hopeless?● little interest or pleasure in doing things?● feeling nervous, anxious or on edge?● not being able to stop or control worrying? Step 2: If any of the responses are positive, further screening should involve: <ul style="list-style-type: none">● assessment of risk factors and symptoms using age, culturally and regionally appropriate tools, such as the Patient Health Questionnaire (PHQ) or the Generalised Anxiety Disorder Scale (GAD7) and/or refer to an appropriate professional for further assessment.	
2.2.6	CPP	Where pharmacological treatment for anxiety and depression is offered in PCOS, the following need consideration: <ul style="list-style-type: none">● Caution is needed to avoid inappropriate treatment with antidepressants or anxiolytics. Where mental health disorders are clearly documented and persistent, or if suicidal symptoms are present, treatment of depression or anxiety need to be informed by clinical regional practice guidelines.● Use of agents that exacerbate PCOS symptoms, including weight gain, need careful consideration.	
2.2.7	CPP	Factors including obesity, infertility, hirsutism need consideration along with use of hormonal medications in PCOS, as they may independently exacerbate depressive and anxiety symptoms and other aspects of emotional wellbeing.	

Justification

Women with PCOS are at increased risk of depressive and anxiety symptoms compared to women without PCOS. Moderate to severe symptoms and clinically diagnosed disorders are increased. These symptoms may be related to the distress associated with PCOS. In the context of PCOS, identification of psychological features and mental health disorders is crucial to address gaps in care identified by affected women, to improve wellbeing and QoL, facilitate appropriate referral and care and optimise engagement with lifestyle and preventive strategies. However, over-diagnosis of depression and anxiety should also be avoided. Life stage, culture and preferred language should be considered. It is not always usual practice to screen women with PCOS for depressive and/or anxiety symptoms and this will change practice. Time, resources and access issues were considered, yet on balance screening is recommended, aligned with international, broadly validated screening approaches in general populations.

2.3 Psychosexual function

In women with PCOS, what is the prevalence and severity of psychosexual dysfunction and should they be screened?

In women with PCOS, what is the most effective tool/method to assess psychosexual dysfunction?

Clinical need for the questions

Psychosexual dysfunction refers to sexual problems or difficulties that have a psychological origin based in cognitions and/or emotions such as depression, low self-esteem and negative body image [225] and both risk factors for and prevalence of psychosexual dysfunction appear increased in PCOS. This may be an important issue for the individual woman and may impact on QoL and relationships. Therapies used in PCOS, including hormonal contraceptives and ovulation induction agents, can affect psychosexual function in the general population although data in PCOS is limited [226]. Hence, clinicians should be aware of potential psychosexual dysfunction in PCOS and screening and assessment should be considered. In this setting, guidance on the most effective way to assess psychosexual dysfunction is needed.

Summary of narrative review evidence

A systematic review was not conducted to answer these questions and they were reviewed narratively based on clinical expertise. The prevalence of psychosexual dysfunction varies from 13.3% to 62.5% in PCOS [227-230]. It appears that women with PCOS suffer from greater psychosexual dysfunction than women in the general population in most studies [207, 231-237]. Whilst there is limited quality research in this area, studies [207, 233, 234] do show a correlation between PCOS and reduced QoL, sexual satisfaction and feminine identity. A recent systematic review on psychosexual dysfunction in PCOS found that a satisfying sex life is important for women with PCOS, however, in women with PCOS sexual function, as well as feelings of sexual attractiveness, are compromised [238]. Women with PCOS judge their appearance and body hair to negatively impact on their sexuality and their ability to engage in relationships. This remains controversial with some studies suggesting the prevalence of psychosexual dysfunction in PCOS group is similar to the general population [229, 230]. A recent systematic review by GDG members identified 18 relevant studies using validated sexual function questionnaires and Visual Analogue Scales (VASs). Small, yet significant differences were detected in sexual function subscales, arousal, lubrication, satisfaction and orgasm were all impaired in PCOS compared to women without PCOS. Large effect sizes were evident for body hair impact, social impact of appearance, sexual attractiveness and satisfaction with sex life was impaired, whereas the importance of sex was similar to that of non-PCOS women. Physical PCOS symptoms such as hirsutism, obesity, menstrual irregularity and infertility may cause loss of feminine identity and a feeling of being unattractive which may impact on sexuality [207, 233, 235]. Women with PCOS also report less sexual satisfaction and lower sexual self-worth than women without PCOS and sexual dysfunction impacts more on relationships in women with PCOS [232]. In considering screening tools the [Female Sexual Function Index](#) (FSFI) [229] and [Arizona Sexual Experience Scale](#) (ASEX) [230] are commonly used to evaluate psychosexual dysfunction.

Recommendations

- 2.3.1 CCR All health professionals should be aware of the increased prevalence of psychosexual dysfunction and should consider exploring how features of PCOS, including hirsutism and body image, impact on sex life and relationships in PCOS. 
- 2.3.2 CCR If psychosexual dysfunction is suspected, tools such as the Female Sexual Function Index can be considered. 
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Justification

As prevalence and severity of psychosexual dysfunction appears increased in women with PCOS, screening and assessment should be considered in sexually active women to facilitate appropriate intervention aiming to optimise sexual function, limit the social impact of PCOS and improve QoL. It is not usual practice to screen and assess women with PCOS for psychosexual dysfunction. Sensitivities and cultural challenges around psychosexual dysfunction from the woman's and health professional perspectives may present barriers to implementation. However, the international, multi-disciplinary GDG, including consumers, agreed that despite implementation challenges, the recommendation was warranted on the basis of prevalence data from a recent systematic review and on potential impact.

2.4 Body image

In women with PCOS, what is the prevalence and severity of body image distress and should they be screened?

In women with PCOS, what is the most effective tool/method to assess body image distress?

Clinical need for the questions

Body image is complex and is influenced by many factors. Body image is defined here as the way a woman may feel, think about and view their body including their appearance. Relevant physical (excess weight and hirsutism), psychological (self-esteem) and sociocultural factors influence body image. Assessment of body image considers body dissatisfaction, disordered eating, body size estimation and weight. Most women from the general population are dissatisfied with their body, yet negative body image appears more prevalent in PCOS and impacts on thoughts and feelings of health, appearance, QoL, mood and physical fitness. In this context, body image should be considered in PCOS. Recommendations for screening and assessment that are easy to use and widely applicable are needed and if identified, addressing negative body and associated mood disorders is important to improve emotional wellbeing and QoL in PCOS.

Summary of narrative review evidence

A systematic review was not conducted to answer these questions; therefore, the literature was reviewed narratively based on clinical expertise. Women with PCOS, compared with controls, had a negative body image on the validated Multidimensional Body-Self Relations Questionnaire (MBSRQ) [7]. Evidence is conflicting however, with some case-control studies not finding differences in body image satisfaction and self-esteem compared to women without PCOS [237, 239, 240]. Women with PCOS feel less physically attractive, healthy or physically fit and are less satisfied with their body size and appearance [241], and this negative body image predicts both depression and anxiety [242]. Infertile women with PCOS have lower body satisfaction than non-infertile women with PCOS [243]. Hirsute women experienced lower self-esteem than non-hirsute women [243]. Overall, PCOS features, in particular hirsutism and increased weight, impact negatively on body image and QoL [242, 244], and negative body image is strongly associated with depression in women with PCOS [245, 246], even after controlling for weight [8, 246].

We did not identify any evidence in women with PCOS to address the question on screening tools and therefore, a clinical consensus recommendation has been made based on the expertise of the multidisciplinary GDG and key relevant sources of evidence-based information for the general population. Assessment of body image includes measures of body dissatisfaction and disordered eating [247], body size estimation [248] and weight [249, 250]. The National Institute for Health and Care Excellence (NICE) Guideline 31 – Obsessive Compulsive Disorder: Core interventions in the treatment of obsessive compulsive disorder and body dysmorphic disorder [251] and the Australian Medical Association Position Statement: Body Image and Health 2002 [252] informed the recommendations provided. The Female Sexual Function Index tool is the most commonly used in PCOS studies of psychosexual dysfunction.

Recommendations

2.4.1 CCR Health professionals and women should be aware that features of PCOS can impact on body image.



2.4.2 CPP Negative body image, can be screened according to regional guidelines or by using the following stepped approach:

Step 1: Initial questions could include:

- Do you worry a lot about the way you look and wish you could think about it less?
- On a typical day, do you spend more than 1 hour per day worrying about your appearance? (More than 1 hour a day is considered excessive)
- What specific concerns do you have about your appearance?
- What effect does it have on your life?
- Does it make it hard to do your work or be with your friends and family?

Step 2: If an issue is identified, health professionals could further assess by:

- Identifying any focus of concern of the patient and respond appropriately
- Assessing the level of depression and/or anxiety
- Identifying distortion of body image or disordered eating

Justification

Given that negative body image in PCOS appears to be increased and may result in increased depression and poorer HRQoL, body image in women with PCOS should be considered as part of a comprehensive assessment and management plan. Approaches for screening and assessment that are easy to use and widely applicable are needed. Detection of negative body image provides the opportunity to address both psychological aspects such as self-esteem and self-acceptance as well as working on the physical aspects of the condition such as hirsutism, overweight and acne, if appropriate. It was acknowledged that it is not usual practice to screen PCOS women for negative body image, and an individualised approach focusing on individual priorities is needed. Screening may have resource implications, including length of consultation. Available body image scales can reduce time required in assessment and should also be considered in all clinical, health services and population health research in PCOS.

2.5 Eating disorders and disordered eating

In women with PCOS, what is the prevalence and severity of disordered eating, and should they be screened?

In women with PCOS, what is the most effective tool/method to assess disordered eating?

Clinical need for the questions

Diagnosable eating disorders include anorexia nervosa; bulimia nervosa, binge-eating disorder, other specified feeding or eating disorders, and unspecified feeding or eating disorders that do not meet the full criteria for any of the eating disorder diagnoses. Disordered eating refers to eating and weight related symptoms and can include behavioural (e.g. bingeing, excessive restriction), cognitive (e.g. excessive dietary restraint, negative body image) and emotional factors. Disordered eating affects health and wellbeing and capacity to participate in and contribute to society. Many of those affected are not identified in primary care. Risk factors and prevalence appears increased in PCOS [109]. Increased awareness of these conditions, and effective assessment when clinically suspected, is important as it should increase recognition and management of eating disorders and disordered eating, thereby improving the psychological functioning and overall QoL in women with PCOS and reducing associated health risks.

Summary of narrative review evidence

A systematic review was not conducted to answer these questions, which were reviewed narratively based on clinical expertise. The prevalence of disordered eating is far higher than the prevalence of eating disorders; many women who do not meet full criteria for an eating disorder experience disordered eating and associated distress [253], including binge eating, purging, and strict dieting or fasting. There is a lack of good evidence regarding the prevalence of eating disorders and disordered eating in women with PCOS, although available data suggests a higher prevalence than in the general community, on clinical interview [254] of any eating disorder (21% vs 4%) but not bulimia nervosa (12% vs 4%). A registry study of women with PCOS (n=24 385) and matched controls reported increased bulimia nervosa, but not anorexia nervosa [202]. Surveys in PCOS show mixed results across the different disorders [195, 255, 256], but overall suggest an increased prevalence of eating disorders and disordered eating. Women with PCOS also have more identified risk factors for eating disorders [257] across obesity, depression, anxiety, self-esteem and poor body image [195, 240, 256].

The apparent higher prevalence of eating disorders and disordered eating in women with PCOS, and the negative biopsychosocial consequences of eating disorders and disordered eating, highlight the need to raise awareness of these conditions. The NICE recommendations for Eating Disorders: Recognition and Treatment [258] suggest clinicians think about the possibility of an eating disorder in individuals with a range of symptoms relevant to PCOS. Many women with eating disorders are undiagnosed and unaware that they have an eating disorder, or that their eating and weight-related thoughts and behaviours are unusual and/or cause distress. Unfortunately, there are not standardised, widely implemented processes for screening and assessment and the breadth and complexity of these conditions makes simple screening and assessment difficult. This review highlighted the limited, and low-quality evidence regarding eating disorder screening tools and it was concluded that none of the tools are effective for identifying eating disorders when used in isolation. Instead, the clinician should use their judgement based on a full diagnostic interview. The SCOFF tool is the most commonly used screening tool in adults, takes only a few minutes to administer [258] and is an option. Along with more sensitive tools it is outlined in translation resources (under development). The risk of false positives (and hence inappropriate treatment) was noted with these tools [258] and they cannot replace clinical interview.

Recommendations

- 2.5.1 CCR All health professionals and women should be aware of the increased prevalence of eating disorders and disordered eating associated with PCOS. 
- 2.5.2 CCR If eating disorders and disordered eating are suspected, further assessment, referral and treatment, including psychological therapy, could be offered by appropriately trained health professionals, informed by regional clinical practice guidelines. 
- 2.5.3 CPP Eating disorders and disordered eating can be screened using the following stepped approach.
- Step 1:** The SCOFF (Sick, Control, One stone, Fat, Food) screening tool can be used or initial screening questions can include:
- Does your weight affect the way you feel about yourself?
 - Are you satisfied with your eating patterns?
- Step 2:** If the SCOFF tool or any of these questions are positive, further screening should involve:
- assessment of risk factors and symptoms using age, culturally and regionally appropriate tools;
 - referral to an appropriate health professional for further mental health assessment and diagnostic interview. If this is not the patient's usual healthcare provider, inform the primary care physician.
-

Justification

The increased risk factors for and apparent increased prevalence of eating disorders and disordered eating in women with PCOS, and the negative biopsychosocial consequences of these disorders, highlight the need for greater awareness in women with PCOS. Many women with eating disorders are undiagnosed and unaware of the presence of an eating disorder. Likewise, many women with disordered eating are unaware that their eating and weight-related thoughts and behaviours are unusual and/or causing distress. Therefore, raised awareness and consideration of assessment and diagnosis are important. It was acknowledged that screening is challenging given the breadth and complexity of these conditions and false positives with current tools are noted. Resource and time implications were also considered.

2.6 Information resources, models of care, cultural and linguistic considerations

What is the effectiveness of different models of care compared to usual care?

What are the information, resource and education needs of women and healthcare providers regarding PCOS?

Access to culturally and linguistically diverse appropriate care.

Clinical need for the questions

PCOS can involve diverse clinical features that change across the life course. For models of care, women affected by PCOS may consult multiple health professionals such as a general practitioner/primary care physician, gynaecologist, endocrinologist, infertility specialist, dietitian, dermatologist, psychologist and/or an exercise physiologist. Multidisciplinary care is increasingly required in chronic disease management, with improvements in health related outcomes [259], yet presenting increased complexity, compartmentalisation and communication challenges. An interdisciplinary care model involves “the collaboration between a woman with PCOS and a care team who have shared goals for total wellbeing” and is founded on patient-centred care principles and is well suited to the PCOS context.

In PCOS, there is a well-demonstrated gap and compelling need for improved information provision [13, 260, 261]. Women internationally report inadequate information, delayed diagnosis and variation in care. Provision of information also improves satisfaction with care and patient experience. Culturally and linguistically appropriate care and information are also a key consideration in PCOS. PCOS is a common disorder worldwide and given the significant psychosocial impacts of PCOS, and the cultural differences in perception of features such as hirsutism, infertility and other complications, cultural awareness is important. The majority of consumer information is in English, presenting language barriers for immigrant populations and for women living in countries where English is not the first language. Given current dissatisfaction in care and information provision noted by women internationally, the evidence that health professionals do not adequately address the diverse features of PCOS and the cultural and linguistic considerations in PCOS care, these clinical questions were prioritised.

Summary of systematic review evidence

We did not identify any evidence in our patient population to answer the question about models of care.

Summary of narrative review evidence

Narrative reviews were completed to address all three questions. Four studies described models of care across barriers, enablers and satisfaction of patients and health professionals and benefits of information and socio-emotional support. Evaluation of a multidisciplinary PCOS service showed successful evidence-based care, emotional screening and lifestyle management [262] and was greatly valued by patients and health professionals. Barriers included staffing limitations and turnover, funding challenges and system issues [262]. Support groups have been explored [263, 264] including online peer-support in the UK [263]. Connecting with people who understand, access to information and advice, building confidence in interaction with health care professionals, help with treatment-related decision-making and improvement in adjustment and management were reported. Disempowering experiences included “reading about the negative experiences of others” and “feeling like an outsider”. A nurse-led UK peer support group increased participation, reduced isolation and improved empowerment, provided relevant information and positively affected self-management [264]. A Canadian educational program [265] increased motivation to implement preventive strategies, enhanced satisfaction with health care professional engagement and empowered women to participate in self-management.

A systematic search was completed on i) women’s experiences of PCOS care and PCOS information ii) women’s perceived needs for PCOS care and information, iii) health care providers’ delivery of PCOS care and information, iv) health care providers’ perceived needs for PCOS information, education programs, or professional development. Comprehensive, accurate, personalised information is important in PCOS as a chronic condition requiring self-management [261], enables informed decisions, optimises prevention and is associated with better quality of life [13, 266]. Women often see multiple health professionals before diagnosis [13, 260, 267, 268], flag symptoms multiple times [214, 269] and experience delays in diagnosis [13, 214, 260, 267]. Receiving a diagnosis is important to women [214]; yet may lead to anxiety and frustration without adequate information [267-269]. Reproductive and metabolic features are concerns [13, 270], psychological features are under-appreciated [269], and women report that primary concerns go unrecognised [267]. Specific and practical information is needed, yet often not provided, or does not meet needs [13, 214, 260, 268, 269, 271, 272]. Women’s initial source of information is their healthcare provider [214, 269, 270], yet if inadequate, inaccurate or conflicting, frustration is reported [13, 271]. The internet is accessed yet quality is often poor [214, 269, 271] or conflicted by commercial interests [271], impacting patient experience [267]. Overall, PCOS information needs to be comprehensive, evidence-based and inclusive of the bio-psycho-social dimensions of the condition and care needs to prioritise women’s personal concerns [13, 260, 267, 268, 273]. Women with PCOS are best supported by a range of information resources: respectful and empathetic healthcare providers, websites, leaflets and support groups [214, 264, 265]. Health professional research suggests variation in care by specialty including across rates of undiagnosed PCOS [274] and investigations [275]. Women with PCOS infrequently report seeing a dietitian or receiving dietary advice [276]. Educational programs improve knowledge and confidence in PCOS among doctors [277], with greater activity needed to address gaps identified by women with PCOS.

Regarding culturally and linguistically competent medical care in PCOS, there are few relevant studies. Adaptation of educational resources and longer consultation times may be required [278] and family rather than individual consultations may be relevant. Cultural barriers can include low health literacy, high level of tolerance to problems and unwillingness to see a male physician [278]. Many of the studies in information and care needs and preferences in PCOS are limited to English-speaking women and do not explore cultural issues.

Recommendations

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- 2.6.1 CCR Information and education resources for women with PCOS should be culturally appropriate, tailored and high-quality, should use a respectful and empathetic approach, and promote self-care and highlight peer support groups. 
- 2.6.2 CCR Information and education resources for healthcare professionals should promote the recommended diagnostic criteria, appropriate screening for comorbidities and effective lifestyle and pharmacological management. 
- 2.6.3 CCR PCOS information should be comprehensive, evidence-based and inclusive of the biopsychosocial dimensions of PCOS across the life-span. 
- 2.6.4 CCR Women's needs, communication preferences, beliefs and culture should be considered and addressed through provision of culturally and linguistically appropriate co-designed resources and care. 
- 2.6.5 CCR Interdisciplinary care needs to be considered for those with PCOS where appropriate and available. Primary care is generally well placed to diagnose, screen and coordinate interdisciplinary care. 
- 2.6.6 CCR Care needs to be person centred, address women's priorities and be provided in partnership with those with PCOS and where appropriate, their families. 
- 2.6.7 CPP Guideline dissemination and translation including multimodal education tools and resources is important, with consultation and engagement with stakeholders internationally.
-

Justification

Evidence specific to PCOS models of care remains limited, especially for adolescents transitioning from paediatric to adult care. However, existing evidence suggests integrated multidisciplinary services, support groups and nurse-led education can address identified gaps, increase understanding of PCOS and improve lifestyle change whether online, or nurse-led. New models of care should follow best practice and be co-designed with both women and health professionals. Key gaps in information provision need to be addressed through multi-faceted resources: health professionals, websites, written information and support groups with more comprehensive, evidence-based information that covers diverse PCOS features and prioritises women's personal concerns. Needs differ by individual and life stage and diagnosis is a time of greater need. Cultural influences need to be considered in PCOS in the context of both care and information needs. Culturally appropriate care involves more than linguistic considerations and is just as important for women who speak English but are not of the cultural majority.

Chapter Three

Lifestyle



3.1 Effectiveness of lifestyle interventions

In women with PCOS, are lifestyle interventions (combined compared to minimal or nothing) effective for improving weight loss, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

Clinical need for the question

Rates of weight gain and prevalence of excess weight are increased in adolescents and women with PCOS. The potent combination of excess weight and PCOS is adversely affecting reproductive, metabolic and psychological health, presenting a major public health challenge mandating both prevention and treatment. Insulin resistance affects 75% of lean women and 95% of overweight women [279]. It is independently exacerbated by excess weight [142, 280], increasing prevalence and severity of metabolic, reproductive and psychological features of PCOS [11, 281-283]. Benefits from lifestyle intervention and weight loss have been demonstrated in women with PCOS [284-287] and healthy lifestyle is important in preventing excess weight gain in PCOS and can offer benefits even without weight loss [288-292]. Women with PCOS internationally report that excess weight causes significant distress and concern and that there is inadequate information and support around lifestyle change [13]. Weight was also a highly ranked, prioritised outcome by both health professionals and women during the guideline development process. Overall, in women with PCOS and excess weight, lifestyle interventions which reduced weight by as little as 5% of total body weight have been shown to have health metabolic, reproductive and psychological benefits [284-287, 293-312]. Given the uncertainty on effectiveness and optimal components of lifestyle intervention in PCOS, underpinned by the generally small and uncontrolled trials, variable outcomes and populations, this clinical question was prioritised.

Summary of systematic review evidence

One high quality systematic review with a low risk of bias was identified to answer this question. The systematic review appraised six randomised controlled trials (RCTs) (low to moderate quality and moderate to high risk of bias) for the effectiveness of lifestyle treatment compared to minimal treatment in improving reproductive, metabolic, anthropometric and quality of life (QoL) factors in women with PCOS [313]. Due to the inconsistencies and methodological weaknesses of included studies, caution is recommended when interpreting the combined meta-analyses and results of the systematic review. There were three studies that used exercise and three that used combined lifestyle modification programmes (including diet, exercise and behaviour), with the outcome measurements reported at various times (12, 16, 24, and 48 weeks). Lifestyle intervention was better than minimal treatment for total testosterone (mean difference (MD) -0.27 nmol/L [-0.46 to -0.09] p=0.004), hirsutism by Ferriman-Gallwey score (MD -1.19 [-2.35 to -0.03] p=0.04), weight (MD -3.47 kg [-4.94 to -2.00] p<0.00001), waist circumference (MD -1.95 cm [-3.34 to -0.57] p=0.006), waist-hip-ratio (MD -0.04 [-0.07 to -0.00] p=0.02), fasting insulin (MD -2.02 µU/mL [-3.28 to -0.77] p=0.002) and oral glucose tolerance test insulin (standardised mean difference -1.32 [-1.73 to -0.92] p<0.00001) and percent weight change (MD -7.00% [-10.1 to -3.90] p<0.00001). There was no difference between the two interventions for body mass index (BMI), free androgen index (FAI), sex hormone-binding globulin (SHBG), glucose or lipids. QoL, patient satisfaction and acne were not reported. None of the studies addressed fertility outcomes such as pregnancy, live birth and miscarriage. While some studies reported on menstrual regularity and ovulation, the findings were reported in a variety of ways and it was not possible to estimate the overall effects of lifestyle on these outcomes.

Recommendations

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- 3.1.1 CCR Healthy lifestyle behaviours encompassing healthy eating and regular physical activity should be recommended in all those with PCOS to achieve and/or maintain healthy weight and to optimise hormonal outcomes, general health, and QoL across the life course. 
- 3.1.2 EBR Lifestyle intervention (preferably multicomponent including diet, exercise and behavioural strategies) should be recommended in all those with PCOS and excess weight, for reductions in weight, central obesity and insulin resistance. 
- 3.1.3 CPP Achievable goals such as 5% to 10% weight loss in those with excess weight yields significant clinical improvements and is considered successful weight reduction within six months. Ongoing assessment and monitoring is important during weight loss and maintenance in all women with PCOS.
- 3.1.4 CPP SMART (Specific Measurable, Achievable, Realistic and Timely) goal setting and self-monitoring can enable achievement of realistic lifestyle goals.
- 3.1.5 CPP Psychological factors such as anxiety and depressive symptoms, body image concerns and disordered eating, need consideration and management to optimise engagement and adherence to lifestyle interventions.
- 3.1.6 CPP Health professional interactions around healthy lifestyle, including diet and exercise, need to be respectful, patient-centred and to value women's individualised healthy lifestyle preferences and cultural, socioeconomic and ethnic differences. Health professionals need to also consider personal sensitivities, marginalisation and potential weight-related stigma.
- 3.1.7 CPP Adolescent and ethnic-specific BMI and waist circumference categories need to be considered when optimising lifestyle and weight.
- 3.1.8 CPP Healthy lifestyle may contribute to health and QoL benefits in the absence of weight loss.
- 3.1.9 CPP Healthy lifestyle and optimal weight management appears equally effective in PCOS as in the general population and is the joint responsibility of all health professionals, partnering with women with PCOS. Where complex issues arise, referral to suitably trained allied health professionals needs to be considered.
- 3.1.10 CPP Ethnic groups with PCOS who are at high cardiometabolic risk as per 1.6.1 require greater consideration in terms of healthy lifestyle and lifestyle intervention.
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Justification

Given the high prevalence and important adverse impact of excess weight in PCOS and the apparent efficacy in PCOS and in general populations, lifestyle management was deemed important in this high-risk group. Women with PCOS prioritised weight management and also emphasised the need to optimise healthy lifestyle in lean women and in all women with PCOS, independent of weight loss goals. The recommendations and practice points were informed by general population guidelines, the evidence identified in PCOS and by multidisciplinary health professional and consumer input. They are intended to reduce variation in practice, improve lifestyle advice and support for women with PCOS, and target both prevention of weight gain and where appropriate weight loss. The recommendations also consider important psychosocial, cultural and ethnic aspects in relation to lifestyle interventions and were informed by evidence generated for other clinical questions under emotional wellbeing and under specific lifestyle interventions. These recommendations may increase consultation times, referral to allied health professionals and associated healthcare costs, however long-term benefits are anticipated to reduce the health and economic burden of PCOS. Engagement of health practitioners and financial barriers for patients may present implementation issues.

3.2 Behavioural interventions

In women with PCOS, are behavioural interventions (compared to different types of behavioural interventions) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

Clinical need for the question

With weight gain increasing in women, and even higher rates of weight gain shown in PCOS, preventive strategies area needed [314, 315]. Previous lifestyle intervention studies in PCOS have involved short-term dietary interventions with or without an exercise component. Dietary intervention studies have shown benefit with weight loss [314], however retention and sustainability prove challenging, suggesting a need for additional strategies. Behavioural and cognitive behavioural intervention approaches target behaviours, their antecedents and consequences and cognitions that maintain positive energy balance and promote weight gain [316] and are common in weight management. Behaviour therapy results in significantly greater weight loss than placebo, and behaviour/cognitive behaviour therapy combined with diet and exercise has efficacy. Given the need to improve adherence and impact of lifestyle interventions in PCOS, this question was prioritised.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative review evidence

A multidisciplinary model of care with a dietitian, health psychologist, gynaecologist and endocrinologist, in adolescents with PCOS, showed that a ‘behavioural intervention’ enhanced weight loss when combined with dietary consultation, compared to receiving neither or dietary advice only [317]. The intervention was not well defined or replicable and metabolic, reproductive and psychosocial outcomes were not assessed. Two RCT's included behavioural lifestyle components yet had minimal detail on the theoretical framework or behavioural components. These compared comprehensive lifestyle intervention (diet, behaviour and physical activity) over 24 weeks with placebo [318, 319] with variable but limited benefits.

In this context, recommendations on behavioural lifestyle interventions in women with PCOS are informed by data from general populations. A comprehensive systematic review of lifestyle interventions in populations at risk of type 2 diabetes (DM2) or cardiovascular disease (CVD), summarised key success factors in lifestyle interventions [320]. Behavioural change techniques in combination with diet and exercise interventions, increased weight loss over diet and/or physical activity alone [320]. Self-management has positive impacts [320] and family support improves outcomes, [320]. Mode of delivery and trained intervention facilitator, setting and intensity didn't impact outcomes [320]. Overall, this underpins international guidelines recommending integration of: 1/ established behaviour change techniques 2/ self-management/self-monitoring and 3/ social support to preventative and treatment lifestyle interventions [320, e.g., 321]. Combining behavioural/cognitive behavioural weight loss components with intensive interventions, including very low calorie diets and weight loss medications, also improves weight loss than these interventions alone [322-325].

Guidelines highlight the need for resources (e.g., written, audio-visual) and the potential for e-health to supplement face to face support with strategies including; goal-setting, self-monitoring, stimulus control, problem solving, assertiveness training, slowing the rate of eating, reinforcing changes, and relapse prevention. Continued contact after treatment (face-to-face or telephone) also improves weight-loss maintenance. More intensive behavioural interventions induce greater weight loss [326]. In the general population, behavioural and cognitive behavioural interventions have strong empirical support and are recommended in international guidelines on the treatment of excess weight [e.g., 321, 327].

Recommendations

- 3.2.1 CCR Lifestyle interventions could include behavioural strategies such as goal-setting, self-monitoring, stimulus control, problem solving, assertiveness training, slower eating, reinforcing changes and relapse prevention, to optimise weight management, healthy lifestyle and emotional wellbeing in women with PCOS. 
- 3.2.2 CPP Comprehensive health behavioural or cognitive behavioural interventions could be considered to increase support, engagement, retention, adherence and maintenance of healthy lifestyle and improve health outcomes in women with PCOS.
-

Justification

In other high cardiometabolic risk populations, behavioural change strategies and/or behavioural/cognitive interventions in combination with diet and exercise, improves weight loss over diet and/or physical activity alone. Emphasis on self-management components enhances weight loss and healthy lifestyle behaviour change and are incorporated into advice on lifestyle interventions for the general population. Skill levels among health professionals may vary, presenting implementation challenges.

3.3 Dietary interventions

In women with PCOS, are diet interventions (compared to no diet or different diets) effective for improving weight loss, metabolic, fertility, and emotional wellbeing outcomes?

Clinical need for the question

Specific dietary composition in lifestyle interventions remains controversial. Given the general recommendations to reduce caloric (energy) intake, rather than modifying macronutrient composition, the widespread promotion of specific dietary composition in PCOS and the limited comparative research on efficacy of specific dietary macronutrient approaches in PCOS, this clinical question was prioritised.

Summary of systematic review evidence

Four articles reporting three studies were identified to answer this question. One RCT with a moderate risk of bias investigated the changes in anthropometric, metabolic and non-fertility outcomes by comparing a high protein diet to a high carbohydrate diet [308]; one RCT with a low risk of bias investigating the changes in anthropometric and metabolic outcomes by comparing a DASH (dietary approaches to stop hypertension) diet with a control diet [328, 329]; and one RCT with a high risk of bias investigating the changes in anthropometric and metabolic outcomes by comparing a high protein diet with a normal protein diet [330]. There was no difference for the majority of the anthropometric, metabolic, fertility, non-fertility, QoL and emotional wellbeing outcomes, however, regardless of the type of diet, the overall finding was that a diet aimed at reducing weight was of benefit to women with PCOS.

Summary of narrative review evidence

Given the limitations in evidence in PCOS, evidence was also sought from the general population. A systematic review [331] and more recent large scale studies [332] show that in the general population, there is no benefit of any one diet type and that hormone levels including insulin do not predict responses. Given the above evidence and other systematic reviews in the general population that reported similar or less weight loss and compliance for a low fat diet compared to other approaches [333, 334], and a large RCT reported similar changes in weight for a range of reduced energy diets with different macronutrient content over two years [335], the assertions that specific dietary composition has selective long term advantages at this stage appears to be unjustified.

Recommendations

- 3.3.1 CCR A variety of balanced dietary approaches could be recommended to reduce dietary energy intake and induce weight loss in women with PCOS and overweight and obesity, as per general population recommendations. 
- 3.3.2 CCR General healthy eating principles should be followed for all women with PCOS across the life course, as per general population recommendations. 
- 3.3.3 CPP To achieve weight loss in those with excess weight, an energy deficit of 30% or 500 - 750 kcal/day (1,200 to 1,500 kcal/day) could be prescribed for women, also considering individual energy requirements, body weight and physical activity levels.
- 3.3.4 CPP In women with PCOS, there is no or limited evidence that any specific energy equivalent diet type is better than another, or that there is any differential response to weight management intervention, compared to women without PCOS.
- 3.3.5 CPP Tailoring of dietary changes to food preferences, allowing for a flexible and individual approach to reducing energy intake and avoiding unduly restrictive and nutritionally unbalanced diets, are important, as per general population recommendations.
-

Justification

Given that consumer targeted information about PCOS purport the benefit of specific macronutrient composition, this recommendation is important to ensure that women and health professionals are informed on the evidence on dietary composition and efficacy. Emphasis should be on individual preferences and cultural needs of each woman and on an overall balanced and healthy dietary composition to achieve energy intake reduction for weight loss. Education for both women and health professionals is needed in this area. Specific cost and resource implications were considered but recommendations were approved on balance, informed by recommendations in the general population and benefits in PCOS.

3.4 Exercise interventions

In women with PCOS, are exercise interventions (compared to different exercises) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

Clinical need for the question

Whilst not formally included in the diagnostic criteria, insulin resistance, is involved in the aetiology and clinical features of PCOS [336, 337]. Exercise ameliorates insulin resistance and offers a potentially effective intervention in PCOS, with some evidence of clinical benefit. In general populations, physical activity (any bodily movement produced by skeletal muscles that requires energy expenditure) and structured exercise (activity requiring physical effort, carried out to sustain or improve health and fitness), deliver clear health benefits, whilst sedentary behaviours (activities during waking hours in a seated or reclined position with energy expenditure less than 1.5 times resting metabolic rate) have adverse health impacts. Despite the potential for benefit, women with PCOS report receiving limited lifestyle advice and specific efficacy of different types and intensity of exercise is unclear and was prioritised in PCOS and its associated co-morbidities.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative review evidence

Physical activity and formal exercise interventions are classified as aerobic/endurance (focusing on aerobic capacity/fitness), resistance activities (targeting muscle mass and strength) or a combination, further sub-grouped by exercise intensity into light, moderate, vigorous or high-intensity [338] ([Table 5](#)). Two small RCTs are relevant in PCOS. Regular moderate intensity cycle exercise had greater metabolic benefit over 24 compared to 12 weeks, without impact on reproductive biomarkers [148, 339, 340]. Whilst 20 weeks of aerobic compared to combined exercise, superimposed on a high protein diet, showed similarly improved PCOS features [148, 287, 339, 341]. Small RCTs and high quality mechanistic studies (cohort and case control studies) show physical activity, including formal exercise (aerobic and muscle strengthening), improves body composition and clinical features [148, 206, 287, 290, 339, 341-349], compared to minimum or no interventions. These benefits occur independent of significant weight loss [290] and can occur with exercise alone [290, 350].

The mechanistic impacts of exercise and physical activity on cardiometabolic and reproductive features of PCOS are well described [339, 351-353]. While acknowledging the limitations in quality of evidence (sample size, study type, heterogeneity of interventions), improved glycaemic and reproductive outcomes, QoL and functional capacities have been shown [148, 287, 339, 349, 351-354]. Psychologically, limited community based/epidemiological studies show positive associations between self-reported physical activity and mental health status [206, 342] and vigorous exercise and better health outcomes in women with PCOS [355]. Conversely, there is an increase in sedentary behaviour documented in PCOS [356]. Mechanistically, insulin resistance, underpinned by insulin signalling pathway defects, is involved in the aetiology [336, 337] and clinical features of PCOS [336, 337, 357-359]. Moderate aerobic exercise improves insulin sensitivity short-term in PCOS [360].

Insulin resistance is also ameliorated in groups where exercise reduces DM2 risk [152, 361] and CVD factors [362, 363]. Similarly, resistance or weight-bearing exercise either alone or in combination with aerobic exercise improves health outcomes in groups [364-367]. In general populations, physical activity and structured exercise deliver metabolic, cardiovascular, and psychosocial benefits, whether alone or combined with diet changes [368-370]. Sedentary behaviours link to all-cause mortality and adverse health impacts [371, 372], whilst aerobic and resistance exercise reduce cardiometabolic risk factors [373]. Health impacts of exercise therapy may also reduce long-term healthcare costs [374]. Overall, current guidelines for the general population recommend 150 minutes of exercise per week, with 90 minutes at moderate to high intensity [338, 375-382] ([Table 5](#)).

Recommendations

- 3.4.1 CCR Health professionals should encourage and advise the following for prevention of weight gain and maintenance of health: ♦♦♦
- in adults from 18 – 64 years, a minimum of 150 min/week of moderate intensity physical activity or 75 min/week of vigorous intensities or an equivalent combination of both, including muscle strengthening activities on 2 non-consecutive days/week
 - in adolescents, at least 60 minutes of moderate to vigorous intensity physical activity/day, including those that strengthen muscle and bone at least 3 times weekly
 - activity be performed in at least 10-minute bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days.
- 3.4.2 CCR Health professionals should encourage and advise the following for modest weight-loss, prevention of weight-regain and greater health benefits: ♦♦♦
- a minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensity or an equivalent combination of both, and muscle strengthening activities involving major muscle groups on 2 non-consecutive days/week
 - minimised sedentary, screen or sitting time.
- 3.4.3 CPP Physical activity includes leisure time physical activity, transportation such as walking or cycling, occupational work, household chores, games, sports or planned exercise, in the context of daily, family and community activities. Daily, 10000 steps is ideal, including activities of daily living and 30 minutes of structured physical activity or around 3000 steps. Structuring of recommended activities need to consider women's and family routines as well as cultural preferences
- 3.4.4 CPP Realistic physical activity SMART goals could include 10-minute bouts, progressively increasing physical activity 5% weekly, up to and above recommendations.
- 3.4.5 CPP Self-monitoring including with fitness tracking devices and technologies for step count and exercise intensity, could be used as an adjunct to support and promote active lifestyles and minimise sedentary behaviours.
-

Justification

Exercise should be encouraged and advised in PCOS based on evidence in the general population and in PCOS. It was considered that exercise interventions and physical activity do not require clinical centres, expensive gyms and fitness centres. They can be delivered in community centres, sporting grounds/facilities, in groups and with minimal equipment. Low cost e-health (electronic health) and m-health (mobile health) options may also be used. As such, costs and resources need not be prohibitive. Where available and affordable, and where there is risk from injury, barriers to exercise or additional motivation required, due consideration should be given to involvement of exercise physiologists/specialists in structured exercise intervention, as captured in [Section 3.1 Lifestyle interventions](#).

Table 5: Physical activity intensity and examples.

INTENSITY AND MEASURE	DESCRIPTION	EXAMPLES OF ACTIVITIES AND ADL'S (ACTIVITIES OF DAILY LIVING)
LIGHT 1.6 - 3 [†] METs 40 - 55% *HRmax	<ul style="list-style-type: none"> Aerobic activity that does not cause noticeable changes in breathing rate. An intensity that can be sustained for at least 60 minutes. 	Casual walking, cycling < 8km/hr (5mph), stretching, light weight training, dancing slowly, leisurely sports (playing catch) golf (using cart), light yard/house work.
MODERATE 3 - 6 [†] METs 55 - 70% *HRmax	<ul style="list-style-type: none"> Aerobic activity that can be conducted whilst having an uninterrupted conversation. An intensity that may last between 30 to 60 minutes. 	Brisk walking (5 - 7km/hr, 3 - 4.5mph), walking uphill, hiking, cycling (8 - 15km/hr, 5 - 9mph), low impact or aqua aerobics, yoga gymnastics, weight training, moderate dancing, aerobic machines (stair climber, elliptical, stationary bike) — most competitive tennis, volleyball, badminton, recreational swimming, golf — carrying clubs, intense house/yard work or occupations with extended standing or walking.
VIGOROUS 6 - 9 [†] METs 70 - 90% *HRmax	<ul style="list-style-type: none"> Aerobic activity where an uninterrupted conversation generally can't be maintained Intensity that may last up to 30 minutes 	Race walking, jogging/running, mountain climbing, cycling (> 16km/hr, 10mph), high impact aerobics, karate or similar, circuit weight training, vigorous dancing and aerobic machines, competitive basketball, netball, soccer, football, rugby, hockey, swimming, water jogging, downhill or cross country skiing, non-motorised lawn mowing, occupations with heavy lifting or rapid movement.

* Predicted maximal heart rate (HRmax) = 208 – (0.7 X AGE[years]);

† metabolic equivalent (MET) where 1 MET is the O₂/kg body weight/min required to sustain ones resting metabolic rate [3.5 mL/kg/min])[338] and [383].

3.5 Obesity and weight assessment

Are women with PCOS at increased risk of obesity?

In women with PCOS, does obesity impact on prevalence and severity of hormonal and clinical features?

Clinical need for the questions

Obesity affects the majority of women recruited from clinic populations and is common in community-based studies. The complex pathophysiology and clinical heterogeneity of PCOS has contributed to the lack of a clear understanding of interactions between PCOS, excess body weight and body fat distribution. Obesity, particularly central obesity, increases insulin resistance and hyperandrogenism, may increase PCOS prevalence and exacerbates the clinical features of PCOS. It is also of significant concern to women with PCOS and a key target for prevention and management in this condition. The degree of increased risk of excess weight and the impact on prevalence and severity of features of PCOS remain unclear.

Summary of narrative review evidence

A systematic review was not conducted to answer these questions, which were reviewed narratively based on clinical expertise. This review informs both the recommendations for assessment and screening in chapter 1 and the recommendations in chapter 3. In terms of prevalence of excess weight in PCOS, the great majority of women seeking treatment for PCOS are overweight or obese [384]. Rates of weight gain appear higher in PCOS, and BMI increases of one, are associated with a 9% higher prevalence of PCOS [315]. Women with PCOS also appear to have higher genetic susceptibility to obesity [385]. The temporal trends of obesity prevalence in PCOS show an increase from 51% in the 90s to 74% in the following decades [386]. There is general recognition that women with PCOS who present for diagnosis and care may be more likely to have excess weight than those who do not, however longitudinal community-based data supports higher weight gain and excess body weight in PCOS. Weight gain over 10 years among women with PCOS is significantly greater than in unaffected women in a longitudinal community-based study (mean difference 2.6kg 95% CI 1.2-4.0) [387]. Weight gain escalates from adolescence and early vigilance and intervention is important. Central obesity increases over time with a progressive increase in waist hip ratio between 20 - 25 years and 40 - 45 years [115]. This is consistent with reports from a prospective birth cohort of increased weight gain in early adulthood in women with symptoms of or a diagnosis of PCOS compared with controls [388]. Overall rates of weight gain and excess weight are increased in PCOS.

Obesity influences the phenotypic expression of PCOS, exacerbating metabolic, reproductive, and psychological features [279, 389]. Lipid abnormalities are increased independently in PCOS and are exacerbated by excess weight [386, 389, 390]. Central obesity is associated with more severe metabolic disturbance [389]. The prevalence of impaired glucose tolerance (IGT) and DM2 is further increased in women with PCOS with excess weight, especially in high-risk ethnic groups [391]. Conversely, weight loss reduces abdominal fat and insulin resistance and improves clinical features of PCOS ([see Chapter 3](#)) [294, 392].

Obesity impacts on ovulatory dysfunction, irregular menstrual cycles, time to conception, infertility and response to ovulation induction and is associated with increased miscarriage, hyperglycaemia, pre-eclampsia, perinatal morbidity, fetal macrosomia and greater potential for trans-generational transmission of obesity and adverse metabolic features [294, 386, 390, 393]. When combined with insulin resistance, DM2 and PCOS, the adverse outcomes can be more than additive [386, 390]. Expert opinion recommends that obese women with PCOS delay infertility therapy and pursue lifestyle modification, where possible [384, 387].

Psychological comorbidities of PCOS with overweight/obesity include anxiety, depression, low health-related QoL, sexual dissatisfaction, poor self-esteem and psychological distress [384, 390, 392]. Psychological health also requires consideration when assessing and managing excess weight, especially in PCOS. When assessing weight, related stigma, negative body image and/or low self-esteem should be considered and assessment should be respectful. Consistent with population recommendations, explanations on the purpose, how the information will be used and opportunity for questions and preferences should be provided and permission sought. Implications of results should be explained and support provided as needed.

Overall, healthy lifestyle is recommended in all women with PCOS to maintain healthy weight and prevent excess weight gain and lifestyle intervention is recommended to induce weight loss in women with excess weight. Monitoring of weight is a component of behavioural interventions and self-management associated with better short and long-term weight outcomes. General population guidelines recommend monitoring weight, BMI and where appropriate (especially in high-risk ethnic groups) waist circumference.

Recommendations

-
- 3.5.1 CCR Health professionals and women should be aware that women with PCOS have a higher prevalence of weight gain and obesity, presenting significant concerns for women, impacting on health and emotional wellbeing, with a clear need for prevention. 
- 3.5.2 CCR All those with PCOS should be offered regular monitoring for weight changes and excess weight as per 1.8.1 and 1.8.2. 
- 3.5.3 CPP When assessing weight, related stigma, negative body image and/or low self-esteem need to be considered and assessment needs to be respectful and considerate. Beforehand, explanations on the purpose and how the information will be used and the opportunity for questions and preferences needs to be provided, permission sought and scales and tape measures adequate. Implications of results need to be explained and where this impacts on emotional wellbeing, support provided. 
- 3.5.4 CPP Prevention of weight gain, monitoring of weight and encouraging evidence-based and socio-culturally appropriate healthy lifestyle is important in PCOS, particularly from adolescence. 
-

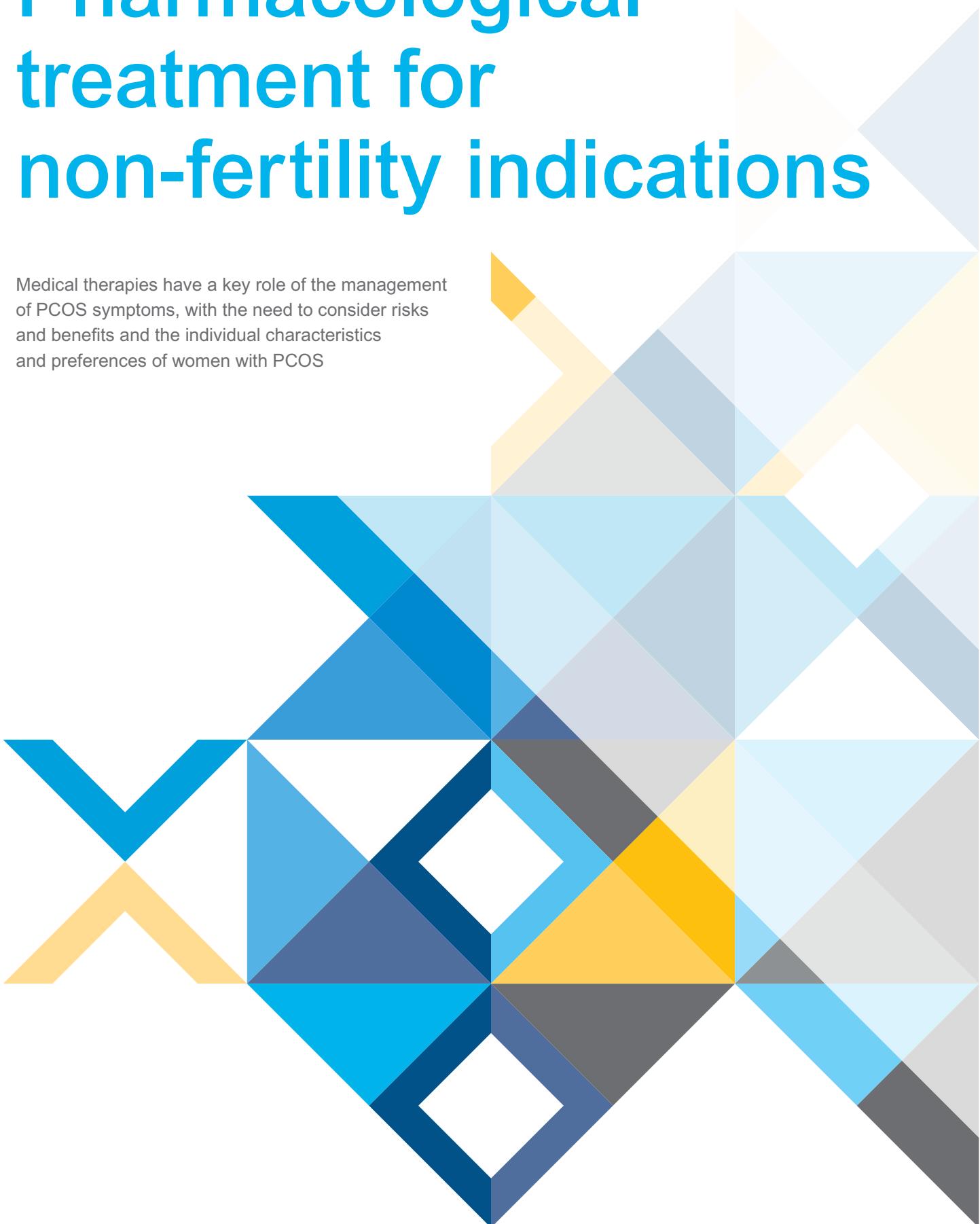
Justification

Rate of weight gain and excess weight/obesity is more prevalent in women with PCOS, compared to women without PCOS, and causes considerable concern for affected women. Obesity exacerbates the clinical features of PCOS and given the significant burden, low adherence rates and challenges with weight loss and maintenance, prevention of weight gain through healthy lifestyle is vital, consistent with international public health recommendations. Awareness, respectful monitoring and early intervention are important considerations from adolescence. The GDG recognised the need for adequate training of health professionals in the empathetic partnering with women to enable weight management.

Chapter Four

Pharmacological treatment for non-fertility indications

Medical therapies have a key role of the management of PCOS symptoms, with the need to consider risks and benefits and the individual characteristics and preferences of women with PCOS



4.1 Pharmacological treatment principles in PCOS

In reviewing the literature on pharmacological treatments, general principles emerged that apply across all pharmacological therapies. These have been extracted into a set of clinical practice points to inform women and guide health professionals when considering or recommending pharmacological therapy in PCOS. These practice points apply to all pharmacological treatments prioritised and addressed in the guideline.

Recommendations

-
- 4.1.1 CPP Consideration of the individual's personal characteristics, preferences and values is important in recommending pharmacological treatment.
 - 4.1.2 CPP When prescribing pharmacological therapy in PCOS, benefits, adverse effects and contraindications in PCOS and general populations need to be considered and discussed before commencement.
 - 4.1.3 CPP COCPs, metformin and other pharmacological treatments are generally off label# in PCOS. However off label use is predominantly evidence-based and is allowed in many countries. Where it is allowed, health professionals need to inform women and discuss the evidence, possible concerns and side effects of treatment.
 - 4.1.4 CPP Holistic approaches are required and pharmacological therapy in PCOS needs to be considered alongside education, lifestyle and other options including cosmetic therapy and counselling.
-

'Off label' prescribing occurs when a drug is prescribed for an indication, a route of administration, or a patient group that is not included in the approved product information document for that drug by the relevant regulatory body. Prescribing off label is often unavoidable and common and does not mean that the regulatory body has rejected the indication; more commonly there has not been a submission to request evaluation of the indication or that patient group for any given drug.

4.2 and 4.3 Combined Oral Contraceptive Pills and combined oral contraceptive pills in combination with other agents

Is the combined oral contraceptive pill (COCP) alone or in combination effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?

Clinical need for the question

Combined contraceptives, including oral contraceptive pills, are commonly prescribed for adults and adolescents with PCOS to ameliorate the clinical symptoms and associated hormonal disturbances. The effects of COCPs on menstrual cycle, hirsutism, weight loss, waist/hip ratio, testosterone concentrations, lipid profile and blood sugar levels are variably reported and depend on type of COCP used, duration of use, severity of presentation/phenotype, adherence to the regimen, among other factors. Different combinations of COCPs are available with heterogeneous estrogen and progestin preparations with varying pharmacological and clinical properties. Thus, the efficacy and consequences of COCPs in PCOS may vary. Some preparations also comprise natural estrogen instead of synthetic ethynodiol (EE) with benefits and contraindications considered similar.

Summary of systematic review evidence – COCP alone

Research evidence - ADOLESCENTS

COCP versus placebo

One randomised controlled trial (RCT) was identified to address this comparison in adolescents [319]. There was a statistically significant improvement with COCP (compared to placebo) for high-density lipoprotein (HDL) in this very low quality study with low certainty. No statistically significant differences were found for outcomes: body mass index (BMI) (kg/m^2); Waist (cm); Total testosterone (ng/dl); sex hormone-binding globulin (SHBG) (nmol/liter); free androgen index (FAI); Hirsutism (FG score); Total cholesterol (mg/dl); LDL (mg/dl); Triglycerides (mg/dl); Fasting insulin (IU/ml); Fasting blood sugar (mg/dl); CRP (mg/l); PAI-1. Side effects were not reported.

COCP versus lifestyle

One RCT was identified to address this comparison in adolescents [319]. There was a statistically significant improvement with lifestyle (compared to COCP) for low-density lipoprotein (LDL) in this very low quality study with very low certainty. No statistically significant differences were found for: BMI (kg/m^2); Total testosterone (ng/dl); SHBG (nmol/liter); FAI; Hirsutism (FG score); Total cholesterol (mg/dl); HDL (mg/dl); Triglycerides (mg/dl); Fasting insulin (IU/ml); Fasting blood sugar (mg/dl); CRP (mg/l); PAI-1. Side effects were not reported.

COCP versus metformin

A systematic review including four RCTs that address this comparison in adolescents was identified [394]. The evidence team conducted additional analysis of outcomes not addressed in the systematic review. While a statistically significant improvement was found in BMI and LDL with use of metformin over COCP; and a statistically significant improvement was found in menstrual regulation with use of COCP over metformin, we remain cautious due to very low certainty in effect estimates and the quality of evidence. A statistically significant improvement in dysglycemia (OGTT) was found with the use of metformin over COCP, however it should be noted that there is low certainty in the effect estimates and the quality of evidence. No statistically significant differences were found for: Hirsutism; Total Testosterone (nmol/L); Triglyceride (mg/dL); Total Cholesterol (mg/dL); HDL (mg/dL); Weight (kg); Fasting insulin; SHBG; FAI; Fasting blood sugar (mg/dL); CRP (mg/L); PAI-1. Side effects included weight gain with COCP; and side effects were not specified with metformin.

COCP versus metformin + anti-androgen

One RCT was identified to address this comparison in adolescents [395]. Due to the lack of direct comparisons between groups (no p values reported for between groups) it is uncertain whether there were any differences in this very low quality study with very low certainty for outcomes: BMI (kg/m²); Hirsutism (FG score); Glucose/insulin ratio; SHBG (ug/dl); Testosterone (ng/dl); Triglycerides (mg/dl); HDL (mg/dl); LDL (mg/dl); Cycle regularity; Weight. Side effects were not reported.

Research evidence - ADULTS

COCP versus metformin

Nine RCTs were identified to address this comparison [396-404]. There were statistically significant improvements with metformin (compared with COCP) for fasting insulin, including for both BMI subgroups. Metformin improved HDL in the BMI > 25 subgroup but not in the BMI < 25 subgroup or when all participants were combined; and improved triglycerides when all participants were combined, in the BMI > 25 subgroup and in the subgroup where BMI was not defined, but not in the BMI < 25 subgroup. There were statistically significant improvements with COCP (compared with metformin) for SHBG, FAI, total testosterone and irregular cycles, including for all BMI subgroups. COCP improved LDL in the BMI > 25 subgroup but not in the BMI < 25 subgroup or when all participants were combined. No statistically significant differences were found for: Weight; Clamp (M value); homeostatic model assessment (HOMA) (change from baseline); BMI (kg/m²); waist-hip-ratio (WHR); Hirsutism [FG score]; Fasting glucose [mmol/l], Total cholesterol [mmol/l]. Metformin use increased GI-related events, whereas the COCP group had none. While one of the included studies was of moderate quality and certainty, the majority of studies in these meta-analyses were of low to very low certainty in effect estimates and the quality of evidence and therefore all findings should be interpreted with caution.

COCP versus COCP + metformin

Six RCTs were identified to address this comparison [402, 404-408]. There was a statistically significant improvement with COCP alone (compared with COCP plus metformin) for triglycerides. COCP alone improved SHBG in the BMI < 25 subgroup but not in the BMI > 25 subgroup or when all participants were combined. There were statistically significant improvements with COCP plus metformin (compared with COCP alone) for FAI. COCP plus metformin improved testosterone when all participants were combined but not in BMI subgroups; improved hirsutism and fasting glucose when all participants were combined and in the BMI > 25 subgroup but not in the BMI < 25 subgroup; improved SHBG and fasting insulin in the BMI < 25 subgroup but not when all participants were combined or in the BMI > 25 subgroup; and improved total cholesterol in the BMI > 25 subgroup but not when all participants were combined or in the BMI < 25 subgroup. No statistically significant differences were found for: HOMA; Weight (kg); BMI (kg/m²); WHR; HDL [mmol/l]; LDL [mmol/l]. The addition of metformin to COCP increased GI-related events, whereas the COCP alone group had none. While one of the included studies was of moderate quality and certainty, the majority of studies in these meta-analyses were of low to very low certainty in effect estimates and the quality of evidence and therefore all findings should be interpreted with caution.

COCP versus COCP + metformin + anti-androgen

One RCT was identified to address this comparison in adults [395]. Due to the lack of direct comparisons between groups (no p values reported for between groups) it is uncertain whether there were any differences in this very low quality study with very low certainty for outcomes: BMI (kg/m²); Hirsutism (FG score); Glucose/insulin ratio; SHBG (ug/dl); Testosterone (ng/dl); Triglycerides (mg/dl); HDL (mg/dl); LDL (mg/dl); Cycle regularity; Weight. Side effects were not reported.

COCP versus anti-androgen

One RCT was identified to address this comparison in adults [409]. Due to the lack of direct comparisons between groups (no p values reported for between groups) it is uncertain whether there were any differences in this very low quality study with very low certainty for the outcome hirsutism (FG score).

Summary of systematic review evidence – COCP combined with other agents

Research evidence - ADOLESCENTS

COCP + metformin+ lifestyle versus COCP + lifestyle + placebo

One RCT was identified to address this comparison in adolescents [319]. There was a statistically significant improvement with the addition of metformin to COCP and lifestyle (compared to COCP and lifestyle plus placebo) for testosterone and HDL in this very low quality study with very low certainty. No statistically significant differences were found for: BMI (kg/m^2); Waist (cm); SHBG (nmol/l); FAI; Hirsutism (FG score); Total cholesterol (mg/dl); LDL (mg/dl); Triglycerides (mg/dl); Fasting insulin (IU/ml); Fasting blood sugar (mg/dl); CRP (mg/liter). One in each group stopped metformin or placebo due to GI effects.

COCP + anti-androgen versus COCP + anti-androgen + metformin

One RCT was identified to address this comparison in adolescents [410]. Due to the lack of direct comparisons between groups (no p values reported for between groups) it is uncertain whether there were any differences in this very low quality study with very low certainty for outcomes: BMI (kg/m^2); Fasting glucose/insulin ratio SHBG ($\mu\text{g}/\text{dl}$); Testosterone (ng/dl); LDL (mg/dl); HDL (mg/dl); Triglycerides (mg/dl). Side effects were not reported.

Research evidence - ADULTS

COCP versus COCP + metformin

Six RCTs were identified to address this comparison [402, 404-408]. There was a statistically significant improvement with COCP alone (compared with COCP plus metformin) for triglycerides. COCP alone improved SHBG in the BMI < 25 subgroup but not in the BMI > 25 subgroup or when all participants were combined. There were statistically significant improvements with COCP plus metformin (compared with COCP alone) for FAI. COCP plus metformin improved testosterone when all participants were combined but not in BMI subgroups; improved hirsutism and fasting glucose when all participants were combined and in the BMI > 25 subgroup but not in the BMI < 25 subgroup; improved SHBG and fasting insulin in the BMI < 25 subgroup but not when all participants were combined or in the BMI > 25 subgroup; and improved total cholesterol in the BMI > 25 subgroup but not when all participants were combined or in the BMI < 25 subgroup. No statistically significant differences were found for: HOMA; Weight (kg); BMI (kg/m^2); WHR; HDL [mmol/l]; LDL [mmol/l]. The addition of metformin to COCP increased GI-related events, whereas the COCP alone group had none. While one of the included studies was of moderate quality and certainty, the majority of studies in these meta-analyses were of low to very low certainty in effect estimates and the quality of evidence and therefore all findings should be interpreted with caution.

COCP versus COCP + metformin + anti-androgen

One RCT was identified to address this comparison in adults [395]. Due to the lack of direct comparisons between groups (no p values reported for between groups) it is uncertain whether there were any differences in this very low quality study with very low certainty for outcomes: BMI (kg/m^2); Hirsutism (FG score); Glucose/insulin ratio; SHBG ($\mu\text{g}/\text{dl}$); Testosterone (ng/dl); Triglycerides (mg/dl); HDL (mg/dl); LDL (mg/dl); Cycle regularity; Weight. Side effects were not reported.

COCP versus COCP + anti-androgen

Four RCTs were identified to address this comparison in adults [411-414]. There was a statistically significant improvement with COCP alone (compared with COCP plus anti-androgen) for BMI and LDL. No statistically significant differences were found for: Weight (kg); WHR; Hirsutism (FG score); FAI (%); Testosterone (nmol/L); SHBG [nmol/l]; Fasting insulin (uIU/ml); Fasting glucose [mmol/l]; Total cholesterol [mmol/l]; HDL [mmol/l]; Triglycerides (mg/dL); HOMA; CRP (mg/l); Headache; Breast-related side effects; Vomit/Nausea; Minor depressive state; Liver function. The majority of studies in these meta-analyses were of low to very low certainty in effect estimates and the quality of evidence and therefore all findings should be interpreted with caution.

COCP + metformin + lifestyle versus COCP + metformin + lifestyle

One study was identified to address this comparison in adults [415]. There were no statistically significant differences reported between the two interventions (differing by the combination in the COCP) in this very low quality study of very low certainty for outcomes: WHR; Fasting plasma glucose (mmol/L); HbA1c (%); Total cholesterol (mmol/L); LDL (mmol/L). Side effects were not reported.

Summary of narrative review evidence

Evidence on COCP use from the general population also informed recommendations. Consideration of adverse effects is needed before prescribing COCPs. Absolute contraindications for COCP use according to world health organisation (WHO) include a history of migraine with aura, deep vein thrombosis (DVT)/pulmonary emboli (PE), known thrombogenic mutations, multiple risk factors for arterial cardiovascular disease, history of ischemic heart disease or stroke, complicated valvular heart disease, breast cancer, neuropathy, severe cirrhosis and malignant liver tumours [416]. Other risk factors for DVT need consideration including postpartum immobility, transfusion at delivery, BMI > 30 kg/m², postpartum haemorrhage, immediately post-caesarean delivery, preeclampsia or smoking. Current evidence suggests that COCPs containing levonorgestrel, norethisterone and norgestimate are associated with the lowest relative risk of DVT. Also, WHO recommends that COCPs with 35 micrograms of EE and cyproterone acetate should only be used when treating moderate to severe hirsutism or acne due to higher DVT risk. For contraception, irregular menstrual cycles and mild to moderate hirsutism, other lower risk preparations are recommended first line [417].

Recommendations – COCP alone

4.2.1	EBR	The COCP alone should be recommended in adult women with PCOS for management of hyperandrogenism and/or irregular menstrual cycles.	❖❖❖❖ ⊕⊕○○
4.2.2	EBR	The COCP alone should be considered in adolescents with a clear diagnosis of PCOS for management of clinical hyperandrogenism and/or irregular menstrual cycles.	❖❖❖ ⊕⊕○○
4.2.3	EBR	The COCP could be considered in adolescents who are deemed “at risk” but not yet diagnosed with PCOS, for management of clinical hyperandrogenism and irregular menstrual cycles.	❖❖❖ ⊕⊕○○
4.2.4	EBR	Specific types or dose of progestins, estrogens or combinations of COCP cannot currently be recommended in adults and adolescents with PCOS and practice should be informed by general population guidelines.	❖❖❖ ⊕⊕○○
4.2.5	CCR	The 35 microgram ethinyloestradiol plus cyproterone acetate preparations should not be considered first line in PCOS as per general population guidelines, due to adverse effects including venous thromboembolic risks.	❖
4.2.6	CPP	When prescribing COCPs in adults and adolescents with PCOS: <ul style="list-style-type: none">• various COCP preparations have similar efficacy in treating hirsutism• the lowest effective estrogen doses (such as 20-30 micrograms of ethinyloestradiol or equivalent), and natural estrogen preparations need consideration, balancing efficacy, metabolic risk profile, side effects, cost and availability• the generally limited evidence on effects of COCPs in PCOS needs to be appreciated with practice informed by general population guidelines (WHO Guidelines)• the relative and absolute contraindications and side effects of COCPs need to be considered and to be the subject of individualised discussion• PCOS specific risk factors such as high BMI, hyperlipidemia and hypertension need to be considered.	

Recommendations – COCP in combination with other agents

4.3.1	EBR	In combination with the COCP, metformin should be considered in women with PCOS for management of metabolic features where COCP and lifestyle changes do not achieve desired goals.	
4.3.2	EBR	In combination with the COCP, metformin could be considered in adolescents with PCOS and BMI $\geq 25\text{kg}/\text{m}^2$ where COCP and lifestyle changes do not achieve desired goals.	
4.3.3	CPP	In combination with the COCP, metformin may be most beneficial in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.	
4.3.4	EBR	In combination with the COCP, antiandrogens should only be considered in PCOS to treat hirsutism, after six months or more of COCP and cosmetic therapy have failed to adequately improve symptoms.	
4.3.5	CCR	In combination with the COCP, antiandrogens could be considered for the treatment of androgen-related alopecia in PCOS.	
4.3.6	CPP	In PCOS, antiandrogens must be used with effective contraception, to avoid male foetal undervirilisation. Variable availability and regulatory status of these agents is notable and for some agents, potential liver toxicity requires caution.	

Justification

Although relatively safe, COCPs have absolute and relative contraindications and risks and benefits in the general population that need consideration by health professionals and women. Although combined metformin and COCP offers additional benefits, these did not surpass the impact of COCP plus lifestyle intervention. Hence the combination is indicated where COCP and lifestyle have failed to meet goals. A combination regime may also lead to increased mild gastrointestinal side effects, which can impact on adherence. Strategies to reduce side effects are available (see metformin recommendations below). With metformin therapy in addition to COCP, women with PCOS and obesity may yield the greatest benefit. The PCOS phenotype, BMI, ethnicity and the informed preference of the individual with PCOS need to be considered when recommending pharmacological agents for the treatment of PCOS.

COCPs, metformin and anti-androgens are off label treatments specifically for treatment of PCOS. However, use is evidence-based for the treatment of clinical features of PCOS and is generally not restricted for use in PCOS. Women should be informed of the benefits and risks and the regulation status of relevant medications. The combination of off label treatments with the COCP is not routine practice and will require education and integration into algorithms. This is anticipated to significantly change practice. Due to subgroup differences in recommendations, the personal characteristics of all women need to be considered.

4.4 Metformin

Is metformin alone, or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

Clinical need for the question

Metformin is a low cost, readily available medication that has been extensively used as an insulin sensitiser for over seven decades in DM2 and for several decades in PCOS. Insulin resistance is documented on clamp studies in 75% of lean women and 95% of overweight women [279] and addressing this has underpinned the use of metformin in PCOS. Metformin is currently widely used by women with PCOS, yet there is variability in recommendations across health professional specialties, with endocrinologists familiar with metformin and more likely to prescribe this therapy. Also the efficacy of metformin in terms of improving clinical outcomes remains uncertain. Mild side effects do cause some concern, and metformin use in PCOS is generally off label. Yet metformin is a low cost, readily available medication and off label use in PCOS is allowed in many countries. A multitude of studies have been completed in PCOS for a range of clinical outcomes and synthesis of the literature and recommendations on metformin use was prioritised.

Summary of systematic review evidence

Metformin versus placebo

Twenty RCTs that address outcomes for this comparison were identified [318, 319, 418-435], of which 19 RCTs were in adults [318, 418-435], and 1 was in adolescents [319].

Weight: When 5 RCTs were combined in meta-analysis, there was no statistically significant difference between metformin and placebo [418, 424, 427, 433, 434]. When three of the studies in those with BMI > 25kg/m² were subgrouped [424, 427, 433], metformin was better than placebo.

BMI: When 15 RCTs were combined in meta-analysis [318, 319, 418-422, 424, 425, 428-432, 435], and when 11 of the RCTs in those with BMI > 25kg/m² was subgrouped [318, 319, 419-422, 424, 425, 429, 431, 432, 435], metformin was better than placebo.

WHR: When 8 RCTs were combined in meta-analysis, there was no statistically significant difference between metformin and placebo ($p=0.06$ in favour of metformin) [418, 419, 421, 424, 427, 429, 431, 434]. When 3 of the RCTs in those with BMI < 25kg/m² were subgrouped [418, 429, 431], metformin was better than placebo.

Hirsutism: When 6 RCTs were combined in meta-analysis, there was no statistically significant difference between metformin and placebo, regardless of BMI subgroups [319, 423, 425, 429-431].

SHBG: When 13 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo, regardless of BMI subgroups [318, 319, 418-421, 423-425, 428, 430, 431, 434]. In one very small RCT (n=20), where BMI was not reported, there was a statistically significant difference in favour of metformin [423].

FAI: When 6 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo, regardless of BMI subgroups [318, 319, 423, 424, 430, 431].

Testosterone: When 15 RCTs were combined in meta-analysis metformin was better than placebo, however there was no statistically significant difference for any of the BMI subgroups [318, 319, 418-421, 423-425, 428, 430, 431, 433-435].

Fasting insulin: When 9 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo [318, 419-421, 424, 425, 429, 433, 434]. In one small RCT (n=60) of those with BMI < or > 25kg/m², there was a statistically significant difference in favour of metformin [434].

Fasting glucose: When 13 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo [318, 319, 418-421, 424, 425, 428, 429, 433-435]. In one small RCT (n=58) of those with BMI <or> 25kg/m², there was a statistically significant difference in favour of metformin [434].

Cholesterol: When 10 RCTs were combined in meta-analysis [319, 419, 421, 422, 424, 425, 428, 429, 431, 434], and when 6 of the RCTs in those with BMI > 25kg/m² was subgrouped [319, 419, 421, 424, 425, 429], metformin was better than placebo.

HDL: When 9 RCTs were combined in meta-analysis, there was no statistically significant difference between metformin and placebo, regardless of BMI subgroups [319, 419, 424, 425, 429-431, 433, 434].

LDL: When 9 RCTs were combined in meta-analysis, there was no statistically significant difference between metformin and placebo (p=0.07 in favour of metformin) [319, 419, 423-425, 429-431, 434]. When 6 of the RCTs in those with BMI > 25kg/m² were subgrouped, metformin was better than placebo.

Triglycerides: When 13 RCTs were combined in meta-analysis, metformin was better than placebo, however there was no statistically significant difference for any of the BMI subgroups [319, 419, 421, 423-425, 428, 429, 431, 434].

There were no statistically significant differences between metformin and placebo for HOMA, menstrual cycles, CRP (C-reactive protein) or PAI-1 (plasminogen activator inhibitor-1).

It is important to remain cautious due to low to very low certainty in effect estimates and the quality of evidence across all outcomes.

Gastrointestinal side effects were more prevalent in the metformin groups, but only 5 out of 20 studies including in total 358 women and metformin doses of 1500 - 1700mg/day reported on side effects without specific details. 10 to 62% of women taking metformin reported side effects. The majority of gastrointestinal side effects were mild to moderate and were self-limiting. The side effects reported included nausea, vomiting, diarrhoea, abdominal pain or non-specified gastrointestinal disturbance. Only one study reported higher drop out in the metformin treated due to unacceptable gastrointestinal side effects and suggested lower start metformin dose (500 mg/day),

There were no reports on Vitamin B12 levels.

Metformin versus metformin + COCP

Three RCTs that address this comparison in adults were identified [402, 404, 436]. While a statistically significant improvement was found in WHR and triglycerides with use of metformin over metformin plus COCP, regardless of BMI, we remain cautious due to very low certainty in effect estimates and the quality of evidence.

No statistically significant differences were found for: Weight, BMI, FAI, testosterone, Fasting glucose (mg/dl), Fasting insulin [mIU/ml], fasting glucose-insulin ratio, HOMA, OGTT, Total cholesterol [mg/dl], HDL [mg/dl] and LDL [mg/dl].

Side effects were not reported.

Metformin versus lifestyle

Three RCTs that address this comparison in adolescents and adults were identified [318, 319, 437]. While a statistically significant improvement was found in testosterone with use of metformin over lifestyle; and in SHBG with the use of lifestyle over metformin, we remain cautious due to very low certainty in effect estimates and the quality of evidence. While not statistically significant, fasting glucose tended to favour metformin.

No statistically significant differences were found for: BMI, WHR, PAI-1, Hirsutism (FG score), Menstruation (cycle/mnth), FAI, Fasting glucose (mg/dl), Fasting insulin [mIU/ml], HOMA, Total cholesterol [mg/dl], HDL [mg/dl], LDL [mg/dl], Triglycerides [mg/dl], CRP [mg/dl].

Side effects were GI related with metformin and only reported in one study including adult women.

Metformin + lifestyle versus lifestyle ± placebo

A systematic review including seven relevant RCTs that address this comparison in adults and adolescents was identified [438]. The evidence team conducted additional analysis of outcomes not addressed in the systematic review. No statistically significant differences were found for any of the outcomes in this body of evidence of low to very low certainty and quality.

Side effects were not reported.

Metformin versus metformin (dose)

One study was identified to address this comparison [439]. Age was not reported. There was no difference in weight between the two interventions in this very low quality of very low certainty. Other relevant outcomes were mentioned in this study, however no useable data was reported.

The highest metformin dose used was 850mg twice a day.

Metformin versus anti-androgen + COCP

One study was identified to address this comparison in adults [440]. 500mg of metformin was better for fasting glucose; and 850mg was better for CRP; however, there was no difference for BMI, HDL or triglycerides in this moderate quality study with low certainty.

Metformin + lifestyle versus anti-androgen + lifestyle

Four RCTs that address this comparison in adults was identified [441-444]. While a statistically significant improvement was found in cycles per year and HOMA-IR (homeopathic model assessment of insulin resistance) with use of metformin plus lifestyle over anti-androgen plus lifestyle, and a statistically significant improvement found in hirsutism, SHBG, fasting insulin and fasting glucose-insulin ration with use of anti-androgen plus lifestyle over metformin plus lifestyle, we remain cautious due to low to very low certainty in effect estimates and the quality of evidence.

No statistically significant differences were found for: Weight (kg); BMI; WHR; Testosterone (nmol/L); Fasting glucose (mg/dL); QUICKI [mg/dl]; FAI (pg/ml); OGTT (mg/dl) and HOMA-IR (mIU · mmol/L²).

Side effects were only reported in one study and included vomiting, nausea and diarrhoea with metformin plus lifestyle; and abdominal pain, polyuria, menstrual irregularity and dryness of the mouth with anti-androgen plus lifestyle.

Three subjects in the metformin group and four in the spironolactone group withdrew due to side effects.

Total cholesterol, HDL and LDL were reported in two studies however units were unclear and there was missing data. Of the data presented, there were no differences between interventions for these outcomes in one study and in the other, p values were not reported for direct comparisons.

Metformin + diet versus metformin + anti-androgen + diet

Four RCTs that address this comparison in adults was identified [441, 442, 444, 445]. While a statistically significant improvement was found in testosterone and fasting glucose with use of metformin plus anti-androgen plus lifestyle over metformin plus lifestyle, we remain cautious due to very low certainty in effect estimates and the quality of evidence.

No statistically significant differences were found for: Weight; BMI; WHR; cycles; hirsutism, SHBG, FAI, fasting insulin; OGTT (mg/dl) and HOMA-IR, total cholesterol, HDL, LDL and triglycerides.

Side effects were only reported in one study and included vomiting, nausea, diarrhoea symptoms with metformin plus lifestyle; and nausea, diarrhoea, abdominal pain and metrorrhagia with metformin plus anti-androgen plus lifestyle.

There was stronger evidence in higher BMI groups for metabolic outcomes. Overall there was inadequate evidence to make a recommendation about the use of metformin for menstrual regulation. The maximum dose used in the included studies was 850bd and the optimum dose is not known.

Gastrointestinal side effects may be present. Side effects are usually mild, self-limiting and may be minimised with lower metformin starting dose. Extended release preparations and administration with food might also decrease gastrointestinal side effects.

Summary of narrative review evidence

Given the gaps in evidence in some areas in PCOS, the relevant literature on metformin in other populations was reviewed to inform recommendations. Metformin works by decreasing gluconeogenesis, lipogenesis and enhancing glucose uptake in the liver, skeletal muscle, adipose tissue and ovaries [446]. It is known in other populations to prevent weight gain and appears to assist with weight loss, to prevent and manage DM2, gestational diabetes (GDM), and to reduce microvascular and cardiovascular disease in DM2 [446, 447]. Side effects have are not uncommon, yet these are primarily gastrointestinal, appear mild and self-limiting, with more severe side effects rare and primarily affecting those with other comorbidities [446]. Concerns on Vitamin B12 deficiency with longer term metformin use have also emerged [448], however more research is needed. Data from other populations suggests that side effects can be minimised with lower metformin starting dose, extended release preparations and/or administration with food [449].

Recommendations

4.4.1	EBR	Metformin in addition to lifestyle, could be recommended in adult women with PCOS, for the treatment of weight, hormonal and metabolic outcomes.	❖❖❖ ⊕⊕○○
4.4.2	EBR	Metformin in addition to lifestyle, should be considered in adult women with PCOS with $BMI \geq 25\text{kg}/\text{m}^2$ for management of weight and metabolic outcomes.	❖❖❖ ⊕⊕○○
4.4.3	EBR	Metformin in additional to lifestyle, could be considered in adolescents with a clear diagnosis of PCOS or with symptoms of PCOS before the diagnosis is made.	❖❖❖ ⊕⊕○○
4.4.4	CPP	Metformin may offer greater benefit in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups (see 1.6.1).	
4.4.5	CPP	Where metformin is prescribed the following need to be considered:	
		<ul style="list-style-type: none">adverse effects, including gastrointestinal side-effects that are generally dose dependent and self-limiting, need to be the subject of individualised discussionstarting at a low dose, with 500mg increments 1-2 weekly and extended release preparations may minimise side effectsmetformin use appears safe long-term, based on use in other populations, however ongoing requirement needs to be considered and use may be associated with low vitamin B12 levelsuse is generally off label and health professionals need to inform women and discuss the evidence, possible concerns and side effects.	

Justification

Study numbers were considerable however, the quality and certainty of the evidence was limited. Metformin also has clear benefits in other relevant populations including those with DM2, which also informed GDG recommendations. In PCOS, evidence indicated that metformin is effective overall and /or in specified subgroups, in improving weight, BMI, WHR ratio, testosterone and TG in women with PCOS including those defined by Rotterdam criteria. In providing these recommendations, the GDG considered the very high rating that women with PCOS credited to BMI as an outcome of importance and value. Evidence of metabolic benefits was generally stronger in women with increased BMI. There was inadequate evidence to make a recommendation about the use of metformin for irregular menstrual cycles and efficacy for infertility is addressed later in this guideline. Gastrointestinal side effects were noted, but appear to be mild, self-limiting and could be minimised with lower metformin starting dose, extended release preparations or administration with food. Overall, the beneficial effects in PCOS favoured the use of metformin, the undesirable effects were generally mild and self-limiting and on balance, evidence was felt to probably favour metformin use in PCOS. Whilst use is off label, it is also generally allowed. Cost was relatively low and availability generally widespread and implementation of recommendations were judged to be feasible.

4.5 Anti-obesity pharmacological agents

Are anti-obesity pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

Clinical need for the question

As previously outlined, excess weight is a significant concern for adolescents and women with PCOS and is more prevalent than in women without PCOS. Whilst lifestyle intervention has a first line role in the prevention and management of excess weight in PCOS, the role of anti-obesity pharmacological agents in achieving and maintaining weight loss and in delivering potential health benefits is being increasingly recognised in general and other high-risk populations. Challenges with adherence, efficacy and sustainability all appear to benefit from the addition of these agents to lifestyle interventions. Recent guidelines, systematic and Cochrane reviews have focused on the role of these agents in general and high-risk populations including in obese adolescents. A range of different agents are now approved as anti-obesity medications in adults, although approval status varies across countries, costs remain generally high and there are challenges in access and availability. Despite the challenges, these medications are increasingly being used in adults for assistance with weight loss and weight maintenance in obesity management in other populations [450]. However, in PCOS and in reproductive-aged women generally, the role of anti-obesity pharmacological agents remains unclear. Anti-obesity agents reviewed here were sibutramine and orlistat.

Summary of systematic review evidence

We did not identify any evidence in adolescents with PCOS and below is a summary of the evidence identified in adults.

Anti-obesity versus placebo

One study was identified to address this comparison [451]. Due to the lack of direct comparisons between groups (no p values reported for between groups for end of treatment data), it is uncertain whether there were any differences in this low quality study with low certainty for outcomes: Weight loss (kg); WHR (cm); Menstrual periods (n/6 months); Triglycerides (mmol/L); Fasting glucose (mmol/L); Fasting insulin (mU/L); Fasting glucose/insulin ratio; HOMA-IR; Hs-CRP (mg/L); Testosterone (nmol/L); SHBG (nmol/L); FAI. Side effects were not reported.

Anti-obesity versus anti-obesity

One study was identified to address this comparison [452]. Due to the lack of direct comparisons between groups (no p values reported for between groups for end of treatment data), it is uncertain whether there were any differences in this low quality study with low certainty for outcomes: BMI (kg/m²); WHR (cm); Testosterone (ng/dl); Δ4- Androstenedione (ng/ml); DHEA-S (ng/ml); FAI; SHBG (nmol/l); Fasting glucose (mg/dl); Fasting insulin (μIU/ml); Fasting glucose/insulin; AUC OGTT; HOMA-IR; QUICKI; PAI-1 (ng/ml). Side effects were not reported.

Summary of narrative review evidence

Given the gaps in evidence in some areas in PCOS, the relevant literature on anti-obesity agents in other populations was reviewed to inform recommendations. Recent US Endocrine Society guidelines [450], systematic and Cochrane reviews [453] have focused on the role of these agents in general and high-risk populations including in obese adolescents. A range of different agents are now approved as anti-obesity medications in adults, although approval status varies across countries, costs remain generally high and there are challenges in access, efficacy and availability. Despite the challenges, these medications are increasingly being used and recommended in adults for assistance with weight loss and weight maintenance in obesity management in other populations [450]. It was noted that cost effectiveness of these agents is yet to be established [454].

Recommendations

-
- 4.5.1 CCR Anti-obesity medications in addition to lifestyle, could be considered for the management of obesity in adults with PCOS after lifestyle intervention, as per general population recommendations. 
- 4.5.2 CPP For anti-obesity medications, cost, contraindications, side effects, variable availability and regulatory status need to be considered and pregnancy needs to be avoided whilst taking these medications.
-

Justification

Despite recommendations in the general population, in reproductive-aged women generally, including those with PCOS, the role of anti-obesity pharmacological agents remains unclear. Given the absence of useful evidence in PCOS and in reproductive aged women generally, the GDG were unable to make any evidence-based recommendations in women with PCOS. However, informed by evidence and guidelines on the use of anti-obesity pharmacological agents in the management of obesity in non-PCOS adults, a consensus recommendation has been made. There are known contraindications and side effects of these medications that need to be considered and monitored. Concerns about cost effectiveness was also considered by the group, based on evidence in the general population.

4.6 Anti-androgen pharmacological agents

Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

Clinical need for the question

The most common androgen-related features of PCOS are hirsutism, acne and androgen-related alopecia (see [Chapter 1: Screening, diagnostic assessment, risk assessment and life-stage](#)). Given the adverse impact of clinical hyperandrogenism on emotional wellbeing and QoL (see [Chapter 2: Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing](#)), and the high priority given to clinical hyperandrogenism outcomes during guideline development, this clinical question was prioritised. Cosmetic and COCP therapy are first line treatments for hirsutism in women, including in PCOS. There are few studies of anti-androgen pharmacological agents in the treatment of PCOS and there are limited relevant studies on the use of anti-androgens in other populations that can guide practice in PCOS, with the majority of studies involving anti-androgen pharmacological agents combined with COCPs (see [Section 4.3 COCP in combination with other agents](#)). Overall, the role of anti-androgens remains controversial and this question was prioritised. Pure anti-androgens were prioritised and reviewed here across flutamide, finasteride and spironolactone. Other agents such as synthetic progestin with anti-androgenic properties were not prioritised for review in this guideline.

Summary of systematic review evidence

Anti-androgen versus placebo

One study of adolescents was identified to address this comparison [455]. Due to the lack of direct comparisons between groups (no p values reported for between groups for end of treatment data), it is uncertain whether there were any differences in this very low quality study with very low certainty for outcomes: BMI (kg/m^2); Modified Ferriman-Gallwey score (mFG); SHBG ($\mu\text{g}/\text{ml}$); Testosterone (ng/dL); DHEAS ($\mu\text{mol}/\text{L}$); Androstenedione (ng/ml); GI related adverse effects. Side effects were not reported.

Anti-androgen + lifestyle versus placebo + lifestyle

One study was identified to address this comparison in adults [442]. Due to the lack of direct comparisons between groups (no p values reported for between groups for end of treatment data), it is uncertain whether there were any differences in this moderate quality study with moderate certainty for outcomes: Weight (kg); BMI (kg/m^2); Number of cycles in previous 6 months; Hirsutism (FG score); SHBG (nmol/L); FAI (pg/ml); Testosterone (ng/ml); DHEAS ($\mu\text{g}/\text{ml}$); Androstenedione (ng/dl); Fasting insulin ($\mu\text{U}/\text{ml}$); Fasting glucose (mg/ml); Response of glucose to OGTT- glucose AUC ($\text{mg}/\text{ml}\cdot\text{min}$); Response of insulin to OGTT- insulin AUC ($\mu\text{U}/\text{ml}\cdot\text{min}$); QUICKI; ISI; HDL (mg/dL); LDL (mg/dl); Triglycerides (mg/dl).

The only side effect reported in the anti-androgen group was a mild increment in transaminase levels.

Anti-androgen (daily) versus anti-androgen (every 3 days)

Two RCTs that address this comparison in adults were identified [456, 457]. While a statistically significant improvement was found in hirsutism FG score with use of the frequency of every 3 days over daily anti-androgens, we remain cautious due to very low certainty in effect estimates and the quality of evidence. No statistically significant differences were found for: BMI, testosterone, SHBG and fasting insulin.

GI related side effects were found in the group taking anti-androgen every 3 days (compared to those on daily treatment).

Anti-androgen + diet versus metformin + anti-androgen + diet

Three RCTs that address this comparison in adults were identified [441, 442, 444]. While a statistically significant improvement was found in fasting glucose and HOMA-IR with the addition of metformin to anti-androgen and lifestyle; and in triglycerides with anti-androgens and lifestyle (without metformin); we remain cautious due to low to very low certainty in effect estimates and the quality of evidence. No statistically significant differences were found for: Weight, WHR, BMI [kg/m²], Number of cycles/year, Number of cycles in previous 6 months, FAI (pg/ml), Hirsutism [FG score], SHBG [nmol/l], Testosterone [nmol/l], Fasting insulin [?IU/mL], QUICKI, OGTT [mg/dl], Total cholesterol (mM/l), HDL (mmol/l), LDL (mmol/l).

As noted above, it is difficult to offer definitive evaluation of the use of anti-androgens because of the poor quality of evidence and lack of valid randomised controlled studies.

As the undesirable effect of antiandrogens is mostly related to mild hepatotoxicity, lifestyle does not seem to alleviate such a risk. Conversely, it seems that the addition of metformin does not increase either the risk of elevated liver indices or general side effects (same of, even increased, compliance with treatment in one study). The potential for teratogenicity for anti-androgens especially when used as a single agent in women at risk for conception limits the use of these medications. There is no evident dose-response relationship.

Summary of narrative review evidence

Other relevant evidence and guidelines not specific to the PCOS population, were considered to inform these recommendations, include those around side effects of anti-androgens. The GDG considered it is mandatory to use concomitant contraception with anti-androgens in order to avoid foetal male under virilisation in the event of unplanned pregnancy [458]. Consistent with the Endocrine Society guidelines we recommend against antiandrogen monotherapy unless adequate contraception is used and note that cosmetic and COCP therapy are first line treatments for hirsutism in women including in PCOS [459]. Due to the growth cycle of hair, at least a 6 – 12 months course treatment is optimal to evaluate the effectiveness of the antiandrogen treatment in improving hirsutism and/or acne [458].

Recommendations

-
- | | | |
|-----------|--|--|
| 4.6.1 EBR | Where COCPs are contraindicated or poorly tolerated, in the presence of other effective forms of contraception, anti-androgens could be considered to treat hirsutism and androgen-related alopecia. | 
 |
| 4.6.2 CPP | Specific types or doses of antiandrogens cannot currently be recommended with inadequate evidence in PCOS. | |
-

Justification

There was insufficient evidence to make an evidence-based recommendation. The group recognised plausible reasons for anticipating differences in the relative effectiveness of anti-androgens for different PCOS phenotypes, ages and anthropometric characteristics. It was also acknowledged that the various anti androgens have different efficacy and side effects. However, evidence to inform use of these agents alone was poor for all identified agents. There is no evidence on the direct and indirect costs of using anti-androgens, however the cost of available treatment is relatively high. Approval status and cost of these agents also varies across countries, with challenges in access and availability and contraception is considered mandatory in reproductive age women. For these reasons, most anti-androgen use in PCOS is in combination with COCPs (see [Section 4.3](#)), however use could be considered with other forms of contraception.

4.7 Inositol

Is inositol alone or in combination with other therapies, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

Clinical need for the question

Women with PCOS are commonly treated with insulin sensitising agents due to insulin resistance and hyperinsulinemia, common features of the syndrome both in obese and non-obese women. Mild gastrointestinal side effects related to metformin, and more serious adverse effects related to glitazones, other medical options are needed in treating insulin resistance in women with PCOS. Inositol (myo-inositol and di-chiro inositol) is a nutritional supplement that acts as a second messenger and has been shown to play a role in insulin signaling transduction [460]. Previous studies have focused on insulin resistance and hormonal profiles and gestational diabetes in women with PCOS.

Summary of systematic review evidence

A Cochrane systematic review [461] was identified to address this question and compared inositol with placebo. No further, more current evidence was identified. Findings from meta-analysis demonstrated that whilst serum SHBG (nmol/L) favoured inositol, there were no statistically significant differences between inositol and placebo for BMI, waist-hip ratio, ovulation (no. that ovulated), serum testosterone (nmol/L), triglyceride (mmol/L), cholesterol (mmol/L), fasting glucose (mmol/L) or fasting insulin (uIU/L).

Summary of narrative review evidence

In a more recent systematic review published after the evidence synthesis for this guideline, yet completed before the GDG meeting, ovulation rate and menstrual cycles appear to improve with inositol in women with PCOS [460, 462]. Furthermore, some data also suggests inositol may be effective in decreasing risk for GDM [463]. The literature however is limited, many key questions remain [460] and research is prioritised. Many of the included studies focused on combinations of therapy such as inositol and folate and adequate studies of inositol alone were not available.

Recommendations

-
- 4.7.1 EBR Inositol (in any form) should currently be considered an experimental therapy in PCOS, with emerging evidence on efficacy highlighting the need for further research.    
-
- 4.7.2 CPP Women taking inositol and other complementary therapies are encouraged to advise their health professional.
-

Justification

Whilst the evidence at this time on the benefit of inositol (in all forms) was inadequate to make an evidence-based recommendation, there is some emerging data suggesting metabolic, hormonal and ovulatory benefits. As this agent is freely available as a nutritional supplement, at low to moderate cost and appears to have a limited side effect profile, it may warrant consideration for use despite limited and low quality evidence. As with other supplements or complementary therapies, women taking this agent are encouraged to advise their health care team.

Chapter Five

Assessment and treatment of infertility

The evidence synthesis team, guideline lead and guideline development group (GDG) members were involved in the original Australian evidenced-based guideline in PCOS, and in 2014 the World Health Organisation (WHO) commissioned evidence synthesis update and development of guidelines for the management of anovulatory infertility in women with PCOS [464].

Here we expand the prioritised questions aligned with international consultation, extend the GDG, update and expand evidence synthesis, and complete a full Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework evaluation. The WHO guidance document is referenced below where relevant, and a summary of subsequent and expanded evidence is provided.



5.1a Assessment of factors that may affect fertility, treatment response or pregnancy outcomes

Should women with PCOS undergo pre-conception (pre-pregnancy) evaluation (assessment) for (and where possible correction of) risk factors that may adversely affect fertility and response to infertility therapy?

Should women with PCOS, and with or without infertility, undergo pre-conception (pre-pregnancy) evaluation (assessment) for (and where possible correction of) risk factors that may lead to adverse (early or late) pregnancy outcomes?

Should women with PCOS undergo close (early or late) pregnancy monitoring for adverse pregnancy outcomes?

Clinical need for the questions

Ovulatory disturbance is a key diagnostic feature of PCOS, leading to infertility, and women with PCOS also have adverse pregnancy outcomes. Modifiable lifestyle factors, especially excess weight, exacerbate infertility, response to infertility treatment and pregnancy health and prevention of weight gain and where needed lifestyle intervention for weight loss is recommended ([Chapter 3](#)). The prevalence of miscarriage appears increased in PCOS with more research needed. Whilst there is clear recognition of the need to optimise preconception and pregnancy health in the general population, there is currently no evidence-based guideline in these areas in high-risk women with PCOS.

Summary of narrative evidence

A systematic review was not conducted to answer this question, which was reviewed narratively based on clinical expertise.

Modifiable risk factors known to impact fertility and response to Assisted Reproductive Technology (ART): BMI < 18 or > 25kg/m², waist to hip ratio (WHR – central adiposity), smoking status, alcohol consumption, prescribed and recreational drug use, untreated sexually transmitted infections, nutritional status, supplementation with folate, vitamin D and dental health have been identified as modifiable risk factors preconception (2, 3, 5, 13, 26). Anxiety, depression and psychological symptoms can impact relationship health, sexual intimacy and ART treatment adherence (19), whilst mental health care supports treatment adherence, relationship health and quality of life (QoL). These factors should be optimised, aligned with WHO guidance, and priority areas and recommendations for the general population [465].

Pregnancy and fertility complications: Women with PCOS are at an increased risk of gestational diabetes (GDM), preterm birth, pre-eclampsia, miscarriage, still birth, longer time to conception and poor embryo development, reduced embryo implantation rates, ovarian hyper stimulation syndrome (OHSS) (1) and ectopic pregnancy (18), which are also exacerbated by obesity.

Weight loss: Lifestyle management is recommended for weight loss when the BMI is $>25\text{kg}/\text{m}^2$ (see Chapter 3). A 2014 systematic review on weight loss prior to ART, noted improved natural conception, number of embryos for transfer, ART pregnancies, live birth rate, cancelled cycles, miscarriage rates and number of ART cycles required to achieve a pregnancy (20). A 2017 systematic review and meta-analysis, (14) found that lifestyle interventions benefited weight loss and natural pregnancy rate, with limited evidence for live birth rate or birth weight, yet natural birth rate did increase (16, 27). Lifestyle intervention also results in significant broader health benefits in pregnancy and beyond. Intensive weight loss is usually avoided just prior to conception with associated adverse outcomes including cycle cancellation and decrease in fertilisation, implantation, ongoing pregnancy and live birth (17). Bariatric surgery is generally considered second-line to improve fertility outcomes in PCOS with anovulation and significant obesity ($\text{BMI} \geq 35\text{kg}/\text{m}^2$) resistant to intensive lifestyle modification and/or pharmacotherapy (17).

Prospective randomised studies of preconception interventions that evaluate broad screening and lifestyle intervention are lacking in the general population and in PCOS [466], especially when considering pregnancy outcomes. However, aligned with lifestyle recommendations in PCOS outlined in Chapter 3, healthy lifestyle and lifestyle intervention should be considered in all women with PCOS, especially preconception and those with infertility based on risk, potential benefit and unlikely risk of adverse effects, whilst highlighting the critical need for more research.

Antenatal care: Close monitoring of weight and screening for hyperglycaemia early in pregnancy are recommended, especially in high-risk populations given the associated morbidity in pregnancy [467, 468]. In antenatal care, there was no evidence to guide screening for GDM or hypertension specifically in women with PCOS, although evidence shows an increased risk in PCOS and screening approaches in the general population involve identification of women at high risk.

Recommendations

- 5.1.1 CPP Factors such as blood glucose, weight, blood pressure, smoking, alcohol, diet, exercise, sleep and mental, emotional and sexual health need to be optimised in women with PCOS, to improve reproductive and obstetric outcomes, aligned with recommendations in the general population.
Refer to [Lifestyle](#), [Emotional Wellbeing](#) and [Diabetes](#) risk sections
- 5.1.2 CPP Monitoring during pregnancy is important in women with PCOS, given increased risk of adverse maternal and offspring outcomes.

Justification

General population recommendations highlight the vital role of healthy lifestyle, weight loss where women are overweight, smoking cessation, omitting alcohol, exercise and management of mental health issues to optimise reproductive outcomes, especially in high-risk groups, which includes in PCOS. Recommendations here are expected to improve efficacy and potentially reduce ART costs. Women with infertility and their health professionals are attuned to the need for healthy lifestyle and prevention strategies and are likely to accept these recommendations and consider them feasible. In antenatal care, recommendations for screening and monitoring in PCOS can only be informed by increased risks in pregnancy in PCOS with a lack of PCOS specific intervention studies. Additional resources may be required in implementation.

5.1b Tubal patency testing

Should women with PCOS and infertility due to anovulation alone with normal semen analysis, have tubal patency testing prior to starting ovulation induction with timed intercourse or IUI treatment or delayed tubal patency testing?

Clinical need for the question

One of the leading causes of female infertility is tubal pathology, potentially affecting around 30% of infertile women [469]. The diagnostic assessment of infertility often includes tubal testing by hysterosalpingography or laparoscopy as outlined in the WHO evidence report on infertility management in PCOS. PCOS is the most frequent cause of anovulation in infertile women and ovulation induction is the most common treatment, however there is little information about the prevalence of tubal pathology or the need for intrauterine insemination with normal semen analysis in infertile women with PCOS.

Summary of narrative evidence

A systematic review was not conducted to answer this question and this was reviewed narratively based on clinical expertise. There is no evidence to support that hydrosalpinges or other fallopian tube disorders are more frequent in PCOS women [470]. Yet the assessment of tubal patency is considered in infertility workup, as outlined in the WHO evidence report on infertility treatment in PCOS. Whilst adverse effects from this intervention are not common, false positives have been described and tubal patency testing may be more appropriate when targeted to those at increased risk of tubal infertility [471]. In this context, consideration of risks for tubal pathology are clinically appropriate, including:

- a. Previous abdominal or pelvic sepsis,
- b. Previous pelvic and/or abdominal surgery
- c. Cases of recurrent acute pelvic pain [472],
- d. History of sexual transmitted diseases or pelvic inflammatory disease or
- e. Endometriosis

Recommendations

5.1.3 CCR In women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing of tubal patency testing should be discussed on an individual basis.



5.1.4 CCR Tubal patency testing should be considered prior to ovulation induction in women with PCOS where there is suspected tubal infertility.



Justification

If the patient has a clinical history of factors associated with tubal infertility it was deemed that hysterosalpingography could be considered, consistent with routine assessment of infertility. Hysterosalpingography requires dilation of the cervix that generally produces some discomfort, false positives are described and other related complications are uncommon. A lack of evidence to guide practice was noted in PCOS when considering these recommendations, however general population approaches were judged as applicable in this population, where other risk factors are present.

5.2 Ovulation induction principles

In reviewing the literature on pharmacological treatment for ovulation induction, general principles emerged that apply across all recommendations. These have been extracted into a set of clinical practice points to inform women and guide health professionals when considering or recommending pharmacological therapy for ovulation induction in PCOS. These practice points apply to all pharmacological treatments prioritised and addressed in the guidelines. In addition, duration of ovulation induction was considered under general principles.

5.2.1 CPP The use of ovulation induction agents, including letrozole, metformin and clomiphene citrate is off label in many countries. Where off label use of ovulation induction agents is allowed, health professionals need to inform women and discuss the evidence, possible concerns and side effects.

5.2.2 CPP Pregnancy needs to be excluded prior to ovulation induction.

5.2.3 CPP Unsuccessful, prolonged use of ovulation induction agents needs to be avoided, due to poor success rates.

5.3 Letrozole

In women with PCOS, are aromatase inhibitors effective for improving fertility outcomes?

Clinical need for the question

Aromatase inhibitors (AI) are effective as ovulation-inducing agents, including letrozole and anastrozole, with letrozole being the most widely used [473, 474]. These agents prevent the aromatase-induced conversion of androgens to oestrogens, including in the ovary. Yet their mechanisms of ovulation induction are unknown, however they increase secretion of follicle-stimulating hormone (FSH) stimulating ovarian follicle development and maturation [475]. The efficacy, adverse effects and overall role of letrozole in oral ovulation induction have remained controversial.

Summary of systematic review evidence

*Al*s versus placebo

One small RCT [476] with a low risk of bias compared letrozole to placebo in women with clomiphene citrate (CC) resistant PCOS and found that letrozole was better than placebo for ovulation rate per patient (Letrozole: 6 patients/18 patients (33.33%), Placebo: 0 patients/18 patients (0%), $p=0.006$) but there was no difference between letrozole and placebo for pregnancy rate per patient or live birth rate per patient. It is important to note that the findings from this study are of low certainty due to serious risk of imprecision. This study was included in a meta-analysis by Franik 2014 [477] and Misso 2012 [478], however since there is only one study, the meta-analyses do not provide additional evidence.

*Al*s versus CC

Thirteen RCTs compared letrozole with CC. Seven of these RCTs had a high risk of bias [479-485], two had a moderate risk of bias [486, 487] and four had a low risk of bias [488-491]. Upon meta-analysis, we found that letrozole was better than CC for ovulation rate per patient; pregnancy rate per patient; and live birth rate per patient. There was no difference between letrozole and CC for multiple pregnancy rate per patient; and miscarriage rate per patient. When subgroup analysis was conducted for studies that included women with PCOS who were therapy naïve, there was no difference between the two interventions for any outcome though we note that for pregnancy rate per patient the OR 1.68 [95% CI 0.96, 2.94] had an I^2 of 0% and a p value of 0.07.

Al versus CC + metformin

One RCT with moderate risk of bias found that there is no statistical difference between letrozole and CC plus metformin for ovulation rate per cycle, pregnancy rate per cycle, miscarriage rate per pregnancy and multiple pregnancy rate per pregnancy in CC-resistant women with PCOS [492]. This study was included in a meta-analysis by Franik 2014 [477] and Misso 2012 [478], however since there is only one study, the meta-analysis does not provide additional evidence.

Al versus laparoscopic ovarian surgery

Three RCTs with low risk of bias [493-495] compared letrozole to laparoscopic ovarian surgery (LOS) and found that there was insufficient evidence of a difference between letrozole and LOS. One of the RCTs in 147 women with CC resistance found that letrozole was better than LOS for ovulation rate per cycle [493], however the evidence is of low certainty. The systematic review by Farquhar 2012 [496] combined these studies in meta-analysis for pregnancy rate per patient, multiple pregnancy rate per pregnancy and miscarriage rate per pregnancy and there was no statistical difference between the two interventions.

Summary of narrative review evidence

Aromatase catalyses the conversion of androgens to oestrogens, including in the ovary and increase FSH secretion [475], stimulating ovarian follicle development and maturation. AIs prevent this conversion. These agents were originally used to improve pregnancy rates and limit adverse effects [497, 498], especially with clomiphene resistance and failure [498-501]. Letrozole has side effects include gastrointestinal disturbances, hot flushes, headache and back pain [502, 503] and concerns have been raised on potential teratogenic effects [504] in an abstract, as yet unconfirmed in peer-reviewed publications, yet this has sparked a series of warnings to avoid use of AI in infertility. Multiple subsequent case series [486, 505-508], multi-centre RCTs [503, 509] and a recent systematic review and meta-analysis [510], all failed to note an increased congenital anomaly rate with prevalence of anomalies with letrozole or clomiphene under 5% (the expected anomaly rate in this population is 5-8% [511]).

Recommendations

-
- 5.3.1 EBR Letrozole should be considered first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates. 
- 5.3.2 CPP Where letrozole is not available or use is not permitted or cost is prohibitive, health professionals can use other ovulation induction agents. 
- 5.3.3 CPP Health professionals and women need to be aware that the risk of multiple pregnancy appears to be less with letrozole, compared to clomiphene citrate.
-

Justification

Women with PCOS are significantly more likely both to ovulate and to have a live birth after use of letrozole compared to clomiphene, the previous first line agent. The likelihood of live birth is increased 40-60% with letrozole compared to clomiphene. Similarly, failure to ovulate (letrozole resistance) is lower with letrozole versus clomiphene. Multiple pregnancy rates appear lower than clomiphene. Hot flushes, generally the least desired side effect of any anti-oestrogen, is less common with letrozole than clomiphene, but still present. Fatigue and dizziness are more common. The balance of benefits in terms of improved live births with letrozole and less hot flushes was considered to currently outweigh the adverse effects of relatively increased fatigue and dizziness, multiple pregnancy, and unconfirmed concerns about higher congenital anomalies.

5.4 Clomiphene citrate and/or metformin

In women with PCOS, is clomiphene citrate effective for improving fertility outcomes?

In women with PCOS, is metformin effective for improving fertility outcomes?

In women with PCOS and a BMI > 30-32, what is the effectiveness of metformin compared to clomiphene citrate for improving fertility outcomes?

Clinical need for the questions

Clomiphene citrate (CC) is a selective oestrogen receptor modulator with both oestrogenic and anti-oestrogenic properties [512]. It was first approved for use in women with anovulation in 1967 [513] and acts as an anti-oestrogen [475]. CC resistance and failure is well documented [514] and a discrepancy is noted between good ovulation rates and lower pregnancy rates, due to the anti-oestrogenic effects of CC on the endometrium and cervical mucus. Twin pregnancy and triplets with CC are 5–7% and 0.3%, respectively and OHSS is less than 1% [515]. The potential for borderline increased risk of ovarian tumours with 12 cycles or more has been noted [516].

Insulin resistance is common in PCOS [517, 518], driving ovarian androgen biosynthesis and increased bioavailability of free androgens. Excess local ovarian androgen production augmented by hyperinsulinaemia causes premature follicular atresia and anovulation [519]. This has led to insulin-sensitising drugs use in ovulation induction. Metformin has been most widely studied in PCOS and has the most reassuring safety profile [520]. Efficacy has been controversial and therapeutic regimens are not well standardised in clinical practice, with variable doses in use [319].

Summary of systematic review evidence

Metformin versus placebo

One systematic review [521] with up to fourteen studies; and one RCT [522] were identified to address this comparison. Metformin was better than placebo for live birth rate per participant, pregnancy rate per participant and ovulation rate per participant. Pregnancy rate and ovulation rate remained statistically significantly better than placebo when subgrouped by BMI ($BMI < 30\text{kg}/\text{m}^2$ and $BMI > 30$ or $32\text{kg}/\text{m}^2$ subgroups); however live birth rate lost statistical significance when subgrouped by BMI. There was no statistically significant difference between metformin and placebo for miscarriage rate per pregnancy (including when subgrouped). Gastrointestinal upsets were statistically significantly lower with placebo than metformin (including when subgrouped). Multiple pregnancy and OHSS were not reported in the systematic review. It is important to note that the findings for live birth rate and miscarriage rate are of low certainty due to serious risk of bias and serious risk of imprecision in the body of evidence; and findings for pregnancy rate, ovulation rate and adverse events are of moderate certainty due to serious risk of bias. Risk of bias appraisals and GRADE assessments have been adopted from previous versions of this guideline [464].

In an RCT of 149 participants, with moderate certainty, there were no statistically significant differences between metformin and placebo for pregnancy rate per participant, multiple pregnancy rate per pregnancy or miscarriage rate per pregnancy. The majority of the trials stopped metformin at diagnosis of pregnancy or at week 12. Note: insufficient evidence of a differential effect of metformin on BMI.

Clomiphene citrate v placebo

One high quality systematic review with low risk of bias found that CC was better than placebo for pregnancy rate per participant and ovulation rate per participant, however the evidence was of very low certainty due to very serious risk of bias and imprecision.

Metformin versus clomiphene citrate

One systematic review [521] with up to seven studies was identified to address this comparison. There were no statistically significant differences between metformin and clomiphene for live birth rate per pregnancy, multiple pregnancy per pregnancy, miscarriage rate per pregnancy, pregnancy rate or ovulation rate. When subgrouped by BMI, CC was better than metformin for live birth rate, pregnancy rate and ovulation rate in $BMI > 30\text{kg}/\text{m}^2$; and metformin was better than CC for pregnancy rate in $BMI < 30\text{kg}/\text{m}^2$. Adverse events and OHSS were not reported in the systematic review. It is important to note that the findings for live birth rate, multiple pregnancy rate and pregnancy rate are of very low certainty due to very serious risk of bias, serious risk of imprecision and for live birth rate, also serious risk of inconsistency; findings for miscarriage rate and ovulation rate are of low certainty due to serious risk of bias and serious risk of imprecision in the body of evidence.

Metformin versus metformin + clomiphene citrate

One high quality systematic review with low risk of bias evaluating two RCTs with a mean $BMI \geq 30\text{ kg}/\text{m}^2$ [523] and two RCTs (one medium quality RCT with moderate risk of bias [524] and one low quality RCT with high risk of bias [525] were identified by the search. Metformin plus CC was better than metformin alone for ovulation rate, pregnancy rate and live birth rate. There was no statistically significant difference between metformin plus CC and metformin alone for miscarriage rate or adverse events.

Clomiphene citrate versus metformin + clomiphene citrate

One systematic review [521] with up to twenty-one studies; and one RCT [526] were identified to address this comparison. Metformin plus CC was statistically significantly better than CC alone for pregnancy rate per participant and ovulation rate per participant, including when subgrouped by BMI ($BMI < 30\text{kg}/\text{m}^2$ and $BMI > 30$ subgroups). Adverse events were statistically significantly better with CC alone than with metformin plus CC. There was no statistically significant difference between metformin plus CC and CC alone for live birth rate per pregnancy, multiple pregnancy rate per pregnancy or miscarriage rate per pregnancy. OHSS was not reported in the systematic review. It is important to note that the findings for live birth rate, multiple pregnancy and miscarriage rate are of low certainty due to serious risk of bias and serious risk of imprecision in the body of evidence; and findings for pregnancy rate, ovulation rate and adverse events are of moderate certainty due to serious risk of bias. The additional RCT Maged 2015 [526] was insufficient evidence to supplement the findings of Morley 2017 [521].

Clomiphene citrate versus aromatase inhibitors (letrozole)

Thirteen RCTs (level II) compared letrozole with CC. Seven of these RCTs had a high risk of bias [479-485], two had a moderate risk of bias [486, 487] and four had a low risk of bias [488-491]. Upon meta-analysis, we found that letrozole was better than CC for ovulation rate per patient [479, 480, 482, 484, 486, 487, 490, 491]; pregnancy rate per patient [479-491]; and per cycle [482, 483, 491]; and live birth rate per patient [480, 486, 488, 490, 491]. There was no difference between letrozole and CC for ovulation rate per cycle [482, 483, 488, 489, 491]; multiple pregnancy rate per patient [479, 481, 482, 485, 486, 489-491]; and miscarriage rate per patient [480-482, 486-491]. When subgroup analysis was conducted for studies that included women with PCOS who were therapy naïve, there was no difference between the two interventions for any outcome though we note that for pregnancy rate per patient the OR 1.68 [95% CI 0.96, 2.94] had an I² of 0% and a p value of 0.07.

Clomiphene citrate versus gonadotrophin

Two RCTs were identified by the search to address this comparison. One RCT was low quality with high risk of bias [527] compared recombinant FSH with CC in women with PCOS who were therapy naïve and found that there was no difference between the two interventions for all fertility outcomes. The second was a multi-centre RCT with moderate risk of bias [528] comparing CC with low dose gonadotrophins, as the first line therapy for ovulation induction in anovulatory women with PCOS who were therapy naïve. They reported with per protocol analysis that the clinical pregnancy rate was significantly higher in the gonadotrophin treated group. Furthermore, the chance of pregnancy

was almost double in the first treatment cycle when compared to CC. Brown 2016 [529] meta-analysed these same two RCTs combining data for live birth rate and ongoing pregnancy rate and found that gonadotrophins were better than CC (OR 0.64 [0.41, 0.98] p=0.041, I²=0%). Meta-analysis of the two studies for clinical pregnancy rate found that CC was better than gonadotrophins (OR 0.61 [0.40, 0.93] p=0.021, I²=0%). It is important to be cautious of these results (using per protocol event rates), as the number of participants randomised has been used as the denominator when the denominator should have been the number of participants per protocol.

Clomiphene citrate versus clomiphene citrate + gonadotrophin)

Two RCTs were identified to address this comparison, however there was insufficient evidence to determine whether one intervention was better than the other [530, 531].

Recommendations

5.4.1	EBR	Clomiphene citrate could be used alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and pregnancy rates.	❖❖❖ ⊕○○○
5.4.2	EBR	Metformin could be used alone in women with PCOS, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates, although women should be informed that there are more effective ovulation induction agents.	❖❖❖ ⊕⊕⊕○
5.4.3	EBR	Clomiphene citrate could be used in preference, when considering clomiphene citrate or metformin for ovulation induction in women with PCOS who are obese (BMI is $\geq 30 \text{ kg/m}^2$) with anovulatory infertility and no other infertility factors.	❖❖❖ ⊕⊕○○
5.4.4	EBR	If metformin is being used for ovulation induction in women with PCOS who are obese ($\text{BMI} \geq 30\text{kg/m}^2$) with anovulatory infertility and no other infertility factors, clomiphene citrate could be added to improve ovulation, pregnancy and live birth rates.	❖❖❖ ⊕⊕○○
5.4.5	EBR	Clomiphene citrate could be combined with metformin, rather than persisting with clomiphene citrate alone, in women with PCOS who are clomiphene citrate-resistant, with anovulatory infertility and no other infertility factors, to improve ovulation and pregnancy rates.	❖❖❖ ⊕⊕○○
5.4.6	CPP	The risk of multiple pregnancy is increased with clomiphene citrate use and therefore monitoring needs to be considered.	

Justification

CC therapy requires specialist care. Costs to the patient of monitoring (tests and specialist visits) and accessibility to specialist care may present barriers, however increased costs will be offset by reduced multiple pregnancies. Metformin is low cost, accessible and can be used alone and/or in combination with CC, given efficacy on systematic review. Usual doses of metformin range from 1500mg (most commonly) to 1700mg per day for non-fertility studies. A change in usual care may result as clinicians may now be more likely to prescribe metformin. Metformin may be associated with mild gastrointestinal related adverse events (see [Chapter 4](#)). Whilst use is evidence-based, patient explanation and consent is appropriate as metformin therapy for infertility is off label.

5.5 Gonadotrophins

In women with PCOS, are gonadotrophins effective for improving fertility outcomes?

Clinical need for the question

Gonadotropin therapy is used clinically in anovulatory PCOS who have been treated with other first line ovulation induction agents if they have failed to ovulate or if responses reduce chances of conception (e.g., persistent hypersecretion of luteinizing hormone (LH), or an anti-estrogenic endometrial effects). To prevent overstimulation and multiple pregnancy, the traditional standard step-up regimens [532] were replaced by either low-dose step-up regimens [533, 534] or step-down regimens [535] with gonadotropins used alone and different gonadotropin preparations appearing to work equally well [536]. It can be difficult to predict stimulation responses in PCOS and to achieve a single dominant follicle to reduce multiple pregnancy and OHSS and careful monitoring of follicular development by ultrasound is required with triggers only used with two or less follicles over 14mm. The efficacy, safety and role of gonadotrophins compared to other alternatives including single or combined oral ovulation induction agents or laparoscopic surgery remains unclear.

Summary of systematic review evidence

Gonadotrophin versus clomiphene citrate

Two RCTs were identified by the search to address this comparison. One RCT was low quality with high risk of bias [527] compared recombinant FSH with CC in women with PCOS who were therapy naïve and found that there was no difference between the two interventions for all fertility outcomes. The second was a multi-centre RCT with moderate risk of bias [528] comparing CC with low dose gonadotrophins, as the first line therapy for ovulation induction in anovulatory women with PCOS who were therapy naïve. They reported with per protocol analysis that the clinical pregnancy rate was significantly higher in the gonadotrophin treated group. Furthermore the chance of pregnancy was almost double in the first treatment cycle when compared to CC. Brown [529] meta-analysed these same two RCTs combining data for live birth rate and ongoing pregnancy rate and found that gonadotrophins were better than CC (OR 0.64 [0.41, 0.98] p=0.041, I²=0%). Meta-analysis of the two studies for clinical pregnancy rate found that CC was better than gonadotrophins (OR 0.61 [0.40, 0.93] p=0.021, I²=0%). It is important to be cautious of these results (using per protocol event rates), as the number of participants randomised has been used as the denominator when the denominator should have been the number of participants per protocol.

Gonadotrophins versus clomiphene citrate + metformin

Two RCTs compared FSH with CC plus metformin [537, 538]. The RCTs found that FSH was better than CC plus metformin for ovulation rate per participant and pregnancy rate per participant. There was no statistical difference between the two interventions for live birth rate per participant, multiple pregnancy rate per pregnancy, OHSS, miscarriage rate per pregnancy or gastrointestinal (GI) side effects or adverse events. A systematic review by Abu Hashim [539] conducted meta-analysis including studies that do not meet our PICO (patient, intervention, comparison, outcome), however some sensitivity analysis was conducted with the two RCTs listed below. A sensitivity analysis for ovulation rate in 263 patients demonstrated that gonadotrophins are better for ovulation rate (OR 0.13; 95% CI 0.07–0.25; p < 0.00001, I² = 7%); but there was no statistically significant difference between the two interventions for multiple pregnancy rate (n = 263, OR 0.33; 95% CI 0.06–1.68; p = 0.18, heterogeneity not reported).

Gonadotrophins versus gonadotrophins + metformin

One RCT with moderate risk of bias found that FSH plus metformin was better than FSH alone for live birth rate per participant, ovulation rate per participant and pregnancy rate per participant [538]. There was no statistical difference between the two interventions for multiple pregnancy rate per pregnancy, miscarriage rate per pregnancy or adverse events.

Gonadotrophins versus laparoscopic ovarian surgery

One high quality systematic review of RCTs (level I) with low risk of bias compared LOS to gonadotrophins and found that there was no difference between the interventions for live birth rate per patient and pregnancy rate per patient, ovulation rate per patient and miscarriage rate per pregnancy, but LOS was better than gonadotrophins for multiple pregnancy rate (OR 0.13 [0.03 to 0.59] I² = 0%, 4 studies, 303 participants) [496].

Gonadotrophins versus gonadotrophins + clomiphene citrate

One RCT [540] with moderate risk of bias found that FSH plus CC was better than FSH alone for ovulation rate per woman randomised and per protocol, total FSH dose used per woman randomised and per protocol, and duration of stimulation per woman randomised and per protocol. There was no statistical difference between the two interventions for pregnancy rate and live birth rate per woman randomised and per protocol.

Recommendations

5.5.1	EBR	Gonadotrophins could be used as second line pharmacological agents in women with PCOS who have failed first line oral ovulation induction therapy and are anovulatory and infertile, with no other infertility factors.	❖❖❖ ⊕⊕○○
5.5.2	EBR	Gonadotrophins could be considered as first line treatment, in the presence of ultrasound monitoring, following counselling on cost and potential risk of multiple pregnancy, in women with PCOS with anovulatory infertility and no other infertility factors.	❖❖❖ ⊕⊕○○
5.5.3	EBR	Gonadotrophins, where available and affordable, should be used in preference to clomiphene citrate combined with metformin therapy for ovulation induction, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates.	❖❖❖❖ ⊕⊕⊕○
5.5.4	EBR	Gonadotrophins with the addition of metformin, could be used rather than gonadotrophin alone, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates.	❖❖❖ ⊕⊕⊕○
5.5.5	EBR	Either gonadotrophins or laparoscopic ovarian surgery could be used in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, following counselling on benefits and risks of each therapy.	❖❖❖❖ ⊕⊕⊕○
5.5.6	CPP	Where gonadotrophins are prescribed, considerations include:	
		<ul style="list-style-type: none">● cost and availability● expertise required for use in ovulation induction● degree of intensive ultrasound monitoring required● lack of difference in clinical efficacy of available gonadotrophin preparations● low dose gonadotrophin protocols optimise monofollicular development● risk and implications of potential multiple pregnancy	
5.5.7	CPP	Gonadotrophin induced ovulation is only triggered when there are fewer than three mature follicles and needs to be cancelled if there are more than two mature follicles with the patient advised to avoid unprotected intercourse.	

Justification

Gonadotrophin therapy is suitable for improving infertility in women with PCOS in specialist care, with close monitoring. Gonadotrophin therapy provides better per cycle and cumulative pregnancy and live birth rates compared with the use of oral anti-oestrogens and/or no therapy in anovulatory women with PCOS; and there is no evidence of teratogenicity. It is important to note that gonadotrophin therapy requires daily injections and the need for intensive monitoring with ultrasound; with a risk of multiple pregnancy and increased cost of medication compared with oral agents.

5.6 Anti-obesity agents

In women with PCOS, are anti-obesity pharmacological agents effective for improving fertility outcomes?

Clinical need for the question

A 2017 systematic review and meta-analysis [541], found that lifestyle interventions benefited weight loss and natural pregnancy rate, with limited evidence for live birth rate or birth weight, yet natural birth rate did increase [294, 301]. Hence, the impact of non-pharmacological lifestyle interventions on live birth rates remains controversial. Engagement and adherence in lifestyle interventions are challenging. There is a need to assess other weight loss methods, such as pharmacological agents commenced in the preconception period, with some evidence they can induce weight loss and improve fertility outcomes in PCOS.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative evidence

A randomised trial (that did not meet the inclusion criteria for this systematic review due to a change in interventions and combination of treatments) evaluated pre-conception treatment in women with PCOS with a) lifestyle weight loss intervention incorporating caloric restriction, increased physical activity and pharmacological agent (initially sibutramine, and then orlistat), b) oral contraceptive pill c) combined lifestyle and contraceptive pill on fertility outcomes [542]. The trial randomised 149 women and was prematurely stopped due to supposed futility with a low likelihood of showing a clinically meaningful difference. Given the small sample size in a three-arm trial, with no control group, no meaningful conclusions can be inferred. Within the lifestyle arm, including anti-obesity agents, there was a significant reduction in weight from baseline (-6.2Kg, 95% CI -07.1 to -5.3), and compared to the women on COCP pre-conception, those on lifestyle with anti-obesity agents showed no differences in pregnancy outcomes. Evidence for these agents in other relevant population groups is lacking.

Recommendations

-
- 5.6.1 CCR Pharmacological anti-obesity agents should be considered an experimental therapy in women with PCOS for the purpose of improving fertility, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy.
-



Justification

With inadequate evidence in both PCOS and infertility generally, the risk/benefit ratio is currently too uncertain to advocate this as a fertility treatment and it was deemed that it should remain an experimental treatment for this indication.

5.7 Laparoscopic ovarian surgery

In women with PCOS, is ovarian surgery effective for improving fertility outcomes?

Clinical need for the question

Observations that women with PCOS resumed regular ovulation following ovarian biopsies, led to development of surgical wedge resection via laparotomy [543]. Observational data looked promising, but surgery was surpassed by ovulation induction agents, until less invasive laparoscopic surgery [544], with potential for less adhesions and lower cost. Minor methodological variations are reported (electrocautery, laser vaporization, multiple ovarian biopsies and others), all seemingly with effects on the endocrine profile. OHSS and multiple pregnancy risks are lower than with other options, but other risks potentially are higher, and clarification of the role of LOS, particularly in comparison to other treatments, is needed in infertile women with PCOS.

Summary of systematic review evidence

Laparoscopic ovarian surgery versus metformin

Two medium quality RCTs (level II) (published across three papers) with a moderate risk of bias compared LOS to metformin and found that there was insufficient evidence to make a recommendation about LOS compared to metformin for live birth rate per patient, ovulation rate per cycle, pregnancy rate per cycle, pregnancy rate per patient, multiple pregnancies, miscarriage rate per pregnancy, adverse effects and QoL [545-547] largely because the evidence was conflicting. One RCT reported that LOS was better than metformin for ovulation (OR 2.05; [1.4–2.9] p=0.001) and pregnancy rate (per cycle: OR 2.19 [1.03–4.63] p=0.03; per patient: OR 2.47 [1.05–5.81] p=0.03) [545] and the other study reported that metformin was better than LOS for live birth rate (metformin: 82.1%, LOS: 64.5%, p<0.05), pregnancy rate per cycle (metformin: 18.6%, LOS: 13.4%, p<0.05), and miscarriage rate (metformin: 15.4%, LOS: 29.0%, p<0.05) [546, 547]. Both medium quality single centre studies had a small sample size and moderate risk of bias and therefore need to be interpreted with caution.

Laparoscopic ovarian surgery versus clomiphene citrate

Two high quality RCTs (level II) with a low risk of bias compared LOS to CC [548, 549] and found that there was no difference between LOS and CC for live birth rate per patient and pregnancy rate per patient, ovulation rate per patient and miscarriage rate per pregnancy [548, 549]. There was insufficient evidence to support or refute the use of LOS over CC for multiple pregnancies [548, 549].

Laparoscopic ovarian surgery versus clomiphene citrate + metformin

Three low to moderate quality RCTs with low to moderate risk of bias compared LOS to CC plus metformin (all three studies reported in Farquhar 2012 systematic review [496]). Meta-analyses found that CC plus metformin (CC+M) was better than LOS for live birth rate, but there was no difference for pregnancy rate per patient, multiple pregnancy rate, or miscarriage rate per pregnancy [496]. There was insufficient evidence to support or refute the use of LOS over CC plus metformin for ovulation rate per patient, and OHSS [496].

Laparoscopic ovarian surgery versus aromatase inhibitors

Three RCTs with low risk of bias [493-495] compared letrozole to LOS and found that there was insufficient evidence of a difference between letrozole and LOS. One of the RCTs in 147 women with CC resistance found that letrozole was better than LOS for ovulation rate per cycle [493], however the evidence is of low certainty. The systematic review by Farquhar 2012 [496] combined these studies in meta-analysis for pregnancy rate per patient, multiple pregnancy rate per pregnancy and miscarriage rate per pregnancy and there was no statistical difference between the two interventions.

Laparoscopic ovarian surgery versus aromatase inhibitors + metformin

One low quality RCT with moderate risk of bias compared LOS with letrozole plus metformin and found that there was insufficient evidence of a difference between the two interventions for ovulation, pregnancy and miscarriage rate per pregnancy [550].

Laparoscopic ovarian surgery versus gonadotrophins

One high quality systematic review of RCTs (level I) with low risk of bias compared LOS to FSHs and found that there was no difference between the interventions for live birth rate per patient and pregnancy rate per patient, ovulation rate per patient and miscarriage rate per pregnancy, but LOS was better than FSH for multiple pregnancy rate (OR 0.13 [0.03 to 0.59] $I^2 = 0\%$, 4 studies, 303 participants) [496].

Summary of narrative review evidence

Observational data was sourced to evaluate long-term impacts. A 15-25 year follow-up of nearly 150 women after ovarian wedge resection shows that regular menstrual patterns lasting up to 25 years after surgery were restored in 88% of patients with a cumulative pregnancy/live birth rate of 78% [551]. This was considered along with the RCT data.

Recommendations

5.7.1	EBR	Laparoscopic ovarian surgery could be second line therapy for women with PCOS, who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors.	❖❖❖ ⊕⊕○○
5.7.2	CCR	Laparoscopic ovarian surgery could potentially be offered as first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors.	❖❖❖
5.7.3	CPP	Risks need to be explained to all women with PCOS considering laparoscopic ovarian surgery.	
5.7.4	CPP	Where laparoscopic ovarian surgery is to be recommended, the following need to be considered:	
		<ul style="list-style-type: none">● comparative cost● expertise required for use in ovulation induction● intra-operative and post-operative risks are higher in women who are overweight and obese● there may be a small associated risk of lower ovarian reserve or loss of ovarian function● periadnexal adhesion formation may be an associated risk.	

Justification

LOS is an intervention that can lead to a singleton birth in women with PCOS. There is no convincing evidence of inferiority over other common ovulation induction agents, there is no need for monitoring (because of mono-ovulation) and only a background risk of multiple pregnancy. However, it is important to note that LOS is an invasive surgical intervention; there is a small risk of reduced ovarian reserve or loss of ovarian function; and adhesion formation should be considered. Issues covered in the clinical practice points should be carefully considered.

5.8 Bariatric surgery

In women with PCOS, what is the effectiveness of lifestyle interventions compared to bariatric surgery for improving fertility and adverse outcomes?

Clinical need for the question

Obesity is increasing in prevalence throughout the world, as is morbid obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$) [552]. Women with PCOS have higher rates of weight gain and of obesity, adversely affecting fertility. Weight loss improves outcomes as previously outlined. In severe obesity, lifestyle interventions have limited efficacy. Substantial efficacy of bariatric surgery on weight loss has been demonstrated in severely obese women. Potential benefits need to be balanced with the delay in infertility treatment and pregnancy for surgery and stabilisation of weight, the risks of bariatric surgery and the potential risks of pregnancy after bariatric surgery. Controversy persists around efficacy for fertility and pregnancy outcomes, optimal timing, adverse effects and comparative efficacy with other treatments, as well as on adverse effects on subsequent pregnancies.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative review evidence

UK clinical guidelines for obesity management in the general population [553] recommend considering bariatric surgery with a $\text{BMI} \geq 35 \text{ kg/m}^2$ with one or more severe complications, expected to improve with weight loss and failure of structured lifestyle intervention [553]. Obesity surgery can be considered after non-surgical treatment has failed with a $\text{BMI} \geq 40 \text{ kg/m}^2$ and obesity surgery can be first line treatment with a $\text{BMI} \geq 50 \text{ kg/m}^2$ [554]. Other guidelines recommend lower barriers to surgery [555]. For type of surgery, Vertical Sleeve Gastrectomy (VSG) has overtaken the Roux-en-Y Gastric Bypass (RYGB) and gastric band surgery as the most commonly performed bariatric surgery with lower operative morbidity [556]. Adjustable gastric banding, once the choice for women planning pregnancy is now less common given complications and overall lower long-term weight loss [556].

High quality RCTs of bariatric surgery versus medical management in DM2 show persistent benefits and superiority of weight loss and bariatric surgery in curing or ameliorating diabetes [557, 558]. Yet these studies are absent in PCOS for fertility and pregnancy outcomes, with current PCOS studies poorly designed [559], and with failure to report key perinatal outcomes to inform risk to benefit ratio. In PCOS, the balance between delaying infertility treatment and pregnancy whilst undertaking bariatric surgery and attaining stable post-operative weight, is also unclear [560], as is the optimal type of bariatric surgery.

Bariatric surgery can cause malabsorption and psychological issues including disordered eating [254] and may adversely affect maternal and neonatal health. Adequate intake and absorption of iron, folate, iodine and other nutrients are of concern. While supplement use is widely recommended following bariatric surgery especially for pregnant women, there are reports of poor compliance [561] and challenges tolerating fortified foods such as bread. National registries (surgery, pregnancy, infants) show that obese women who undergo bariatric surgery and conceive compared to similarly obese controls, had more small for gestational age babies, shorter gestations, and a trend towards increased neonatal mortality [562], with similar findings in retrospective studies [563]. Benefits have included less GDM and large for gestational age babies.

Recommendations

5.8.1 CCR Bariatric surgery should be considered an experimental therapy in women with PCOS, for the purpose of having a healthy baby, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy.



5.8.2 CPP If bariatric surgery is to be prescribed, the following needs to be considered:

- comparative cost
- the need for a structured weight management program involving diet, physical activity and interventions to improve psychological, musculoskeletal and cardiovascular health to continue post-operatively
- perinatal risks such as small for gestational age, premature delivery, possibly increased infant mortality
- potential benefits such as reduced incidence of large for gestational age fetus and gestational diabetes
- recommendations for pregnancy avoidance during periods of rapid weight loss and for at least 12 months after bariatric surgery with appropriate contraception.

If pregnancy occurs, the following need to be considered:

- awareness and preventative management of pre-and post-operative nutritional deficiencies is important, ideally in a specialist interdisciplinary care setting
- monitoring of fetal growth during pregnancy.

Justification

Bariatric surgery improves weight loss and can improve comorbidities associated with PCOS. However, evidence in relation to fertility and pregnancy outcomes is limited, with some concerns about potential perinatal adverse effects of bariatric surgery. Overall, the indications, role and comparative effectiveness with other fertility therapies, ideal timing, optimal type of surgery, adverse effects and risk to benefit ratio in PCOS are still to be resolved. Given the concerns about the potential perinatal adverse effects of bariatric surgery and the remaining controversies, no recommendation can be made at this time about the use of bariatric surgery to improve fertility and pregnancy outcomes in women with PCOS.

5.9a In-vitro fertilisation

In women with PCOS, is stimulated In-vitro fertilisation/Intracytoplasmic Sperm Injection effective for improving fertility outcomes?

Clinical need for the question

Ovulation induction therapies are first and second line in infertility management in women with PCOS, anovulation and no other fertility factors. Yet resistance to and failure of ovulation induction therapies and inability to overcome other concomitant causes of infertility means that Assisted Reproductive Technology (ART) therapies including In-vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) used in male factor infertility, have a role in PCOS. IVF has risks and limitations, yet also offers the opportunity for pregnancy and live birth. Challenges exist across the diversity of protocols available for IVF and concerns in PCOS including OHSS, high oestradiol levels, accelerated endometrial maturation and optimally the use of “freeze all” interventions. The clinical practice questions here include indications, timing and comparative efficacy with other treatments, yet RCTs in this area are very limited in women with anovulatory PCOS.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative review evidence

There are no RCTs identified by the guideline development team, comparing stimulated IVF ± ICSI therapy with ovulation induction in women diagnosed with PCOS. The role of IVF in PCOS was explored by the WHO guidance group, and the review and recommendations were considered here by the GDG in making their recommendations [464]. Factors that influenced considerations here include access, cost and risks. The patient and societal benefits of ovulation induction compared with IVF treatments in anovulatory PCOS women require RCTs and systematic analysis. Outcomes as time to conception, cost of therapy, QoL, OHSS risk, multiple pregnancy, miscarriage and livebirth rates should be investigated.

Recommendations

-
- 5.9.1 CCR In the absence of an absolute indication for IVF ± ICSI, women with PCOS and anovulatory infertility could be offered IVF as third line therapy where first or second line ovulation induction therapies have failed. ❖❖❖
-
- 5.9.2 CPP In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used, multiple pregnancies can be minimised.
-
- 5.9.3 CPP Women with PCOS undergoing IVF ± ICSI therapy need to be counselled prior to starting treatment including on:
- availability, cost and convenience
 - increased risk of ovarian hyperstimulation syndrome
 - options to reduce the risk of ovarian hyperstimulation.
-

Justification

The GDG deemed IVF should be considered after failed ovulation induction treatment with high pregnancy rates per cycle, especially in younger women. Given the risks and the high costs that can be prohibitive for many patients, IVF should be considered third line medical therapy. It was noted that conception and delivery are highly valued by health professionals and women with PCOS and even when cost and risks are increased, many may elect to undertake IVF. Health Professionals must weigh benefits and risk when advising PCOS patients to enable an informed decision.

5.9b Gonadotropin releasing hormone protocol

In women with PCOS undergoing IVF/ICSI treatment, is the gonadotropin releasing hormone antagonist protocol or gonadotropin releasing hormone agonist long protocol the most effective for improving fertility outcomes?

Clinical need for the question

Women with PCOS are particularly vulnerable to OHSS with IVF ± ICSI treatment, prompting caution and leading to exploration of different protocols including with gonadotropin releasing hormone (GnRH) and other options including in-vitro maturation (see below) [564]. One of the proposed methods to reduce the risk of OHSS is to use a GnRH antagonist (as opposed to an agonist) [565-568]. There is acknowledged complexity in interpreting outcomes from IVF treatments in PCOS, with variable protocols and endpoint reporting, requiring close evaluation of the literature. One of the proposed methods to reduce the risk of OHSS is to use a GnRH antagonist (as opposed to an agonist) to suppress pituitary luteinising hormone (LH) secretion.

Summary of systematic review evidence

In the eight included studies of low [569-571], moderate [572-575], and high risk of bias [576] comparing an antagonist protocol with a long agonist protocol, there were statistically significant differences in the amount of gonadotropin required (5 studies in favour of the antagonist protocol) [569-571, 574, 576], in the duration of gonadotropin use (6 studies in favour of the antagonist protocol) [570-574, 576], in OHSS rates (2 studies in favour of the antagonist protocol) [571, 573]. No statistically significant differences were found between groups for clinical pregnancy rates, miscarriage rates, number of oocytes collected, cancellation rates, and multiple pregnancy rates.

Recommendations

-
- 5.9.6 EBR A gonadotrophin releasing hormone antagonist protocol is preferred in women with PCOS undergoing an IVF ± ICSI cycle, over a gonadotrophin releasing hormone agonist long protocol, to reduce the duration of stimulation, total gonadotrophin dose and incidence of ovarian hyperstimulation syndrome (OHSS). 

-
- 5.9.7 CPP Human chorionic gonadotrophins is best used at the lowest doses to trigger final oocyte maturation in women with PCOS undergoing an IVF ± ICSI cycle to reduce the incidence of OHSS.
-
- 5.9.8 CPP Triggering final oocyte maturation with a gonadotropin-releasing hormone (GnRH) agonist and freezing all suitable embryos could be considered in women with PCOS having an IVF/ICSI cycle with a GnRH antagonist protocol and at an increased risk of developing OHSS or where fresh embryo transfer is not planned.
-
- 5.9.9 CPP In IVF ± ICSI cycles in women with PCOS, consideration needs to be given to an elective freeze of all embryos.
-

Justification

The duration of stimulation with a GnRH antagonist approach is around a day shorter than the standard 'long-down regulation' approach with a GnRH agonist. The rate of OHSS appears less with a GnRH antagonist approach in comparison to the standard 'long-down regulation' approach with a GnRH agonist. The effect size is difficult to quantify, as all most of these studies used a high dose human chorionic gonadotrophin (hCG) trigger in both arms, whereas this may not reflect clinical practice. There does not appear to be an increase in undesirable side effects with an antagonist down-regulation approach. The choice to trigger final oocyte maturation with GnRH agonist instead of hCG is important to prevent OHSS.

5.9c Trigger type

In women with PCOS undergoing GnRH antagonist IVF/ICSI treatment, is the use of hCG trigger or GnRH agonist trigger the most effective for improving fertility outcomes?

Clinical need for the question

One of the prominent causes of OHSS is the occurrence in women with PCOS undergoing ovarian hyperstimulation for IVF, particularly where hCG is used to trigger ovulation. Early in 1990 an alternative to exogenous hCG triggering emerged with GnRH-agonist use, providing an additional ovulatory option for IVF. A single bolus of GnRH-agonist administration during late follicular development in women with PCOS treated with gonadotropins, results in a surge of endogenous FSH and LH for final oocyte maturation and fertilisation. OHSS appears reduced yet lower pregnancy rates with GnRH-agonist triggers are observed and may vary when transferring fresh versus frozen thawed embryos in cycles from the same cohort, suggesting that the pregnancy rate is dependent of endometrial quality. An alternative option therefore in women with PCOS at high risk of OHSS, is to freeze oocytes or embryos after GnRH agonist triggering and transfer the embryos in subsequent cycles. The choice to trigger final oocyte maturation with GnRH-agonist, instead of hCG, and to transfer frozen embryos requires clarification.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative review evidence

This question was addressed in a Cochrane review in 2014 [577]. In 17 RCTs ($n = 1847$), in fresh autologous cycles, GnRH-agonists were associated with a lower live birth rate than HCG (OR 0.47, 95% CI 0.31 to 0.70; five RCTs, 532 women, $I^2 = 56\%$, moderate-quality evidence), yet there was also a lower incidence of mild, moderate or severe OHSS than with HCG (OR 0.15, 95% CI 0.05 to 0.47; eight RCTs, 989 women, $I^2 = 42\%$, moderate-quality evidence). In fresh autologous cycles, GnRH-agonists were associated with a lower ongoing pregnancy rate than HCG (OR 0.70, 95% CI 0.54 to 0.91; 11 studies, 1198 women, $I^2 = 59\%$, low-quality evidence) and a higher early miscarriage rate (OR 1.74, 95% CI 1.10 to 2.75; 11 RCTs, 1198 women, $I^2 = 1\%$, moderate-quality evidence). However, the effect was dependent on the type of luteal phase support provided. Multiple pregnancy rates were similar. The authors concluded that final oocyte maturation triggering with GnRH-agonist instead of hCG in fresh autologous GnRH-antagonist IVF \pm ICSI cycles prevents OHSS to the detriment of the live birth rate. In donor-recipient cycles, use of GnRH agonists instead of hCG resulted in a lower incidence of OHSS, with no evidence of a difference in live birth rate. GnRH agonist as an oocyte maturation trigger could be useful for women who choose to avoid fresh transfers, where donate oocytes are used or in women who wish to freeze their eggs for later use.

Recommendations

See recommendations in [5.9b GnRH protocol](#).

Justification

The choice to trigger final oocyte maturation with GnRH-agonist instead of hCG is important in prevention of OHSS as hCG alone induces oocyte maturation but is associated with OHSS. GnRH-agonist triggers are associated with lower pregnancy rates, primarily in fresh embryo transfers, which can be overcome in frozen cycles.

5.9d Choice of FSH

In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, does the choice of FSH effect fertility outcomes?

Clinical need for the question

FSH can be purified from human urine (uFSH) or synthesised from recombinant DNA techniques (rFSH). Urinary preparations have impurities with LH activity known to stimulate androgen production in theca cells and completing maturation of follicles. However, it is known that less than 1% of follicular LH receptors needs to be occupied in order to elicit maximal steroidogenesis and it is therefore possible that enough endogenous LH is present during controlled ovarian stimulation to promote androgen synthesis and oocyte maturation without the need for extra LH activity in FSH preparations. The perceived clinical benefits of rFSH versus uFSH are the subject of ongoing debate and both types of preparations remain commonly used.

Summary of systematic review evidence

One small study (80 participants) of moderate risk of bias compared rFSH with human menopausal gonadotropin (hMG) and found that rFSH was better for the duration of ovarian stimulation required and the number of oocytes retrieved; whereas hMG was better for the maximum serum estradiol level [578]. No statistically significant differences were found between groups for the total dose of gonadotropin used, OHSS rate, clinical pregnancy rate per cycle and take home baby rate per cycle.

Summary of narrative review evidence

Given the limited evidence in PCOS, additional information was sought from rFSH and uFSH use in the general population. In a Cochrane systematic review and meta-analysis, 42 trials with a total of 9606 couples compared rFSH against three different uFSH preparations [579]. rFSH irrespective of the down-regulation protocol, did not result in a statistically significant different live birth rate or OHSS rate, concluding that clinical choice of gonadotrophin should depend on availability, convenience and costs and that further research on these comparisons is unlikely to identify substantive differences in effectiveness or safety.

Recommendation

5.9.4 CCR Urinary or recombinant follicle stimulation hormone can be used in women with PCOS undergoing controlled ovarian hyperstimulation for IVF ± ICSI, with insufficient evidence to recommend specific follicle stimulating hormone (FSH) preparations.



Justification

Only one small study in PCOS has been identified investigating uFSH versus rFSH in PCOS during ovarian stimulation for IVF/ICSI [578]. This study shows similar results to a systematic review and meta-analysis in the general IVF population, where extensive research has concluded no significant difference in birth rate or OHSS was detected and no further research in the general population was recommended. Hence clinical choice of gonadotrophin should depend on availability, convenience and costs.

5.9e Exogenous luteinizing hormone (LH)

In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is exogenous LH treatment during IVF ± ICSI effective for improving fertility outcome?

Clinical need for the question

Options have been explored to reduce OHSS risk in IVF/ICSI in PCOS. The chronic low dose step-up protocol with exogenous FSH in securing single (fewer) dominant follicle selection is an alternative method to avoid multi-follicular development. During late follicular development, LH is essential to achieve adequate ovarian steroidogenesis and develop the subsequent capacity of the follicle to ovulate and luteinize. Increased LH secretion or elevated LH/FSH ratio in PCOS may influence fertility, with inhibition of oocyte maturation, deleterious effects on granulosa cell steroidogenesis and endometrial receptivity and with potential increased early pregnancy loss [580-582]. The lack of clarity around the role of exogenous LH in the setting of IVF/ICSI prompted this clinical question.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative review evidence

Obesity adversely impacts on ovulation and on responses to ovulation induction in PCOS [282]. In PCOS, granulosa cells respond to LH at a relatively earlier follicular stage and are significantly more responsive than for ovulatory women with PCOS or women without PCOS [581]. Granulosa cell differentiation may be prematurely advanced. Controlled ovarian stimulation for multiple follicular development in ART can be performed in a variety of ways to increase efficacy and reduce risks. Systematic reviews and meta-analysis have demonstrated that there is no significant difference between different ovarian stimulation protocols (hMG, purified FSH, recombinant FSH) regarding the fertility outcomes. Therefore, clinical gonadotropin choice depends on availability, convenience, and cost. In standard IVF/ICSI protocols, the types of controlled ovarian stimulation (FSH alone or addition of LH as a supplement) have little impact on the fertility outcomes [579, 583]. Endogenous LH levels may fall too low in older women (>35) during ovarian stimulation, especially with GnRH-antagonist use and LH supplementation has been proposed. However, a multicentre RCT of exogenous LH during the follicular phase showed no fertility benefits outcomes in women over 35 [584]. No current study investigates efficacy of exogenous LH supplement for fertility outcomes in PCOS during IVF/ICSI. Careful monitoring of follicular development during ovarian stimulation is critical.

Recommendation

5.9.5 CCR Exogenous recombinant luteinising hormone treatment should not be routinely used in combination with follicle stimulating hormone therapy in women with PCOS undergoing controlled ovarian hyperstimulation for IVF ± ICSI.



Justification

There is no anticipated effect or benefit to add exogenous LH supplement in women with PCOS undergoing ovarian stimulation for IVF ± ICSI. There is insufficient evidence to determine the benefits of using or not using exogenous LH.

5.9f Adjunct metformin

In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF ± ICSI, is adjunct metformin effective for improving fertility outcomes?

Clinical need for the question

IVF ± ICSI treatment in women with PCOS is usually recommended either third-line (after failed ovulation induction) or in those with other infertility factors such as tubal damage, severe endometriosis or male factors [585]. IVF ± ICSI treatment in PCOS poses challenges, including OHSS [586]. Metformin has been studied to restore ovulation and enhance pregnancy rates in PCOS [587], through a range of mechanisms [522, 588, 589]. These mechanisms provide a physiological rationale for management of insulin resistance in IVF in PCOS. It has also been suggested that metformin may reduce serum estradiol levels during ovarian stimulation and it has also been hypothesised that metformin may reduce the production of vascular endothelial growth factor, both of which are important factors involved in the pathophysiology of OHSS [590]. Therefore, it was deemed important to explore the effectiveness and safety of metformin as a co-treatment in achieving pregnancy or live birth and reducing OHSS in IVF in PCOS.

Summary of systematic review evidence

Six RCTs of low [588, 591, 592], moderate [522], and high risk of bias [593, 594] found that IVF with adjuvant metformin was better for OHSS, clinical pregnancy rate, cancellation rate and live birth rate. No statistically significant differences were found between groups for the amount of gonadotropins used, the duration of ovarian stimulation, miscarriage rates, number of oocytes collected, and multiple pregnancy rates.

Summary of narrative review evidence

A Cochrane review [595] was identified by the search, however it included studies that did not meet the selection criteria for this question. The guideline development group (GDG) considered the meta-analyses in the Cochrane review as clinically relevant and noted that there was no evidence of a difference with adjunct metformin for live birth rate, miscarriage rate, number of oocytes collected, days of ovarian stimulation or cycle cancellation rate; and clinical pregnancy rate was increased with adjuvant metformin whilst OHSS reduced. Mild generally self-limiting side-effects were noted with adjunct metformin, as outlined in [Chapter 4](#).

Recommendations

5.9.10 EBR	Adjunct metformin therapy could be used before and/or during follicle stimulating hormone ovarian stimulation in women with PCOS undergoing a IVF ± ICSI therapy with a GnRH agonist protocol, to improve the clinical pregnancy rate and reduce the risk of OHSS.	❖❖❖ ⊕⊕○○
5.9.11 CCR	In a GnRH agonist protocol with adjunct metformin therapy, in women with PCOS undergoing IVF ± ICSI treatment, the following could be considered: <ul style="list-style-type: none">• metformin commencement at the start of GnRH agonist treatment• metformin use at a dose of between 1000mg to 2550mg daily• metformin cessation at the time of the pregnancy test or menses (unless the metformin therapy is otherwise indicated)• metformin side-effects (see above metformin section)	❖❖❖
5.9.12 CPP	In IVF ± ICSI cycles, women with PCOS could be counselled on potential benefits of adjunct metformin in a GnRH antagonist protocol to reduce risk of ovarian hyperstimulation syndrome (see above for metformin therapy considerations).	

Justification

Women and health professionals would generally value an increased clinical pregnancy rate (with no evidence of a difference in miscarriage rate) and reduced OHSS (with its associated morbidity and rarely mortality). Gastrointestinal side effects were recognised, but noted as mild and self-limiting and may be minimised with lower metformin starting dose and extended release preparations. Metformin was noted to be low cost and readily available, and while off label use was generally allowed, explanation is required for use.

5.9g In-vitro maturation

In women with PCOS, is in-vitro maturation (IVM) effective for improving fertility outcomes?

Clinical need for the question

Where IVF is indicated in PCOS, OHSS risks are increased with gonadotrophin stimulation. IVM of oocytes limits or omits ovarian stimulation prior to oocyte retrieval, with maturation of oocytes post retrieval, avoiding OHSS risk [564]. The definition of an IVM cycle requires clarification [596], as cycles employing an hCG trigger injection are generally associated with asynchronous oocyte maturation rates, poor embryo implantation rates and lower pregnancy rates [597, 598]. There are no RCTs of IVM versus ICSI or ovulation induction in PCOS, however observational studies suggest that offspring from IVM are not adversely affected [599]. Given that IVM is used in practice and has theoretical benefits, this question was prioritised.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative review evidence

With an absence of relevant RCTs [600], retrospective studies suggest IVM is similarly successful for live birth with frozen embryos generated with IVM as embryo transfers generated by standard IVF treatment [564]. However, pregnancy rates are reduced and miscarriage rates are higher if a fresh embryo transfer is performed with IVM [564]. Embryo development appears slower with a greater degree of embryo arrest in IVM [601, 602].

Recommendations

5.9.13 CPP The term in vitro maturation (IVM) treatment cycle is applied to “the maturation in vitro of immature cumulus oocyte complexes collected from antral follicles” (encompassing both stimulated and unstimulated cycles, but without the use of a human gonadotrophin trigger).

5.9.14 CCR In units with sufficient expertise, IVM could be offered to achieve pregnancy and livebirth rates approaching those of standard IVF ± ICSI treatment without the risk of OHSS for women with PCOS, where an embryo is generated, then vitrified and thawed and transferred in a subsequent cycle. 

Justification

The GDG deemed that key elements to consider with IVM included; a clear definition of the term IVM, use in clinical units with sufficient expertise and advantages of reduced risk of OHSS. The group considered the lack of evidence as important. It was considered that IVM could be offered to achieve pregnancy and live birth rates that may approach those of standard IVF ± ICSI treatment, where frozen embryos are used. Given the lack of evidence the group voted for a conditional consensus recommendation that neither favoured this option or other options (IVF), with strong research recommendations.

Chapter Six

Guideline development methods

This guideline was developed as outlined in National Health and Medical Research Council (NHMRC) standards and procedures for rigorously developed external guidelines [603] and according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach [15]. These methods were aligned with European Society of Human Reproduction and Embryology (ESHRE) approaches to guideline development [605].

The work builds on the original Australian guideline in PCOS [148], the update in 2014 as well as the World Health Organisation (WHO) guideline in infertility management [464] and Androgen Excess and PCOS Society (AEPCOS) Statement on improving emotional wellbeing in PCOS [109].

The International evidence-based guideline for the assessment and management of PCOS underpins an international initiative to engage women affected by PCOS and their health professionals to improve health outcomes. Extensive international health professional and consumer engagement informed the gaps, needs, priorities and core clinical outcomes for the guideline. Thirty-seven organisations were engaged with formal partnership with ESHRE and American Society for Reproductive Medicine (ASRM). Guideline development groups (GDGs) included members nominated by the engaged international societies. Society-nominated panel members included women with PCOS, paediatricians, endocrinologists, gynaecologists, primary care physicians, reproductive endocrinologists, psychiatrists, psychologists, dietitians, exercise physiologist, public health experts, researchers and other co-opted experts as required. They were supported by an experienced project management, evidence synthesis and translation team to develop the guideline. Here we provide a comprehensive review of the evidence and formulate recommendations using the GRADE Framework.

Governance and process

Governance included an international advisory board from six continents, a project board, five GDGs, a paediatric advisory panel, advisors and a translation committee (See [Figure 1](#)). The Australian Centre for Research Excellence in PCOS (CREPCOS) and the NHMRC partnered with the ESHRE and ASRM to deliver the guideline. The majority of the funding was provided by the Australian government, with contributions from ESHRE and ASRM. Four advisory, five project board and fifteen GDG face to face meetings occurred across Europe, USA and Australia over 15 months, and enabled guideline training, development and informed translation. Sixty prioritised clinical questions were addressed with evidence synthesis involving 40 systematic and 20 narrative reviews, generating 170 recommendations and practice points. Feedback from the thirty-seven engaged societies and their convened special interest groups of experts and consumers as well as public consultation have informed the final guideline.

Multidisciplinary international guideline development groups

GDGs were convened to address each of the five key clinical areas. Expertise was sought through PCOS networks to ensure multidisciplinary participation within each GDG. Each GDG comprised a chair, professional group members with specific expertise in PCOS and the clinical area of interest (i.e. psychologists/psychiatrist in the emotional wellbeing GDG), a consumer representative, evidence officers and representative to consider cultural aspects.

[See Appendix III](#). Co-opted experts were also included as needed.

Consumer participation

In the development of this guideline, we have sought not only to inform or consult with women affected by PCOS, but to partner with and empower women with PCOS, who are the ultimate beneficiaries of this work. We have engaged with international consumer bodies in PCOS and infertility to this end. This included Polycystic Ovary Syndrome Association Australia (POSAA) (Australia), Verity (United Kingdom), PCOS Challenge (United States), RESOLVE: The National Fertility Association (United States), and Victorian Assisted Reproductive Treatment Authority (VARTA) (Australia), who were actively engaged throughout the guideline process.

An international survey was completed by 1800 women and focus groups were held with women with PCOS to inform gaps in care, guideline priority questions, prioritised outcomes for each intervention and to inform guideline translation, education and support needs and preferred methods of delivery.

Consumer representatives participated in the development of the Centre for Research Excellence funding submission, in the guideline Project Board, International consumer advisory group and in the GDGs. Consumers have been involved in every stage, including development of the guideline scope, public consultation on the scope and developing and refining the clinical questions and recommendations as part of the GDGs. Consumer representatives are also extensively engaged and are partnering in the guideline translation activities.

Indigenous representation and CALD (culturally and linguistically diverse)

Ethnicity and culture was considered when making all recommendations. Indigenous representation was present on the PCOS Australian Alliance Strategic Advisory Group (a member of the Australian Indigenous Doctors Association) and the GDGs comprised clinicians with experience working with CALD and Indigenous communities. The translation of the guideline allows for adaptions on cultural and ethnicity grounds.

Conflict of interest and confidentiality

Conflict of interest has been proactively managed throughout the guideline development process as outlined in NHMRC Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines [603]. All members of the GDGs have provided signed declarations of interest and a confidentiality agreement. Additionally, declarations of interest were a standing agenda item at each monthly meeting and GDG members were requested to detail areas for potential conflict.

The process for managing conflict of interest and confidentiality and recorded declarations can be provided on request (MCHRI-PCOS-Guideline-Group-l@monash.edu).

Training of GDGs in evidence review and guideline development methods

All GDG members attended a workshop, where the methods of reviewing evidence and guideline development were described in detail. The purpose of this workshop was to familiarise the chairs and GDG members with:

- the process of guideline development overall
- the process of identifying, appraising and synthesising evidence in a format to facilitate the formulation of evidence-based recommendations
- grading the strength of evidence and its suitability to support evidence-based recommendations
- when to facilitate discussion and clinical judgement to formulate clinical consensus recommendations in the absence of evidence.

Clinical question development and prioritisation

An International survey and Delphi exercise was conducted to develop and prioritise clinical questions to be addressed. A further prioritisation exercise was conducted within the topic specific GDGs and consumer advisory groups to rank the importance of clinical questions to guide the evidence team and to reach consensus on which clinical questions were to be addressed by a systematic review or by narrative review.

Systematic reviews were performed for highly prioritised questions and for those areas of greatest controversy. Narrative evidence reviews were completed a) where recent or concurrent systematic reviews were being completed by GDG members that could be captured on narrative review; b) where questions were less well suited to a PICO systematic review format; c) for lower prioritised questions or d) where there was insufficient evidence identified for a question where a systematic review was conducted.

Forty questions were addressed by guideline systematic reviews, many others by systematic reviews captured in the narrative reviews and some by narrative reviews of isolated PCOS studies supported by systematic reviews/guidelines in the general population.

The clinical questions addressed by each GDG are as follows:

GDG 1 – Screening, diagnostic assessment, risk assessment and life-stage

- At what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction related to PCOS?
- In women with suspected PCOS, what is the most effective measure to diagnose PCOS related hyperandrogenism (biochemical)?
- In women with suspected PCOS, what is the most effective measure to diagnose PCOS related hyperandrogenism (clinical)?
- What is the most effective ultrasound criteria to diagnose PCOS?
- Is anti-mullerian hormone (AMH) effective for diagnosis of PCOS?
- Is AMH effective to diagnosis of PCOM?
- What is the post-menopausal phenotype of PCOS?
- Are women with PCOS at increased risk for cardiovascular disease (CVD)?
- In women with PCOS, what is the most effective tool/method to assess risk of CVD?
- Are women with PCOS at increased risk for impaired glucose tolerance (IGT), gestational diabetes (GDM) and type 2 diabetes mellitus (T2DM)?
- In women with PCOS, what is the most effective tool/method to assess risk of T2DM?
- Are women with PCOS at increased risk for sleep apnoea?
- What is the method/tool most effective to screen for sleep apnoea in PCOS?
- What is the risk of PCOS in relatives of women with PCOS and should they be screened?
- What is the disease risk in relatives of PCOS (CVD, T2DM)?

GDG 2 - Prevalence, screening, diagnostic assessment and management of emotional wellbeing

- In women with PCOS: 1) What is the prevalence and severity of reduced quality of life (QoL)? And 2) Should QoL be assessed as part of standard care?
- In women with PCOS, what is the most effective tool/method to screen for symptoms of depression and anxiety?
- In women with PCOS, what is the most effective tool/method to assess quality of life?
- Is psychological therapy effective for management and support of depression and/or anxiety, disordered eating, body image distress, self-esteem, feminine identity or psychosexual dysfunction in women with PCOS?
- Is acupuncture effective for management and support of depression and/or anxiety, disordered eating, body image distress, self-esteem, feminine identity or psychosexual dysfunction in women with PCOS?
- Are anti-depressants and anxiolytics effective for management and support of depression and/or anxiety or disordered eating in women with PCOS?
- What is the effectiveness of different models of care compared to usual care?
- In women with PCOS, what is the most effective tool/method to screen body image distress?
- In women with PCOS, what is the most effective tool/method to screen disordered eating?
- In women with PCOS, what is the most effective tool/method to screen psychosexual dysfunction?

GDG 3 – Lifestyle management and models of care

- In women with PCOS, are lifestyle interventions (compared to minimal or nothing) effective for anthropometric, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes?
- In women with PCOS, are diet interventions (compared to different diets) effective for improving anthropometric, metabolic, fertility, and emotional wellbeing outcomes?
- In women with PCOS, are exercise interventions (compared to different exercises) effective for improving anthropometric, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes?
- In women with PCOS, are behavioural interventions (compared to different types of behavioural interventions) effective for improving anthropometric, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes?
- Are women with PCOS at increased risk of obesity?
- In women with PCOS, does obesity impact on prevalence and severity of hormonal and clinical features?

GDG 4 – Medical treatment

- Is the oral contraceptive pill alone or in combination, effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?
- Is metformin alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
- Are anti-obesity pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
- Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
- Is inositol alone or in combination with other therapies, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

GDG 5 – Screening, diagnostic assessment and management of infertility

- Should women with PCOS and infertility undergo pre-conception (pre-pregnancy) evaluation (assessment) for (and where possible correction of) risk factors that may adversely affect fertility and response to infertility therapy?
 - Should women with PCOS undergo pre-conception (pre-pregnancy) evaluation (assessment) for (and where possible correction of) risk factors that may lead to adverse (early or late) pregnancy outcomes?
 - Should women with PCOS undergo close (early or late) pregnancy monitoring for adverse pregnancy outcomes?
 - Should women with PCOS and infertility due to anovulation alone with normal semen analysis have tubal patency testing prior to starting ovulation induction with timed intercourse or intrauterine insemination (IUI) treatment or delayed tubal patency testing?
 - In women with PCOS, is clomiphene citrate (CC) effective for improving fertility outcomes?
 - In women with PCOS, is metformin effective for improving fertility outcomes?
 - In women with PCOS and a BMI <30-32, what is the effectiveness of metformin compared to CC for improving fertility outcomes?
 - In women with PCOS, are aromatase inhibitors (AIs) effective for improving fertility outcomes?
 - In women with PCOS, are gonadotrophins effective for improving fertility outcomes?
 - In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI (In-vitro fertilisation/Intra-cytoplasmic sperm injection), does the choice of follicle-stimulating hormone (FSH) effect fertility outcomes?
 - In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is exogenous luteinizing hormone (LH) treatment during IVF/ICSI effective for improving fertility outcomes?
 - In women with PCOS, is stimulated IVF/ICSI effective for improving fertility outcomes?
 - In women with PCOS undergoing IVF/ICSI treatment, is the gonadotropin-releasing hormone (GnRH) antagonist protocol or GnRH agonist long protocol the most effective for improving fertility outcomes?
 - In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is adjuvant metformin effective for improving fertility outcomes?
 - In women with PCOS undergoing GnRH antagonist IVF/ICSI treatment, is the use of human chorionic gonadotropin (hCG) trigger or GnRH agonist trigger the most effective for improving fertility outcomes?
 - In women with PCOS, is In Vitro Maturation (IVM) effective for improving fertility outcomes?
 - In women with PCOS, are anti-obesity pharmacological agents effective for improving fertility outcomes?
 - In women with PCOS, is ovarian surgery effective for improving fertility outcomes?
 - In women with PCOS, what is the effectiveness of lifestyle interventions compared to bariatric surgery for improving fertility and adverse outcomes?
- * Not all questions resulted in a recommendation. Where evidence was inadequate only research recommendations were made and are captured in a separate document.

Outcome prioritisation using the GRADE method

The most relevant outcomes were prioritised by ranking their importance by health professionals and consumers to help resolve or clarify disagreements and assist with grading the evidence. The importance of outcomes may vary across cultures and from different perspectives e.g. patients, public, health professionals or policy-makers. Table 6 outlines the considerations when deciding importance of outcomes [15]. GDG members, including consumers also participated in this exercise.

Table 6: Steps for considering the relative importance of outcomes

What	Assessment and prioritisation of outcomes as critical, important but not critical, or low importance. Requires judgement of the balance between the desirable and undesirable health outcomes of an intervention.
Why	To focus attention on those outcomes that are considered most important when conducting evidence review and to resolve or clarify disagreements. To support making a recommendation and to determine the strength of the recommendation.
How	Scoping the relevant literature. By asking GDG members, including consumers to prioritise outcomes in light of the considerations for 'what' and 'why'.
Evidence	These judgments are ideally informed by a systematic review of the literature focusing on what the target population considers as critical or important outcomes for decision-making. Prior knowledge of the research evidence through systematic reviews; and information about values, preferences or utilities has been explored in the original guideline, that was systematic in nature, will inform this process. Additionally, the collective experience of the GDG members, including consumers, will be used using transparent methods for documenting and considering them, such as a Delphi process.

To facilitate ranking of outcomes according to their importance the following scale was be used [15].

RATING SCALE:

1	2	3	4	5	6	7	8	9
of least importance							of most importance	
Of limited importance for making a decision (not included in evidence profile)		Important, but not critical for making a decision (included in evidence profile)				Critical for making a decision (included in evidence profile)		

Outcomes considered critical (rated 7-9) most greatly influenced a recommendation and the overall quality of evidence supporting the recommendation and the strength of the recommendation.

Adaptation of existing evidence-based guidelines

Given the time and resource-intensive nature of guideline development, existing high quality evidence-based guidelines that address the clinical questions and PICO (Population, Intervention, Comparison, Outcome) of interest should be sought for adaptation before starting a new one. Apart from the original Australian guideline, to date no international PCOS guideline covering all health aspects related to the syndrome is available. The evidence-based sections of the WHO guideline, supported by this evidence synthesis team is aligned with the scope here, yet is now out of date. The NICE guideline is limited in scope and is not available electronically outside the UK. It too is adapted from the 2011 Australian guideline. Professional society positions statements or clinical practice guidelines are more limited in scope, do not follow AGREE II (Appraisal of Guidelines for Research and Evaluation) process, involve more limited expertise and geographical representation and are often conflicting in recommendations. Here we have updated and expanded the scope and evidence contained in the 2011 Australian guideline and, where appropriate methods have been applied, integrated the WHO guideline.

Evidence reviews to answer the clinical questions

Evidence reviews were conducted for each clinical question and from the evidence reviews, the GDGs were able to develop guideline recommendations. The evidence reviews for each question can be found in the supplementary Technical report. The links between the body of evidence, the clinical need for the question and the clinical impact of the resulting recommendation(s), including potential changes in usual care and the way care is organised, acceptability, feasibility and resource implications are clearly explained in the accompanying GRADE evidence to decision framework supporting the recommendation.

Selection criteria

The PICO framework was used by the GDGs to explore the components of each clinical question and finalise the selection criteria for each question. These components were used to include and exclude studies in the evidence review. Details of the selection criteria for each question can be found in the supplementary Technical report.

The highest form of evidence, the most current (within 5 years), comprehensive (with the most outcomes relevant to PICO) and high quality systematic review that meets our benchmark criteria (see table 7) and meets the selection criteria, was used to inform a recommendation. Additional systematic reviews that met benchmark and selection criteria were used if it reported additional outcomes relevant to the PICO, that were not addressed in the first, most comprehensive systematic review. Additional randomised controlled trials (RCT(s)) that met the selection criteria and were not included in the systematic reviews were also used. Where a systematic review met the benchmark criteria but did not meet the selection criteria, or synthesised studies that did not meet out selection criteria, the risk of bias appraisals from that systematic review were adopted.

Table 7. Benchmark criteria for a systematic review to be included:

-
- 1** Must have completed a search in at least Medline and another relevant database;
 - 2** Must have listed key search terms;
 - 3** Must have listed selection criteria;
 - 4** Must have used an appropriate framework to assess risk of bias/quality appraisal; and
 - 5** Where the evidence is sought for an intervention question and a systematic review has included non-RCTs, the analysis must be subgrouped by RCTs to be eligible for inclusion.
-

Systematic search for evidence

A broad-ranging systematic search for terms related to PCOS was developed by the evidence team. This PCOS search string was then combined with specific searches tailored for each clinical question according to the PICO developed by the GDG. The search terms used to identify studies addressing the population of interest (i.e. women with PCOS) were only limited to PCOS terms. Therefore, studies addressing women with PCOS in all cultural, geographical and socioeconomic backgrounds and settings would be identified by the search. Furthermore, while a formal analysis of cost effectiveness was not performed in this guideline, any study addressing a clinical question (PICO) that also reported cost effectiveness would be captured and addressed in the GRADE process. The search strategy was limited to English language articles and limits on year of publication are specified in the PICO for each clinical question according to whether an update search was conducted or in cases where interventions were only available from a particular point in time.

The following electronic databases were employed to identify relevant literature:

- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- The Cochrane Library
- Cochrane Database of Systematic Reviews (Cochrane Reviews)
- Database of Abstracts of Reviews of Effects (Other Reviews)
- Cochrane Central Register of Controlled Trials (Clinical Trials)
- Cochrane Database of Methodology Reviews (Methods Reviews)
- The Cochrane Methodology Register (Methods Studies)
- Health Technology Assessment Database (Technology Assessments)
- NHS Economic Evaluation Database (Economic Evaluations)
- EMBASE
- EBM Reviews (OVID)
- Medline (OVID)
- Medline in-process and other non-indexed citations (OVID)
- PsycINFO (OVID)

The bibliographies of relevant studies identified by the search strategy and relevant reviews/meta-analysis were also searched for identification of additional studies. Details of the search strategies and search results for each evidence review can be found in the supplementary Technical report.

Inclusion of studies

To determine the literature to be assessed further, a reviewer scanned the titles, abstracts and keywords of every record retrieved by the search strategy. Full articles were retrieved for further assessment if the information given suggested that the study met the selection criteria. Studies were selected by one reviewer in consultation with colleagues, using the PICO selection criteria established a priori. Where there was any doubt regarding these criteria from the information given in the title and abstract, the full article was retrieved for clarification.

Appraisal of the methodological quality/risk of bias of the evidence

Methodological quality of the included studies was assessed using criteria developed a priori according to study design (i.e. quality appraisal criteria used for an RCT is different to that used for a cohort study) [604]. Individual quality items were investigated using a descriptive component approach. Any disagreement or uncertainty was resolved by discussion among the GDG to reach a consensus. Using this approach, each study was allocated a risk of bias rating (see Table 8). Quality appraisal tables for each evidence review can be found in the supporting document titled Technical report.

Table 8. Risk of bias ratings [604]

RATING	DESCRIPTION
Low	All of the criteria have been fulfilled or where criteria have not been fulfilled it is very unlikely the conclusions of the study would be affected.
Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
High	Few or no criteria fulfilled or the conclusions of the study are likely or very likely to be affected.
Insufficient information	Not enough information provided on methodological quality to be able to determine risk of bias.

Data extraction

Data, according to the selection criteria, were extracted from included studies using a specially developed data extraction form [604]. Information was collected on general details (title, authors, reference/source, country, year of publication, setting), participants (age, sex, inclusion/exclusion criteria, withdrawals/losses to follow-up, subgroups), results (point estimates and measures of variability, frequency counts for dichotomous variables, number of participants, intention-to-treat analysis) and validity results. Data extraction tables for each evidence review can be found in the supporting Technical report.

Data synthesis

In order to make a summary statement about the effect of the intervention and thus inform evidence-based recommendations, data were presented qualitatively by presenting the findings narratively in tables or discussion text; or quantitatively, using statistical methods such as meta-analyses. A meta-analysis is a statistical technique for combining (pooling) the results of a number of studies, that report data for the same outcome for the same intervention, to produce a summary statistic to represent the effect of one intervention compared to another. When high-quality trials are used, a meta-analysis summary statistic can be more powerful than an individual study to confirm or refute effectiveness of an intervention and thus to inform an evidence-based recommendation. Data were summarised statistically using meta-analyses if data were available, sufficiently homogenous, and of sufficient quality. Clinical homogeneity was satisfied when participants, interventions, outcome measures and timing of outcome measurement were considered to be similar. The Review Manager 5.3 software was used for meta-analyses. Where appropriate, subgroup analysis was conducted according to factors that may cause variations in outcomes, are likely to be a confounder, or may change the way the treatment works e.g. age, subtype or duration of treatment. These can be found in the supporting Technical report.

Quality (certainty) of the body of evidence using GRADE evidence profiles

A GRADE evidence profile was prepared for each comparison within each clinical question addressed by a systematic review. For each prioritised outcome, a certainty rating was documented with consideration of the following:

- information about the number and design of studies addressing the outcome; and
- judgments about the quality of the studies and/or synthesised evidence, such as risk of bias, inconsistency, indirectness, imprecision and any other considerations that may influence the quality of the evidence.

The definitions of these factors are described below:

- overall quality of evidence rating using the judgments made above (see ratings in table 9);
- key statistical data; and
- classification of the importance of the outcome.

The certainty of evidence reflects the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation [15].

Although the quality of evidence represents a continuum, the GRADE approach results in an assessment of the quality of a body of evidence in one of four grades (adapted from GRADE [15]).

Table 9. Quality of evidence

High	⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	⊕⊕⊕○	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	⊕⊕○○	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	⊕○○○	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

GRADE note that the quality of evidence is a continuum; any discrete categorisation involves some degree of arbitrariness. Nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations [15]. Evidence profiles can be found in the Technical report.

Formulation of recommendations using the GRADE evidence to decision framework

The Evidence to Decision (EtD) framework was used to document the judgments and decisions using the GRADE method for development of evidence-based recommendations. The framework prompts transparent documentation and discussion of decisions through assessment of the evidence, clinical expertise and patient preference for factors including:

- desirable and undesirable effects of the intervention;
- certainty of the evidence;
- values associated with the recommended intervention;
- balance of effects;
- resource requirements;
- cost-effectiveness;
- equity; acceptability;
- feasibility;
- subgroup considerations;
- implementation considerations;
- monitoring and evaluation; and
- research priorities.

Using the framework, each of the evidence-based and consensus recommendations are given an overall grading of conditional or strong [15]. Clinical practice points have also been included, where important issues (such as safety, side effects or risks) arose from discussion of evidence-based or clinical consensus recommendations.

Table 10. Recommendation types

EBR	Evidence sufficient to inform an evidence-based recommendation (EBR)
CCR	In the absence of adequate evidence in PCOS, a clinical consensus recommendation (CCR) was made
CPP	Evidence not sought. A clinical practice point (CPP) was made where important issues arose from discussion of evidence-based or clinical consensus recommendations

The strength of the recommendations can be identified throughout the guideline by the following (adapted from ESHRE manual for guideline development [605] and the GRADE approach [15]):

Table 11: Strength of recommendations (adapted from GRADE [15] and ESHRE Manual [605])

TARGET GROUP	STRONG RECOMMENDATIONS*	CONDITIONAL (WEAK) RECOMMENDATIONS FOR THE OPTION (TEST OR TREATMENT)	CONDITIONAL (WEAK) RECOMMENDATION FOR EITHER THE OPTION OR THE COMPARISON	RESEARCH ONLY RECOMMENDATIONS	CLINICAL PRACTICE POINTS (CPP)**
CONSUMERS	Most people in your situation would want the recommended course of action and only a small proportion would not.	The majority of people in your situation would want the recommended course of action, but some would not.	There is considerable lack of clarity over whether the majority of people in your situation would want the recommended course of action or not.	The test or intervention should only be considered by patients and clinicians within the setting of a research trial for which appropriate approvals and safety precautions have been established.	Clinicians, patients and policy makers are informed on the clinical implications relevant to implementation of recommendations.
HEALTH PROFESSIONALS	Most patients should receive the recommended course of action.	Recognise that different choices will be appropriate for different patients and that greater effort is needed with individuals to arrive at management decisions consistent with values and preferences. Decision aids and shared decision making are important here.		The test or intervention should only be considered by patients and clinicians within the setting of a research trial for which appropriate approvals and safety precautions have been established.	
POLICY MAKERS	The recommendation can be adopted as policy in most situations.	Policy making needs to consider perspectives and involvement of diverse stakeholders.	Policy decisions remain unclear.	Policy makers need to be aware of the need for evidence gaps and health professional and consumer prioritised research gaps.	

* Strong recommendations based on high quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions; no recommendation can take into account all of the often-compelling unique features of individual patients and clinical circumstances.

** A clinical practice point (CPP) is developed by the GDG to support recommendations. Advice can be provided to enhance shared decision making, and on factors to be considered in implementing a specific test or intervention

The words “should”, “could” and “should not” do not directly reflect the strength (strong or conditional) allocated to a recommendation and are independent descriptors intended to reflect the judgment of the multidisciplinary GDG on the practical application of the recommendation, balancing benefits and harms. Where the word “should” is used in the recommendations, the GDG judged that the benefits of the recommendation (whether evidence-based or clinical consensus) clearly exceed the harms, and that the recommendation can be trusted to guide practice. Where the word “could” is used, either the quality of evidence was underpowered, or the available studies demonstrated little clear advantage of one approach over another, or the balance of benefits to harm was unclear. Where the words “should not” are used, there is either a lack of appropriate evidence, or the harms outweigh the benefits.

Evidence to decision frameworks can be found in the supplementary document titled Technical report. Each recommendation is supported by a discussion (in the chapters of this document) about the clinical need for the question, the body of evidence identified to answer the question and a clinical justification for the recommendation(s).

The GDGs acknowledge that lack of evidence is not evidence of lack of effect and have attempted to reflect this in the strength of the grading given to recommendations on interventions that are not supported by evidence. In addition, some interventions were not supported by evidence in the recommendations due to lack of evidence of effect. The GDGs acknowledge that this refers to lack of evidence of effect over placebo; that is, patients may receive some beneficial outcomes from the intervention but these do not exceed the beneficial effects that can be expected from a placebo therapy [606].

Public consultation

Public and targeted consultation will be conducted for a period of thirty days commencing 10th February to 12th March 2018 in accordance with the legislative requirements set out in section 14A of the National Health and Medical Research Council Act 1992 as outlined in the NHMRC Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines [603]. The public consultation strategy is available upon request, email MCHRI-PCOS-Guideline-Group-l@monash.edu.

External review

This guideline was reviewed by the International Advisory Group, independently by relevant professional colleges and societies and through public consultation.

Scheduled review and update of the guideline

The GDGs will be re-convened to review relevant sections of this guideline if any of the following occur within five years:

- a change in the indications registered by regulatory bodies for any drug included in this guideline; or
- publication of any new major randomised controlled trials or systematic reviews that potentially have a bearing on the safety of the recommendations in this guideline

After five years the societies and organisations will be reengaged, the guideline panels revised and reconvened and the guideline updated as per NHMRC processes.

Dissemination and implementation

A comprehensive, international dissemination and implementation program is underway to amplify the impact of the international guideline for the assessment and treatment of PCOS. The three guiding principles underpinning the translation and dissemination program are:

- 1 all components of the translation program are informed by the needs and preferences of PCOS consumers;
- 2 all translation materials are co-created with, and attuned to, the needs of end-users; and
- 3 dissemination strategies are multi-faceted, multi-modal and refined to the communications channels of end-users.

The aims of the 18 month, international translation program are to:

- build the capability of health professionals to deliver high-quality, evidence-based assessment and management of PCOS;
- augment the health literacy of PCOS health consumers, leading to improved health outcomes;
- promote a best-practice PCOS model of care; and
- orientate international health policy towards an evidence-based, best practice approach.

Significant outcomes of the plan include a consistent and improved standard of care and greater consumer empowerment by enhancing both consumer engagement and the capacity of health professionals to deliver high quality, evidence-based care.

Central to the success of the program is the active engagement of thirty-seven international collaborators and partners who represent the leading, invested health organisations such as European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM). Health experts from these organisations have leveraged their extensive influence within the health sector to promote the uptake of PCOS guideline recommendations. In addition, a further essential component is the engagement of leading consumer groups such as the Polycystic Ovary Syndrome Association of Australia (POSAA), Verity in the United Kingdom, PCOS Challenge: The National Polycystic Ovary Syndrome Association in the United States and organisations with strong links to health consumers such as Jean Hailes for Women's Health and the Victorian Assisted Reproductive Treatment Authority (VARTA) in Australia. Guideline leads are involved in the establishment of a core outcome set in PCOS, to be implemented into clinical data sets to evaluate alignment with evidence-based care. Finally, the translation and dissemination plan is supported by a comprehensive evaluation framework, measuring international impacts and outcomes.

See practice algorithms in [Appendix VIII](#).

- | | |
|----------------|---|
| Algorithm I: | Screening, diagnostic assessment, risk assessment and life-stage |
| Algorithm II: | Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing |
| Algorithm III: | Lifestyle |
| Algorithm IV: | Pharmacological treatment for non-fertility indications |
| Algorithm V: | Assessment and management of infertility |

	TRANSLATION STRATEGY	DELIVERABLE/S	COLLABORATOR/S	DISSEMINATION	OUTCOMES
Aim:	Increase the health literacy of women and girls affected by PCOS through the co-creation of a consumer focused, accessible PCOS education and health information platform.				
CONSUMERS	Co-create an internationally accessible, interactive, low cost mobile application providing high quality, evidence-based, PCOS information tailored to the needs of the individual user.	PCOS APP (AskPCOS)	<ul style="list-style-type: none"> ● Monash University ● PCOS-CRE ● PCOS consumers 	<ul style="list-style-type: none"> ● Apple itunes ● Social media channels (Dedicated facebook page, twitter) ● Range of conventional media 	<ul style="list-style-type: none"> ● A low cost, internationally accessible PCOS APP ● Self-diagnosis function ● Interactive personalised functionality tailoring information provision to individual consumer needs ● Referral information to appropriate health professionals ● Peer support access ● Secondary data to inform PCOS research ● Google analytics to enhance PCOS APP
	Provision of translated, e-health, evidence-informed PCOS information, informed by consumer needs and preferences.	e-health PCOS information accessible to a range of consumer groups	<ul style="list-style-type: none"> ● Jean Hailes for Women's Health ● VARTA ● Women's Health Vic ● (POSAA) ● International organisations and consumer groups 	<ul style="list-style-type: none"> ● PCOS Centre for Research Excellence ● International organisations and consumer groups 	Accessible, translated PCOS e-health information informed by the highest quality evidence and consumer needs and preferences
	Co-develop and deliver a PCOS Lifestyle Education Program for women with PCOS	PCOS Lifestyle Education Program	<ul style="list-style-type: none"> ● Victorian Government ● International organisations 	<ul style="list-style-type: none"> ● Health services ● International organisations 	<ul style="list-style-type: none"> ● Provision of an evidence-based, tailored lifestyle education program
	Co-develop and deliver an accessible, interactive, no cost, internationally available online PCOS course for consumers.	PCOS learning course	<ul style="list-style-type: none"> ● Monash University ● PCOS-CRE ● MCHRI 	<ul style="list-style-type: none"> ● Monash University ● MHCRI 	<ul style="list-style-type: none"> ● Accessible, online, interactive, no cost, internationally available PCOS course for consumers

	TRANSLATION STRATEGY	DELIVERABLE/S	COLLABORATOR/S	DISSEMINATION	OUTCOMES
Aim:	Increase the health literacy of women and girls affected by PCOS through the co-creation of a consumer focused, accessible PCOS education and health information platform.				
CONSUMERS	Co-develop PCOS Model of Care with a sustainable, psychosocial multidisciplinary approach, incorporating a comprehensive PCOS translation platform.	PCOS Clinical Model of Care	<ul style="list-style-type: none"> • Australian Health Services • Victorian Government 	<ul style="list-style-type: none"> • Australian Health Services • International scale up 	<p>Sustainable, evidence-based, psychosocial-multidisciplinary PCOS services</p> <ul style="list-style-type: none"> • A comprehensive PCOS translation platform
	To provide a range of translated, accessible PCOS written materials that are tailored to the needs of consumers.	A range of PCOS written materials: fact sheets, booklets for different consumer groups, language translated health materials.	<ul style="list-style-type: none"> • National and International engaged societies and organisations • CaLD and Aboriginal and Torres Strait Islanders 	<ul style="list-style-type: none"> • National and International engaged societies and organisations 	<p>A range of translated, accessible PCOS written materials that are tailored to the needs of consumers.</p> <ul style="list-style-type: none"> • Fact sheets, booklets for different consumer groups, language translated health materials
Aim:	Increase the uptake of PCOS evidence-based practice among health professionals internationally.				
HEALTH PROFESSIONALS	Implement an extensive publication plan targeting international journals, discipline specific publications and in the general medical media domain.	16 publications published in high impact journals and discipline specific publications	Experts from international engaged organisations	<p>High impact international journals</p> <p>Discipline specific publications</p> <p>Medical media</p>	16 publications published in high impact journals and discipline specific publications
	To deliver a co-ordinated, international expert speaker program at international conferences, annual meetings and invited speak events in the US, Aust, Africa, India and Europe, covering of the topics of; fertility, reproduction, chronic disease prevention and lifestyle.	Up to 35 workshops, symposiums, key note speaker and panel speaker events delivered internationally	Experts from international engaged organisations	<p>Multiple conferences, annual meeting and events across US, Aust, Africa, India and Europe</p>	35 workshops, symposiums, key note speaker and panel speaker events delivered internationally

	TRANSLATION STRATEGY	DELIVERABLE/S	COLLABORATOR/S	DISSEMINATION	OUTCOMES
Aim:	Increase the uptake of PCOS evidence-based practice among health professionals internationally.				
HEALTH PROFESSIONALS	Develop a range of PCOS educational resources with high utility with health professionals.	Webinars Face-to-face events Flexible learning opportunities	International and national engaged organisations Peak bodies	International and national engaged organisations Peak body learning portals	A range of PCOS educational resources with high utility with health professionals
	To co-develop and deliver an accessible, interactive, for-fee, accredited, internationally available online PCOS course for health professionals.	PCOS accredited CPD for-fee online course	<ul style="list-style-type: none"> ● Monash University ● PCOS-CRE ● MHCRI International and national engaged organisations	<ul style="list-style-type: none"> ● Monash University ● Futurelearn FOOC (For-fee online course) ● International and national engaged organisations 	<ul style="list-style-type: none"> ● Accessible, accredited, online, interactive, for-fee, internationally available PCOS course for health professionals
GOVERNMENT	To influence international/national health policy leveraging high level health professional expertise and informed by the highest quality evidence and consumer needs and preferences.	PCOS health policy is based on the highest quality evidence and consumer needs and preferences	International and national Governments, health organisations. Health professional experts PCOS health consumers		PCOS health policy based on the highest quality evidence and informed by health professional expertise and consumer needs and preferences

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Appendix I:

Project board

ROLE	NAME	DISCIPLINE	ORGANISATIONAL AFFILIATION / REGION
Chair Senior Supplier Endocrinology Representative	Professor Helena Teede	Endocrinologist	Centre for Research Excellence in Polycystic Ovary Syndrome, Australia
Senior user	Mrs Veryan McAllister	Consumer lead	Polycystic Ovary Syndrome Association of Australia
Senior user Senior Supplier Allied Health Representative	Associate Professor Lisa Moran	Dietitian	Centre for Research Excellence in Polycystic Ovary Syndrome, Australia
Senior user General Practitioner Representative	Doctor Mala Thondan	General Practitioner	Harp Family Medical Centre, Australia
Senior user Senior supplier Gynaecology Representative European Society of Human Reproduction and Embryology Representative	Professor Joop Laven	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Erasmus MC Rotterdam, Netherlands
Senior supplier Gynaecology Representative	Doctor Michael Costello	Obstetrician-Gynaecologist;	University of NSW, Australia
Senior supplier American Society for Reproductive Medicine Representative	Professor Anuja Dokras	Reproductive Endocrinologist	University of Pennsylvania, USA
Senior supplier European Society of Human Reproduction and Embryology Representative	Associate Professor Terhi Piltonen	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Oulu University Hospital, University of Oulu, Finland
Senior supplier Evidence Synthesis Lead and Guidelines Advisor	Doctor Marie Misso	Evidence synthesis and guidelines advisor	Centre for Research Excellence in Polycystic Ovary Syndrome, Australia

Appendix II:

International Advisory Panel

ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Bart Fauser	Obstetrician-Gynaecologist	University Medical Center Utrecht	Netherlands
Deputy Chair	Professor	Robert Norman	Obstetrician-Gynaecologist; Reproductive Endocrinologist; Chemical pathologist	The University of Adelaide	Australia
Member	Professor	Juha Tapanainen	Obstetrician-Gynaecologist	University of Helsinki	Finland
Member	Professor	Zephne van der Spuy	Obstetrician-Gynaecologist Specialist Reproductive Medicine	University of Cape Town	South Africa
Member	Professor	Duru Shah	Obstetrician-Gynaecologist	Gynaecworld	India
Member	Professor	Richard Legro	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Penn State Clinical and Translational Institute	USA
Member	Professor	Frank Broekmans	Gynaecologist Specialist Reproductive Medicine	University Medical Centre Utrecht	Netherlands
Member	Doctor	Anuja Dokras	Reproductive Endocrinologist and infertility	University of Pennsylvania	USA
Member	Doctor	Marie Misso	Evidence Synthesis and Guidelines Advisor	Monash Centre for Health Research and Implementation	Australia
Member	Professor	Chii-Ruey Tzeng	Obstetrician-Gynaecologist	Taipei Medical University Hospital	Taiwan
Member	Professor	Jie Qiao	Obstetrician-Gynaecologist	Peking University Third Hospital	China
Member	Professor	Poli Mara Spritzer	Reproductive Endocrinologist	Federal University of Rio Grande Do Sul	Brazil

Appendix III:

Guideline development groups

Terms of reference for each committee can be provided upon request (MCHRI-PCOS-Guideline-Group-I@monash.edu).

GDG1: Topic area – Screening, diagnostic assessment, risk assessment and life-stage

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Joop Laven	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Erasmus MC Rotterdam	Netherlands
Deputy Chair	Professor	Robert Norman	Obstetrician-Gynaecologist; Reproductive Endocrinologist; Chemical pathologist	The University of Adelaide	Australia
Member	Professor	Marianne Andersen	Endocrinologist	Odense University Hospital	Denmark
Member	Professor	Ricardo Azziz	Reproductive Endocrinologist	State University of New York System Administration	USA
Member	Professor	Preeti Dabadghao	Endocrinologist	Sanjay Gandhi Postgraduate Institute of Medical Sciences	India
Member	Professor	Didier Dewailly	Endocrinologist	University of Lille	France
Member	Professor	Stephen Franks	Endocrinologist	Imperial College London	United Kingdom
Member	Professor	Kathleen Hoeger	Reproductive Endocrinologist	University of Rochester	USA
Member	Doctor	Samantha Hutchison	Endocrinologist	Monash Health	Australia
Member	Professor	Ernest Ng	Obstetrician-Gynaecologist	Department of Obstetrics & Gynaecology, The University of Hong Kong	China
Member	Professor	Sharon Oberfield	Paediatric endocrinologist	Columbia University Medical Center	USA

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Member	Professor	Duru Shah	Obstetrician-Gynaecologist	Gynaecworld	India
Co-opted	Doctor	Jane Woolcock	Obstetrician-Gynaecologist	Women's and Children's Hospital Adelaide	Australia
Co-opted	Assistant Professor	Marla Lujan	Nutritional Science	Cornell University	USA
Co-opted	Associate Professor	Darren Mansfield	Respiratory Physician	Monash Health	Australia
Member	Doctor	Femke Hohmann	General Practitioner	Huisartsenpraktijk Hohmann & De Vet, Rotterdam	Netherlands
Member	Ms	Sasha Ottey	Non-profit Executive Director; Consumer	PCOS Challenge: The National Polycystic Ovary Syndrome Association	USA

GDG2: Topic area – Prevalence, screening, diagnostic assessment and management of emotional wellbeing

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Anuja Dokras	Reproductive Endocrinologist and infertility	University of Pennsylvania	USA
Deputy Chair	Professor	Elisabet Stener-Victorin	Researcher in Reproductive Endocrinology and Metabolism	Karolinska Institutet	Sweden
Member	Associate Professor	Leah Brennan	Psychologist	Australian Catholic University	Australia
Member	Doctor	Rhonda Garad	Registered Nurse	Monash Centre for Health Research and Implementation	Australia
Member	Doctor	Melanie Gibson-Helm	Women's Public Health Researcher	Monash University	Australia
Co-opted	Professor	Jayashri Kulkarni	Psychiatrist	Monash Alfred Psychiatry Research Centre	Australia
Member	Professor	Rong Li	Obstetrician-gynaecologist	Reproductive Medical Center, Peking University Third Hospital	China
Member	Professor	Jane Speight	Health Psychologist	Deakin University	Australia
Member	Associate Professor	Maria Vogiatzi	Pediatric Endocrinologist	Children's Hospital of Philadelphia, University of Pennsylvania	USA
Member	Professor	Bulent Yildiz	Endocrinologist	Hacettepe University	Turkey
Member		Veryan McAllister	Consumer	Polycystic Ovary Syndrome Association Australia	Australia
Member	Doctor	Mala Thondan	General practitioner	Harp Family Medical Centre	Australia

GDG3: Topic area – Lifestyle management and models of care

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Associate Professor	Lisa Moran	Dietitian; Research Fellow	Monash Centre for Health Research and Implementation	Australia
Deputy Chair	Associate Professor	Nigel Stepto	Accredited Exercise Physiologist	Victoria University	Australia
Member	Associate Professor	Jacqueline Boyle	Obstetrician-Gynaecologist	Monash Centre for Health Research and Implementation	Australia
Member	Doctor	Cheryce Harrison	Research Fellow	Monash Centre for Health Research and Implementation	Australia
Member	Professor	Angelica Hirschberg	Obstetrician-Gynaecologist	Karolinska Institutet	Sweden
Member	Doctor	Kate Marsh	Dietitian	Northside Nutrition & Dietetics	Australia
Member	Associate Professor	Leanne Redman	Obesity; Lifestyle Interventions	Pennington Biomedical Research Center	USA
Member	Professor	Chandrika Wijeyaratne	Endocrinology and Reproductive Medicine	Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Colombo	Sri Lanka
Co-opted	Associate Professor	Leah Brennan	Psychologist	Australian Catholic University	Australia
Co-opted	Miss	Eliza Tassone	Consumer	Monash University	Australia
Co-opted	Doctor	Mala Thondan	General practitioner	Harp Family Medical Centre	Australia

GDG4: Topic area - Medical treatment

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Helena Teede	Endocrinologist	Monash Centre for Health Research and Implementation	Australia
Deputy Chair	Associate Professor	Terhi Piltonen	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Oulu University Hospital, University of Oulu	Finland
Member	Doctor	Anju Joham	Endocrinologist	Monash Health	Australia
Member	Professor	Jaideep Malhotra	Obstetrician-Gynaecologist	Rainbow Hospital	India
Member	Professor	Ben Mol	Obstetrician-Gynaecologist	Monash University	Australia
Member	Doctor	Alexia Peña	Paediatric Endocrinologist	The Robinson Research Institute at the University of Adelaide	Australia
Member	Doctor	Daniela Romualdi	Obstetrician-Gynaecologist	Fondazione Policlinico Universitario Agostino Gemelli, Rome	Italy
Member	Professor	Selma Witchel	Paediatric Endocrinologist	Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh	USA
Member	Ms	Veryan McAllister	Consumer	Polycystic Ovary Syndrome Association Australia	Australia
Member	Doctor	Mala Thondan	General practitioner	Harp Family Medical Centre	Australia

GDG5: Topic area – Screening, diagnostic assessment and management of infertility

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Doctor	Michael Costello	Obstetrician-Gynaecologist	University of NSW	Australia
Deputy Chair	Professor	Robert Norman	Obstetrician-Gynaecologist; Reproductive Endocrinologist; Chemical pathologist	The University of Adelaide	Australia
Member	Professor	Adam Balen	Reproductive Medicine	Leeds Teaching Hospitals	United Kingdom
Member	Professor	Luigi Devoto	Reproductive Endocrinologist	University of Chile. Faculty of Medicine	Chile
Member	Professor	Roger Hart	Obstetrician-Gynaecologist; Reproductive Endocrinologist	The University of Western Australia	Australia
Member		Cailin Jordan	Psychologist	Genea Hollywood Fertility	Australia
Member	Professor	Richard Legro	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Penn State Clinical and Translational Institute	USA
Member	Doctor	Edgar Mocanu	Obstetrician-Gynaecologist	Rotunda Hospital	Ireland
Member	Professor	Jie Qiao	Obstetrician-Gynaecologist	Peking University Third Hospital	China
Member	Professor	Raymond Rodgers	Reproductive Endocrinologist	The Robinson Research Institute at the University of Adelaide	Australia
Member	Professor	Luk Rombauts	Obstetrician-Gynaecologist; Infertility Specialist	Monash Health	Australia
Member	Professor	Shakila Thangaratinam	Obstetrician-Gynaecologist; Clinical Academic	Queen Mary University of London	United Kingdom
Member	Professor	Eszter Vanky	Obstetrician-Gynaecologist	Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology	Norway
Member		Louise Johnson	Consumer focused organisation representative	Victorian Assisted reproductive Treatment Authority	Australia

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- Doctor Marie Misso, Evidence Synthesis Lead and Guidelines Advisor, Monash Centre for Health Research and Implementation, Monash Public Health, Monash University
- Ms Linda Downes, Project Manager – Monash Centre for Health Research and Implementation
- Doctor Rhonda Garad, Senior Project Officer, Knowledge Translation in Polycystic Ovary Syndrome, Monash Centre for Health Research and Implementation, Monash Public Health, Monash University
- Miss Eliza Tassone, Evidence Synthesis Officer, Monash Centre for Health Research and Implementation
- Mr Estifanos Baye, Evidence Synthesis Officer, Monash Centre for Health Research and Implementation
- Ms Ching Shan Wan, Evidence Synthesis Officer, Monash Centre for Health Research and Implementation

Paediatric GDG panel membership

ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Helena Teede	Endocrinologist	Monash Centre for Health Research and Implementation	Australia
Member	Professor	Kathleen Hoeger	Reproductive Endocrinologist	University of Rochester	USA
Member	Professor	Sharon Oberfield	Paediatric endocrinologist	Columbia University Medical Center	USA
Member	Professor	Selma Witchel	Paediatric Endocrinologist	Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh	USA
Member	Doctor	Alexia Peña	Paediatric Endocrinologist	The Robinson Research Institute at the University of Adelaide	Australia

Appendix IV:

Berlin Questionnaire

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Sleep Evaluation in Primary Care

1 Complete the following:

Height

Weight

Age

Male / Female

Category 1

2 Do you snore?

- Yes No
 Don't know

If you snore:

3 Your snoring is?

- Slightly louder than breathing
 As loud as talking
 Louder than talking
 Very loud. Can be heard in adjacent rooms.

4 How often do you snore

- Nearly every day 3-4 times a week
 1-2 times a week 1-2 times a month
 Never or nearly never

5 Has your snoring ever bothered other people?

- Yes No

6 Has anyone noticed that you quit breathing during your sleep?

- Nearly every day 3-4 times a week
 1-2 times a week 1-2 times a month
 Never or nearly never

Category 2

7 How often do you feel tired or fatigued after your sleep?

- Nearly every day 3-4 times a week
 1-2 times a week 1-2 times a month
 Never or nearly never

8 During your waketime, do you feel tired, fatigued or not up to par?

- Nearly every day 3-4 times a week
 1-2 times a week 1-2 times a month
 Never or nearly never

9 Have you ever nodded off or fallen asleep while driving a vehicle?

- Yes No

If yes: how often does it occur?

- Nearly every day 3-4 times a week
 1-2 times a week 1-2 times a month
 Never or nearly never

Category 3

10 Do you have high blood pressure?

- Yes No
 Don't know

BMI =

Scoring questions: Any answer within box outline is a positive response.

Scoring categories:

Category 1 is positive with 2 or more positive responses to questions 2-6

Category 2 is positive with 2 or more positive responses to questions 7-9

Category 3 is positive with 1 positive response and / or a BMI >30

Final result: 2 or more positive categories indicates a high likelihood of sleep disordered breathing.



Appendix V:

Abbreviations and acronyms

AUC	Area under the receiver operating characteristic curve (analysis)	NICE	National Institute for Health and Clinical Excellence
BMI	Body mass index	NIH	National Institutes of Health
CI	95% confidence interval	Non-CCR	Non-clomiphene citrate resistant
CVD	Cardiovascular disease	COCP	Combined oral contraceptive pill
CCR	Clomiphene citrate resistant	OGTT	Oral glucose tolerance test
Dietitian	Accredited Practising Dietitian	OHSS	Ovarian hyperstimulation syndrome
DM2	Type 2 diabetes mellitus	OR	Odds ratio
FBG	Fasting blood glucose	OSA	Obstructive sleep apnea
FSH	Follicle stimulating hormone	PCOM	Polycystic ovary morphology
GAD	Generalised Anxiety disorder scale	PCOS	Polycystic ovary syndrome
GDM	Gestational Diabetes	PCOSQ	PCOS quality of life questionnaire
GnRH	Gonadotrophin releasing hormone	PHQ	Patient Health questionnaire
hCG	Human Chorionic Gonadotrophin	OR	Odds ratio
ICSI	Intracytoplasmic sperm injection	PCO	Polycystic ovary
IGT	Impaired glucose tolerance	PCOS	Polycystic ovary syndrome
HbA1c	Glycated haemoglobin	PICO	Participants / Population, Intervention / Exposure, Comparison/Control, Outcome
HDL-C	High density lipoprotein cholesterol	POSAA	Polycystic Ovary Syndrome Association Australia
HOMA-IR	Homeostasis model of assessment-insulin resistance	QoL	Quality of life
IR	Insulin resistance	RCT	Randomised controlled trial
IVM	In vitro maturation	RR	Relative risk
IVF	In vitro fertilisation	SHBG	Sex hormone-binding globulin
LDL-C	Low density lipoprotein cholesterol	TGA	Therapeutic Goods Administration (Australian Government)
LH	Luteinising hormone	P-value	Measure of statistical precision
MPCOSQ	Modified PCOS quality of life questionnaire		

Appendix VI:

Glossary

Sources for this glossary include: The Cochrane Resources Glossary (<http://www.cochrane.org/glossary/5>), Jean Hailes for Women's Health (<http://www.jeanhailes.org.au>), Diabetes Australia (<http://www.diabetesaustralia.com.au>), Better Health Channel (<http://www.betterhealth.vic.gov.au>), the 2009 NHMRC Clinical practice guideline for the prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Australian hospitals [607] and the 2009 NHMRC levels of evidence and grades for recommendations for developers of guidelines [608].

Adverse effect	An adverse event for which the causal relation between the drug/intervention and the event is at least a reasonable possibility.
Aerobic exercise/activity	Any physical activity that produces energy by combining oxygen with blood glucose or body fat.
AGREE II	An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreertrust.org). The AGREE II instrument developed by the collaboration is designed to assess the quality of clinical guidelines.
Algorithm	A flow chart of the clinical decision pathway described in the guideline, where recommendations are presented in boxes, linked with arrows.
Anovulation	A condition in which the ovary does not produce and release an egg each menstrual cycle.
Anxiety	When fears or thoughts that are chronic (constant) and distressing interfere with daily living.
Area under the receiver operating characteristic curve (AUC)	In this guideline, it is used as a method of analysis that measures the ability and reliability of a risk assessment method or diagnostic test to correctly identify the optimal balance between false-positive and false-negative tests.
Assess	In this guideline, assess refers to the process of identifying the severity of the condition
Blood pressure	Blood pressure is the pressure of the blood in the arteries as it is pumped around the body by the heart.
Body image	The way a person may feel, think and view their body including their appearance.
Body mass index (BMI)	A calculated number used to discriminate between lean, overweight, obesity and morbid obesity, calculated from an individual's height (kg) and weight (m). $\text{BMI} = (\text{weight}/\text{height})^2$
Cardiometabolic	Metabolic factors that increase the risk of cardiovascular disease.
Cardiovascular disease (CVD)	A condition that affects either the heart or major blood vessels (arteries) supplying the heart, brain and other parts of the body.
Clinical impact	The potential benefit from application of the recommendations in the guideline on the treatment or treatment outcomes of the target population.
Clinical question (guideline development)	One of a set of questions about an intervention or process that define the content of the evidence reviews and subsequent recommendations in the guideline.

Clomiphene citrate resistant (CCR)	When the patient is unable to ovulate with clomiphene citrate treatment.
Clomiphene citrate failure	When the patient is able to ovulate with clomiphene citrate treatment but does not conceive.
Clomiphene citrate sensitive	When the patient is able to ovulate and conceive with clomiphene citrate treatment.
Cochrane review	Cochrane Reviews are systematic summaries of evidence of the effects of healthcare interventions. The specific methods used in a Review are described in the text of the review. Cochrane Reviews are prepared using Review Manager (RevMan) software provided by the Collaboration, and adhere to a structured format that is described in the Cochrane Handbook for Systematic Reviews of Interventions.
Co-morbidity	The presence of one or more diseases or conditions other than those of primary interest. In a study looking at treatment for one disease or condition, some of the individuals may have other diseases or conditions that could affect their outcomes. (A co-morbidity may be a confounder.)
Compliance	The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as 'adherence' or 'concordance'.
Confidence interval	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Congenital adrenal hyperplasia	Congenital adrenal hyperplasia is a condition where the enzyme needed by the adrenal gland to make the hormones cortisol and aldosterone is lacking and thus the body produces more androgen and causes male characteristics to appear early or inappropriately.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.
Contraindication	A condition or factor that serves as a reason to withhold a certain medical treatment.
Depression	Depression is more than low mood and sadness at a loss and is a serious medical illness. It is the result of chemical imbalances in the brain. The sufferer feels extremely sad, dejected and unmotivated.
Diagnostic accuracy	The accuracy of a test to diagnose a condition which can be expressed through sensitivity and specificity, positive and negative predictive values, or positive and negative diagnostic likelihood ratios.
Disordered eating	Eating and weight related symptoms commonly associated with an eating disorder including behavioural (e.g. bingeing, restriction), cognitive (e.g. dietary restraint, negative body image) and emotional (e.g. Emotional eating) factors.
Dosage	The prescribed amount of a drug to be taken, including the size and timing of the doses.
Eating disorder	Eating disorders include anorexia, bulimia nervosa and other binge eating disorders.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.

Evidence statement table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria (for a systematic evidence review)	Explicit criteria used to decide which studies should be excluded from consideration as potential sources of evidence.
Heterogeneity	<p>Describes the variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies, or the variation in internal validity of those studies. It can be used specifically, as statistical heterogeneity, to describe the degree of variation in the effect estimates from a set of studies. Also used to indicate the presence of variability among studies beyond the amount expected due solely to the play of chance.</p> <p>The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.</p>
Hormonal profile	Cyclical levels of hormones.
Hyperandrogenism	<p>Clinical hyperandrogenism is characterised by hirsutism, acne and male pattern alopecia.</p> <p>Biochemical hyperandrogenism is characterised by excessive production and/or secretion of androgens.</p>
Impaired fasting glucose	When fasting morning blood glucose levels are higher than normal but not high enough to diagnose diabetes.
Impaired glucose tolerance	When glucose levels are above normal during or after an oral glucose tolerance test but are not high enough to diagnose diabetes.
Incidence	The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.
Inclusion criteria (for a systematic evidence review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Infertility (women)	Infertility problems in women include failure to ovulate, blockages in the fallopian tubes, and disorders of the uterus, such as fibroids or endometriosis.
Interdisciplinary care	An interdisciplinary care model is the collaboration between a woman with PCOS and a care team who have shared goals for her total wellbeing.
Intervention	Any action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Insulin resistance (IR)	A rise in glucose occurs because the body can't make enough insulin or the insulin produced is not working properly.
Irregular cycles / oligomenorrhea	When the duration of menstrual cycles is > 35 or < 21 days.
Laparoscopy	A medical procedure used to examine the interior of the abdominal or pelvic cavities to diagnose or treat (or both) a number of different diseases and conditions, including female infertility.
Lean	BMI ≤ 25kg/m ²

Lipid profile	A group of blood tests that are often ordered together to determine risk of cardiovascular disease, including total cholesterol, HDL-C, LDL-C and triglycerides.
Menarche	The onset of the first period of the menstrual cycle, which occurs on average between the ages of 11 and 14 years.
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Morbidly obese	BMI $\geq 35\text{kg/m}^2$
Non-clomiphene citrate resistant (Non-CCR)	Those who are either clomiphene citrate sensitive or who have unknown clomiphene citrate sensitivity.
Obese	BMI $\geq 30\text{-}35\text{kg/m}^2$
Odds ratio (OR)	The ratio of the odds of an event in one group to the odds of an event in another group. In studies of treatment effect, the odds in the treatment group are usually divided by the odds in the control group. An odds ratio of one indicates no difference between comparison groups. For undesirable outcomes an OR that is less than one indicates that the intervention was effective in reducing the risk of that outcome.
Oligo-anovulation	Clinically, irregular cycles lasting <21 or more than 35 days or less than 8 periods per year. Metabolically, hormonally and reproductively, the absence of raised serum progesterone greater than 20nmol/l 7 days prior to a period.
Oligomenorrhea / irregular cycles	When the duration of menstrual cycles is >35 or <21 days.
Oral glucose tolerance test (OGTT)	A test to diagnose diabetes where a high-glucose drink is given and blood samples are checked at regular intervals for two hours.
Ovarian hyperstimulation syndrome (OHSS)	A condition where too many follicles develop (following ovulation induction) which can result in marked abdominal swelling, nausea, vomiting and diarrhoea, lower abdominal pain and shortness of breath.
Overweight	BMI $\geq 25.1\text{-}30\text{kg/m}^2$
Ovulation	Ovulation is the release of an egg from one of the ovaries.
Ovulation induction	Ovulation induction is the use of medication to stimulate the ovary to increase egg production.
Polycystic ovaries	Characterised by clusters of blister-like cysts on the ovary.
Polycystic ovary syndrome (PCOS)	PCOS is a chronic metabolic and hormonal condition, which can impact on physical health and emotional wellbeing.
Placebo	An inactive substance or preparation used as a control in an experiment or test to determine the effectiveness of a medicinal drug. Placebos are used in clinical trials to blind people to their treatment allocation. Placebos should be indistinguishable from the active intervention to ensure adequate blinding.
Post-operative	The period after a patient leaves the operating theatre, following surgery.
Prediabetes	Where blood glucose levels are higher than normal, but not high enough to be classified as diabetes. Pre-diabetes includes impaired fasting glucose and impaired glucose tolerance.
Pre-operative	The period before surgery commences.
Psychosexual dysfunction	Sexual problems or difficulties that have a psychological origin based in cognitions and/or emotions such as depression, low self-esteem and negative body image.

P value	Measure of statistical precision. The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to two or more alternative groups and followed up to examine differences in outcomes between the groups.
Resource implication	The likely impact of the recommendation in terms of cost, workforce or other health system resources.
Risk of bias	Also called methodological quality, it is the degree to which the results of a study are likely to approximate the 'truth' for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and specifically the extent to which the design and conduct of a study are likely to have prevented bias. More rigorously designed (better quality, low risk of bias) trials are more likely to yield results that are closer to the truth.
Relative risk (RR)	The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A relative risk (also called risk ratio) of one indicates no difference between comparison groups. For undesirable outcomes, a relative risk that is less than one indicates that the intervention was effective in reducing the risk of that outcome.
Screen	In this guideline, screen refers to the process of identifying whether the condition exists and is the first step in offering appropriate management
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Stakeholder	Those with an interest in the topic. Stakeholders include healthcare professionals, patient/consumer and carer groups, manufacturers and sponsors.
Statistical power	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Systematic review	A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.
Therapy naive	A patient who has not been administered prior treatment for the condition.
Type 2 diabetes mellitus (DM2)	When the pancreas makes some insulin but it is not produced in the amount your body needs and it does not work effectively. Type 2 diabetes results from a combination of genetic and environmental factors and risk is greatly increased when associated with lifestyle factors such as high blood pressure, overweight or obesity, insufficient physical activity, poor diet and the classic 'apple shape' body where extra weight is carried around the waist.

Appendix VII:

Evidence-based guideline development pathway

Diagram 1: Key steps in seeking NHMRC approval of externally developed guidelines

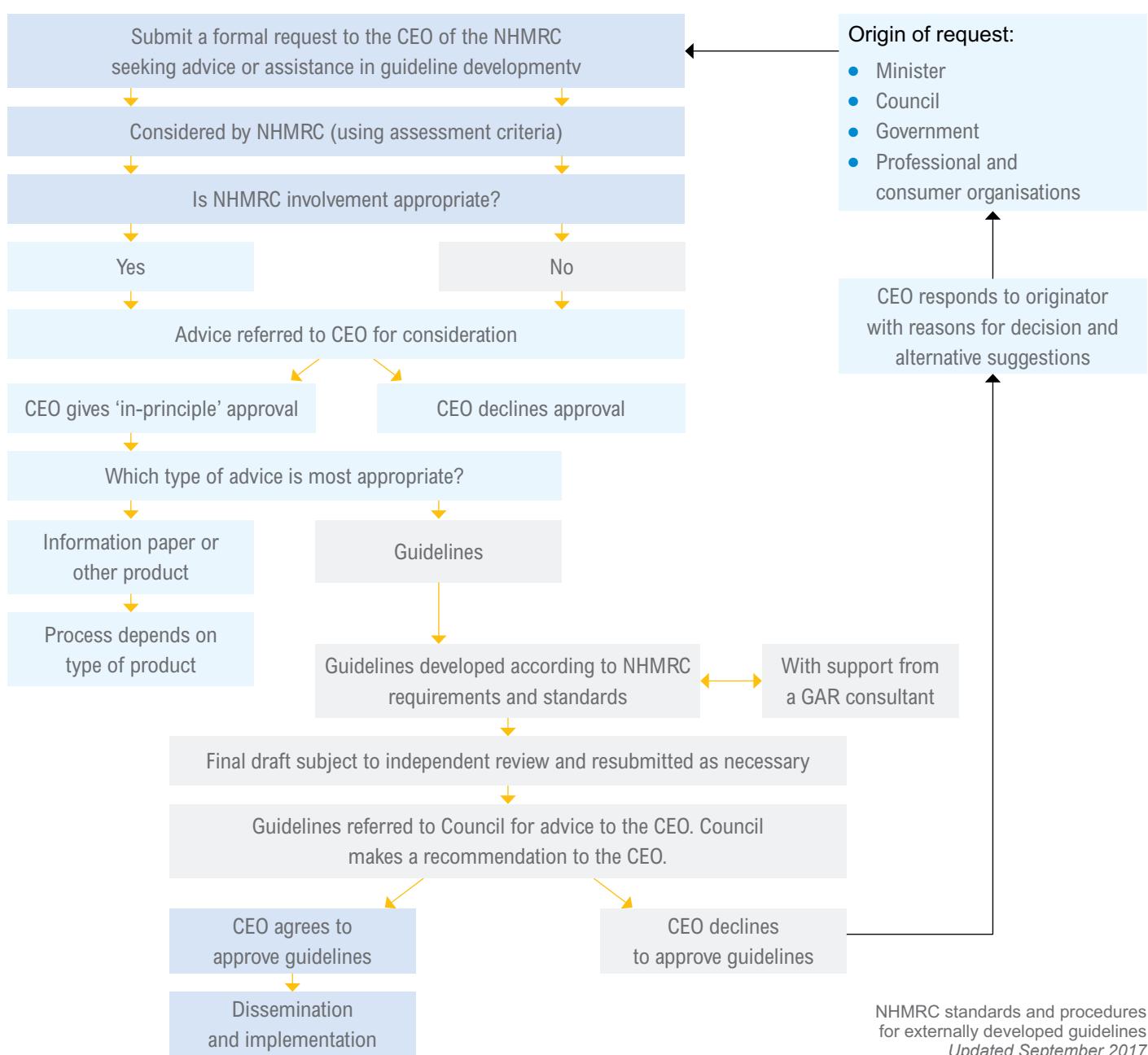
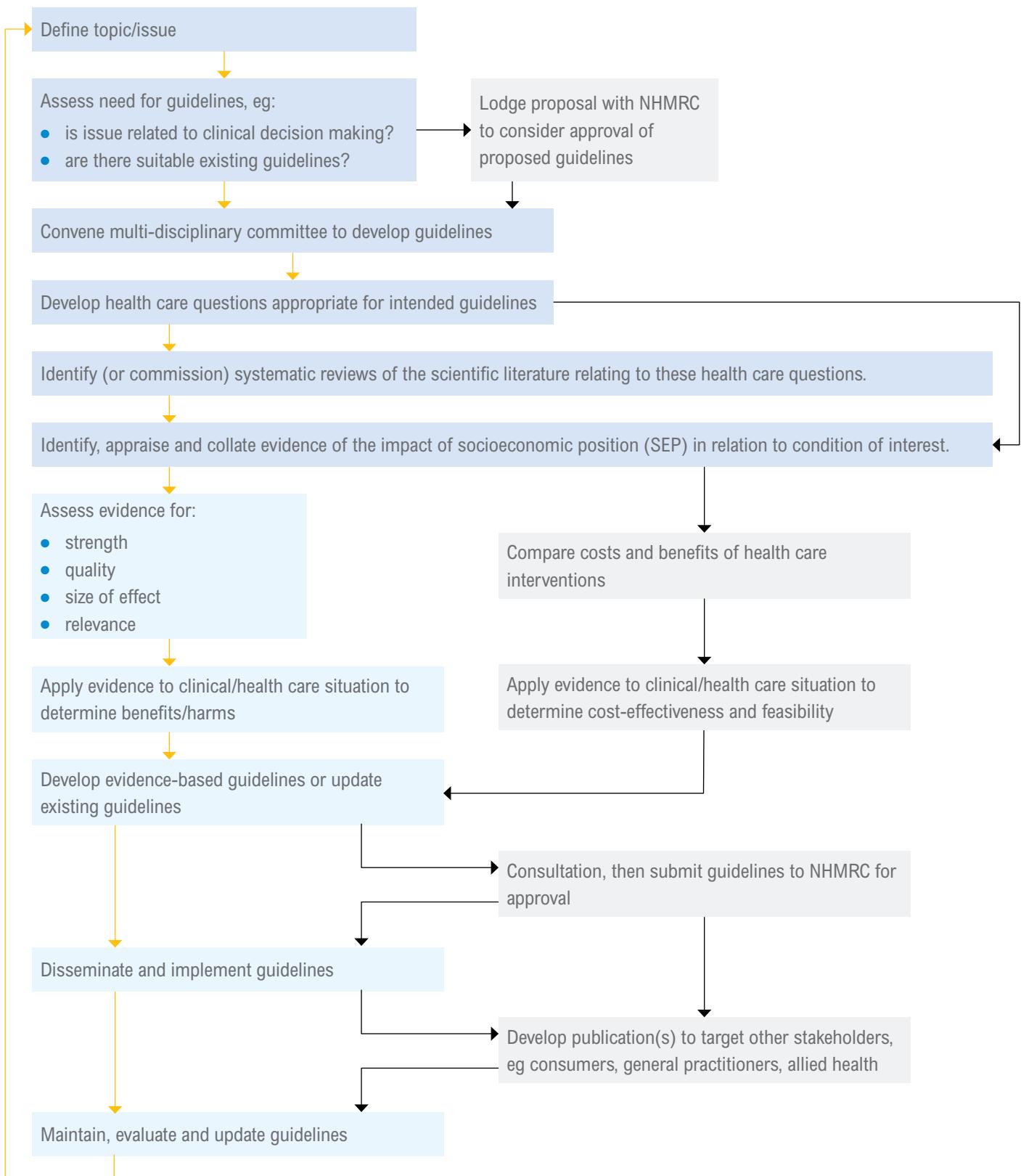


Diagram 2:

Flow chart of the NHMRC's development process for evidence-based guidelines



NHMRC standards and procedures for externally developed guidelines
Updated September 2007

Appendix VIII:

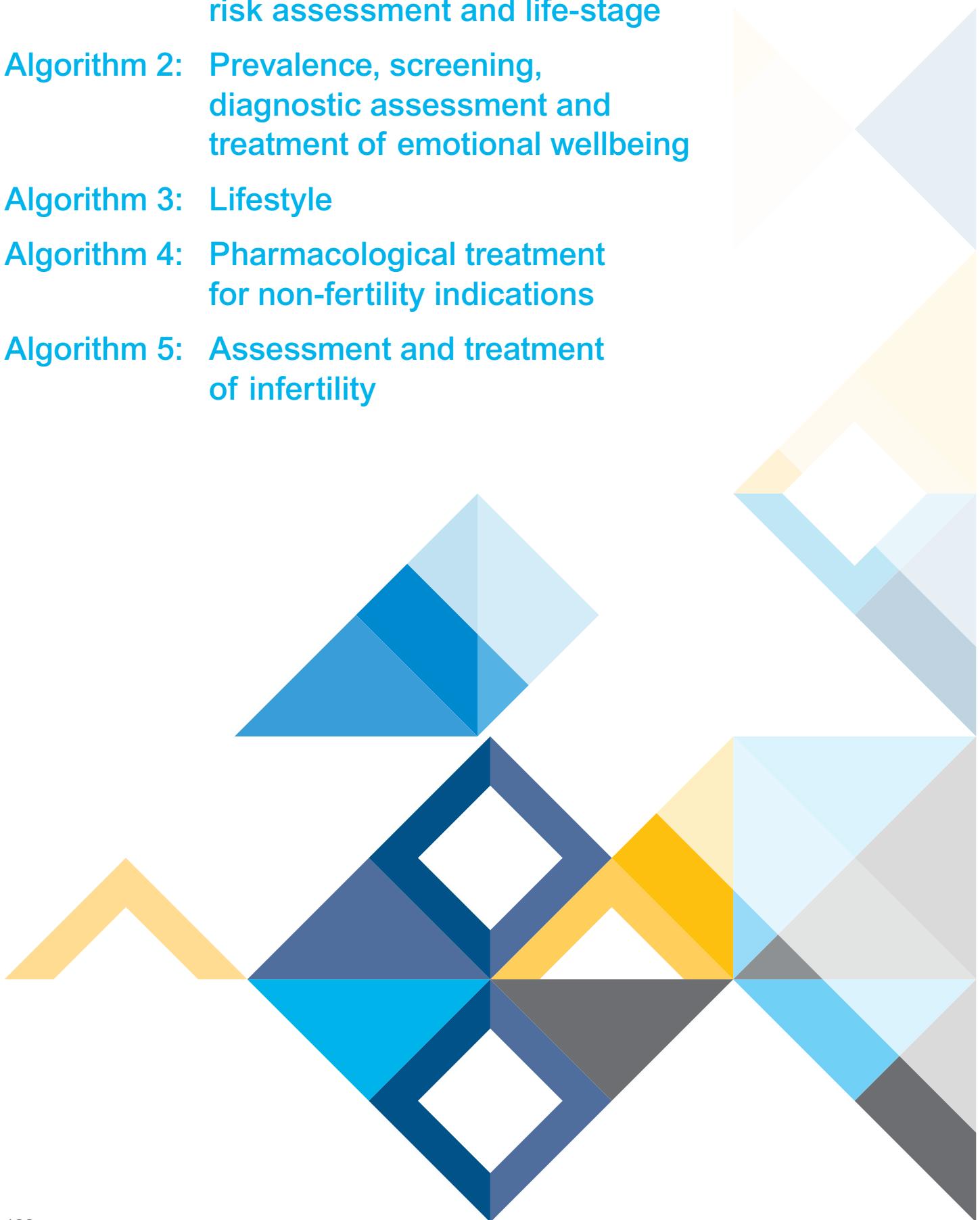
Algorithm 1: Screening, diagnostic assessment, risk assessment and life-stage

Algorithm 2: Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing

Algorithm 3: Lifestyle

Algorithm 4: Pharmacological treatment for non-fertility indications

Algorithm 5: Assessment and treatment of infertility



Algorithm 1: Screening, diagnostic assessment, risk assessment and life-stage

Step 1: Irregular cycles + clinical hyperandrogenism

(exclude other causes)* = diagnosis

Step 2: If no clinical hyperandrogenism

Test for biochemical hyperandrogenism (exclude other causes)* = diagnosis

Step 3: If ONLY irregular cycles OR hyperandrogenism

Adolescents ultrasound is not indicated = consider at risk of PCOS and reassess later

Adults - request ultrasound for PCOM, if positive (exclude other causes)* = diagnosis

* Exclusion of other causes requires TSH, Prolactin levels, FSH and if clinical status indicates other causes need to be excluded
(e.g. CAH, Cushings, adrenal tumours etc)

Hypogonadotropic hypogonadism, generally due to low body fat or intensive exercise, should also be excluded clinically and with LH and FSH levels.

Diagnostic Criteria

Irregular menstrual cycles

- normal in the first year post menarche = pubertal transition.
- > 1 to < 3 years post menarche: < 21 or > 45 days.
- > 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year.
- > 1 year post menarche > 90 days for any one cycle.
- Primary amenorrhea by age 15 or > 3 years post thelarche (breast development).

With irregular cycles, PCOS should be considered and assessed according to the guidelines.

Ovulatory dysfunction can still occur with regular cycles. If anovulation suspected test progesterone levels.

Clinical hyperandrogenism

Comprehensive history and physical examination for clinical hyperandrogenism. Adults: acne, alopecia and hirsutism and in adolescents severe acne and hirsutism.

Be aware of potential negative psychosocial impact of clinical hyperandrogenism. Perception of unwanted face and body hair and/or alopecia are important, regardless of apparent clinical severity.

Standardised visual scales are preferred when assessing hirsutism such as the modified Ferriman Gallway score (mFG). A cut-off score of ≥ 4 -6 indicates hirsutism, depending on ethnicity. It is acknowledged that self-treatment is common and can limit clinical assessment.

The Ludwig visual score is preferred for assessing the degree and distribution of alopecia.

Hirsutism prevalence is same across ethnicities. mFG cut-offs for hirsutism and severity, vary by ethnicity.

Only terminal hairs relevant in pathological hirsutism (untreated > 5 mm long, variable shape and pigmented).

Biochemical hyperandrogenism

Use calculated free testosterone, free androgen index or calculated bioavailable testosterone in diagnosis.

Androstenedione and dehydroepiandrosterone sulfate (DHEAS) have limited role in PCOS diagnosis.

High quality assays needed for most accurate assessment. Direct free testosterone assays not preferred. Interpretation of androgen levels should be guided by the reference ranges of the laboratory used.

Reliable assessment of biochemical hyperandrogenism not possible on hormonal contraception. Consider withdrawal for ≥ 3 months before testing, advising non-hormonal contraception during this time.

In diagnosis, biochemical hyperandrogenism most useful when clinical hyperandrogenism is unclear.

Where levels are well above laboratory reference ranges, other causes should be considered. History of symptom onset and progression is critical in assessing for neoplasia, however, some androgen-secreting neoplasms may only induce mild to moderate increases in biochemical hyperandrogenism.

Ultrasound and polycystic ovarian morphology (PCOM)

Ultrasound should not be used for the diagnosis of PCOS in those with a gynaecological age of < 8 years (< 8 years after menarche), due to the high incidence of multi-follicular ovaries in this life stage.

The transvaginal ultrasound approach is preferred in the diagnosis of PCOS, if sexually active and if acceptable to the individual being assessed.

Using endovaginal ultrasound transducers with a frequency bandwidth that includes 8MHz, the threshold for PCOM should be a follicle number per ovary of ≥ 20 and/or an ovarian volume $\geq 10\text{ml}$ on either ovary, ensuring no corpora lutea, cysts or dominant follicles are present.

If using older technology, the threshold for PCOM could be an ovarian volume $\geq 10\text{ml}$ on either ovary.

In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis; however ultrasound will identify the complete PCOS phenotype.

Transabdominal ultrasound should primarily report ovarian volume with a threshold of $\geq 10\text{ml}$, given the difficulty of reliably assessing follicle number with this approach.

Ethnic variation

Consider ethnic variation in PCOS including:

- relatively mild phenotypes in Caucasians.
- higher BMI in Caucasians, especially North America and Australia.
- more severe hirsutism in Middle Eastern, Hispanic and Mediterranean women.
- increased central adiposity, insulin resistance, diabetes, metabolic risks and acanthosis nigricans in South East Asians and Indigenous Australians.
- lower BMI and milder hirsutism in East Asians.
- higher BMI and metabolic features in Africans.

Anti-müllerian hormone (AMH)

Serum AMH levels should not yet be used as an alternative for the detection of PCOM or to diagnose PCOS.

Cardiovascular disease risk and weight management

All with PCOS should be offered regular monitoring for weight change and excess weight, in consultation with and where acceptable to the individual. Monitoring could be at each visit or at a minimum 6-12 monthly, with frequency planned and agreed between the health professional and the individual.

Weight, height and ideally waist circumference should be measured and BMI calculated.

- BMI categories and waist circumference should follow World Health Organisation guidelines also noting ethnic and adolescent ranges.
- Consideration for Asian and high risk ethnic groups including monitoring waist circumference.

All with PCOS should be assessed for individual cardiovascular risk factors and global CVD risk.

If screening reveals CVD risk factors including obesity, cigarette smoking, dyslipidemia, hypertension, impaired glucose tolerance and lack of physical activity, women with PCOS should be considered at increased risk of CVD.

Overweight and obese women with PCOS, regardless of age, should have a fasting lipid profile (total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level at diagnosis). Thereafter, measurement should be guided by the results and the global CVD risk.

All women with PCOS should have blood pressure measured annually.

CVD risk in women with PCOS remains unclear pending high quality studies, however prevalence of CVD risk factors is increased, warranting awareness and consideration of screening.

Gestational diabetes, impaired glucose tolerance and type 2 diabetes

Regardless of age, gestational diabetes, impaired glucose tolerance and type 2 diabetes (5 fold in Asia, 4 fold in the Americas and 3 fold in Europe) are increased in PCOS, with risk independent of, yet exacerbated by obesity.

Glycaemic status should be assessed at baseline in all with PCOS and thereafter, every one to three years, based on presence of other diabetes risk factors.

In high risk women with PCOS (including a BMI > 25kg/m² or in Asians > 23kg/m², history of abnormal glucose tolerance or family history of diabetes, hypertension or high risk ethnicity) an oral glucose tolerance test (OGTT) is recommended. Otherwise a fasting glucose or HbA1c should be performed.

An OGTT should be offered in all with PCOS when planning pregnancy or seeking fertility treatment, given increased hyperglycaemia and comorbidities in pregnancy.

If not performed preconception, an OGTT should be offered at < 20 weeks gestation, and all women with PCOS should be offered the test at 24-28 weeks gestation

Obstructive sleep apnea (OSA)

Screening should only be considered for OSA in PCOS to identify and alleviate related symptoms, such as snoring, waking unrefreshed from sleep, daytime sleepiness, and the potential for fatigue to contribute to mood disorders. Screening should not be considered with the intention of improving cardiometabolic risk, with inadequate evidence for metabolic benefits of OSA treatment in PCOS and in general populations.

A simple screening questionnaire, preferably the Berlin tool, could be applied and if positive, referral.

A positive screen raises the likelihood of OSA, however it does not quantify symptom burden and alone does not justify treatment. If women with PCOS have OSA symptoms and a positive screen, they should ideally be referred to a specialist centre for further evaluation.

Endometrial cancer

Health professionals and women with PCOS should be aware of a two to six fold increased risk of endometrial cancer, which often presents before menopause; however absolute risk remains relatively low.

Health professionals should have a low threshold for investigation of endometrial cancer in PCOS, with transvaginal ultrasound and/or endometrial biopsy recommended with persistent thickened endometrium and/or risk factors including prolonged amenorrhea, abnormal vaginal bleeding or excess weight. Routine ultrasound screening of endometrial thickness in PCOS is not recommended.

Optimal prevention for endometrial hyperplasia and endometrial cancer is not known. A pragmatic approach could include COCP or progestin therapy in those with cycles longer than 90 days.

Algorithm 2: Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing

Psychological domains	Screening protocol / tools	Intervention
Quality of life (QoL)	Lower QoL scores in general and PCOS specific tools such as the modified PCOSQ tool.	Capture and consider women's perceptions of their symptoms, impact on their QoL and priorities. Target treatment to areas of greatest concern to those with PCOS.
Anxiety and depressive symptoms	<p>High prevalence of moderate to severe anxiety and depressive symptoms in adults; and a likely increased prevalence in adolescents.</p> <p>Routine screening for all at diagnosis and subsequently based on clinical judgement, considering risk factors, comorbidities and life events.</p> <p>Suggested screening based on regional guidelines OR initial questions could include:</p> <p>Over the last 2 weeks, how often have you been bothered by the following problems:</p> <ul style="list-style-type: none"> • Feeling down, depressed or hopeless? • Little interest or pleasure in doing things? • Feeling nervous, anxious or on edge? • Not being able to stop or control worrying? <p>* Factors including obesity, infertility, hirsutism need consideration along with use of hormonal medications in PCOS, which may independently exacerbate depressive and anxiety symptoms and other aspects of emotional wellbeing.</p>	<p>If responses to initial screening questions positive:</p> <p>Assess risk factors and symptoms using age, culturally and regionally appropriate tools, such as the Patient Health Questionnaire (PHQ) or the Generalised Anxiety Disorder Scale (GAD7) and/or refer to an appropriate professional for further assessment.</p> <ul style="list-style-type: none"> • If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered to women with PCOS, informed by regional clinical practice guidelines. <p>Pharmacological treatment:</p> <p>Avoid inappropriate treatment with antidepressants or anxiolytics and consider impact on weight. Where mental health disorders are clearly documented and persistent, or if suicidal symptoms are present, treatment of depression or anxiety should be informed by clinical regional practice guidelines.</p>
Psychosexual dysfunction	<p>Decreased scores on sexual function screen.</p> <p>If concerns identified, screen adult women with PCOS.</p> <p>Note: Obesity and infertility are common in PCOS and also impact sexual function.</p>	If psychosexual dysfunction is suspected, further assessment, referral or treatment should follow as appropriate.
Body Image	<p>Negative body image has been described in PCOS and can be screened based on regional guidelines or by a stepped approach.</p> <p>Initial questions could include:</p> <ul style="list-style-type: none"> • Do you worry a lot about the way you look and wish you could think about it less? • On a typical day, do you spend more than 1 hour per day worrying about your appearance? • What specific concerns do you have about your appearance? • What effect does it have on your life? • Does it make it hard to do your work or be with your friends and family? 	Consider the impact of PCOS features such as hirsutism, acne, and weight gain in assessing and addressing body image in PCOS.
Eating disorders and disordered eating	<p>High prevalence of eating disorders and disordered eating has been described and can be screened based on regional guidelines or by using the following stepped approach.</p> <p>Initial screening questions can include:</p> <ul style="list-style-type: none"> • Does your weight affect the way you feel about yourself? • Are you satisfied with your eating patterns? <p>Or the SCOFF tool can be used.</p>	<p>If concerns are identified, further screening should involve:</p> <ul style="list-style-type: none"> • Assessment of risk factors and symptoms using age, culturally and regionally appropriate tools. • Referral to an appropriate health professional for further mental health assessment and diagnostic interview. If this is not the patient's usual healthcare provider, inform.

Algorithm 3: Lifestyle

Lifestyle

Effectiveness of lifestyle interventions

Healthy lifestyle behaviours (healthy eating and regular physical activity) should be recommended in all women with PCOS including those with excess weight, to achieve and/or maintain healthy weight and to optimise health, and quality of life across the life course. Ethnic groups at high cardiometabolic risk require more consideration.

Achievable goals such as 5% to 10% weight loss in those with excess weight yields significant clinical improvements and is considered successful weight reduction within six months. Ongoing monitoring is important in weight loss and maintenance. Consider referral to a professional to assist with healthy lifestyle.

SMART (Specific, Measurable, Achievable, Realistic and Timely) goal setting and self-monitoring can enable achievement of realistic lifestyle goals.

Psychological factors such as anxiety and depressive symptoms, body image concerns and disordered eating need consideration to optimise healthy lifestyle engagement.

All patient interactions should be patient-centred and value women's individualised healthy lifestyle preferences and cultural, socioeconomic and ethnic differences.

Adolescent and ethnic-specific body mass index and waist circumference categories should be considered when optimising lifestyle and weight.

Behavioural strategies

Lifestyle interventions (may also include cognitive behavioural interventions) could include goal-setting, self-monitoring, stimulus control, problem solving, assertiveness training, slower eating, reinforcing changes and relapse prevention, to optimise weight management, healthy lifestyle and emotional wellbeing in women with PCOS.

Dietary intervention

General healthy eating principles should be followed for all women with PCOS across the life course, with no one dietary type recommended in PCOS.

To achieve weight loss in those with excess weight, an energy deficit of 30% or 500 - 750 kcal/day (1,200 - 1,500 kcal/day) could be prescribed for women, also considering individual energy requirements, body weight, food preferences and physical activity levels and an individualised approach.

Exercise intervention

Health professionals should encourage and advise the following for prevention of weight gain and maintenance of health:

- in adults from 18-64 years, a minimum of 150 min/week of moderate intensity physical activity or 75 min/week of vigorous intensities or an equivalent combination of both including muscle strengthening activities on 2 non-consecutive days/week.
- in adolescents, at least 60 minutes of moderate to vigorous intensity physical activity/day including those that strengthen muscle and bone at least 3 times weekly.
- activity be performed in at least 10 minute bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days.

Health professionals should encourage and advise the following for modest weight-loss, prevention of weight-regain and greater health benefits including:

- a minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensity or an equivalent combination of both, and
- muscle strengthening activities involving major muscle groups on 2 non-consecutive days/week and minimised sedentary, screen or sitting time.

Physical activity can be incidental or structured. Self-monitoring, including with fitness tracking devices and technologies, could support and promote active lifestyles.

Obesity and weight assessment

Women with PCOS have higher weight gain and obesity which can impact health and emotional wellbeing. In addressing this, consider related stigma, negative body image and/or low self-esteem by use of a respectful and considerate approach, considering personal sensitivities, marginalisation and potential weight-related stigma.

Prevention of weight gain, monitoring of weight and encouraging evidence-based and socio-culturally appropriate healthy lifestyle is important in PCOS from adolescence.

Algorithm 4: Pharmacological treatment for non-fertility indications

Off label prescribing: COCPs, metformin and other pharmacological treatments are generally off label in PCOS, as pharmaceutical companies have not applied for approval in PCOS. However, off label use is predominantly evidence-based and is allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment.

In those with a clear PCOS diagnosis or in adolescents at risk of PCOS (with symptoms)

Education + lifestyle + first line pharmacological therapy for hyperandrogenism and irregular cycles

COCP First line

Use lowest effective oestrogen dose (20-30 micrograms ethinyl oestradiol or equivalent)

Consider natural oestrogen preparations balancing efficacy, metabolic risk profile, side effects, cost and availability

Follow WHO COCP general population guidelines for relative and absolute contraindications and risks

35 micrograms ethynodiol diacetate plus cyproterone acetate not first line in PCOS due to increased adverse effects

Hirsutism requires COCP and additional cosmetic therapy for at least 6 months

Consider additional PCOS related risk factors such as high BMI, hyperlipidemia and hypertension

Note:

Other contraceptives don't increase hepatic SHBG production with limited efficacy for hyperandrogenism

Second line pharmacological therapies

COCP + lifestyle + metformin

No COCP preparation is superior in PCOS.

Should be considered in women with PCOS for management of metabolic features, where COCP + lifestyle does not achieve goals.

Could be considered in adolescents with PCOS and $BMI \geq 25\text{kg}/\text{m}^2$ where COCP and lifestyle changes do not achieve desired goals.

Most beneficial in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.

COCP + anti-androgens

Evidence in PCOS relatively limited.

Anti-androgens must be used with contraception to prevent male fetal virilisation.

Can be considered after 6/12 cosmetic treatment + COCP if they fail to reach hirsutism goals.

Can be considered with androgenic alopecia.

Metformin + lifestyle

With lifestyle, in adults should be considered for weight, hormonal and metabolic outcomes and could be considered in adolescents.

Most useful with $BMI \geq 25\text{kg}/\text{m}^2$ and in high risk ethnic groups.

Side-effects, including GI effects, are dose related and self-limiting.

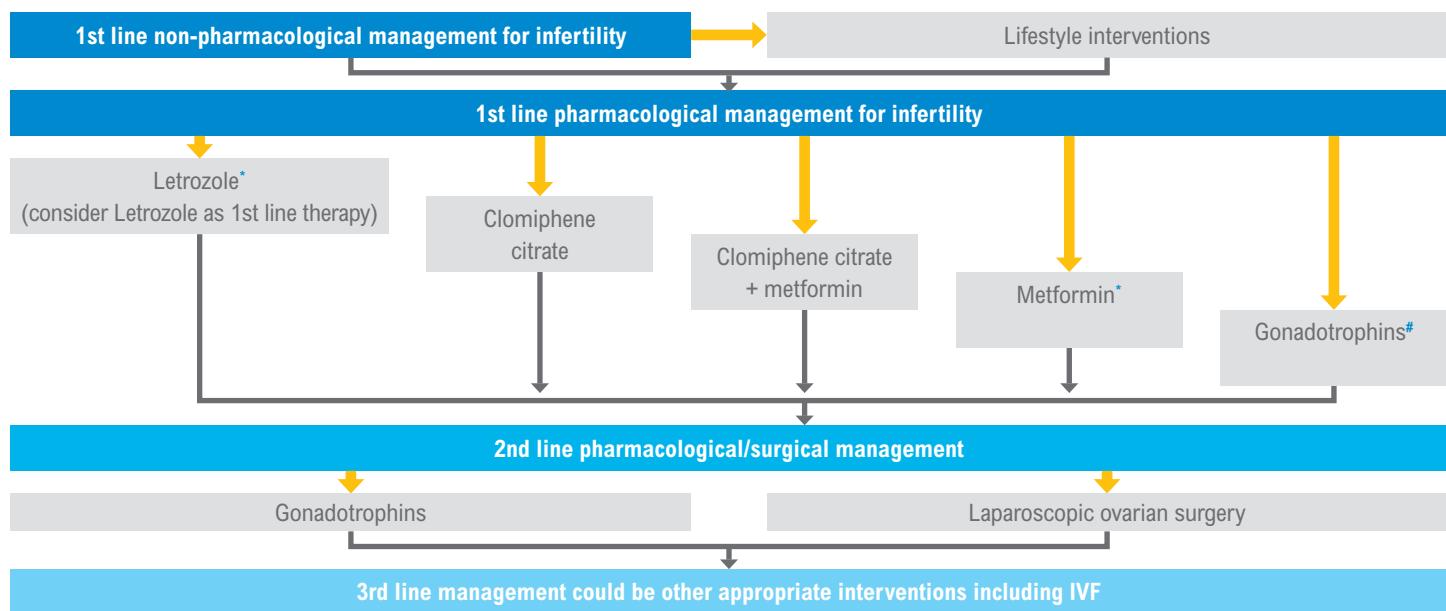
Consider starting low dose, with 500mg increments 1-2 weekly.

Metformin appears safe long-term. Ongoing monitoring required and has been associated with low vitamin B12.

Anti-obesity medications can be considered with lifestyle as per general population guidelines, considering cost, contraindications, side effects, availability and regulatory status and avoiding pregnancy when on therapy.

Inositol (in any form) should currently be considered experimental in PCOS, with emerging evidence of efficacy highlighting the need for further research.

Algorithm 5: Assessment and treatment of infertility



* **Off label prescribing:** Letrozole, COCPs, metformin and other pharmacological treatments are generally off label in PCOS, as pharmaceutical companies have not applied for approval in PCOS. However, off label use is predominantly evidence-based and is allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment.

Assessment and treatment of infertility

Assessment of factors that may affect fertility, treatment response or pregnancy outcomes

Factors such as blood glucose, weight, blood pressure, smoking, alcohol, diet, exercise, sleep and mental, emotional and sexual health should be optimised in women with PCOS, to improve reproductive and obstetric outcomes, aligned with recommendations in the general population.

Refer to the International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 available at: www.monash.edu/medicine/sphpm/mchri/pcos

Monitoring during pregnancy is important for women with PCOS, given increased risk of adverse maternal and offspring outcomes.

For women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing of tubal patency testing should be discussed on an individual basis.

Tubal patency testing should be considered prior to ovulation induction for women with PCOS where there is suspected tubal infertility.

Ovulation induction principles

The use of ovulation induction agents, including letrozole, metformin and clomiphene citrate is off label in many countries*.

Pregnancy should be excluded prior to ovulation induction.

Unsuccessful, prolonged use of ovulation induction agents should be avoided, due to poor success rates.

Letrozole

Letrozole should be considered first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates.

Where letrozole is not available or use is not permitted or cost is prohibitive, health professionals should use other ovulation induction agents.

Health professionals and women should be aware that the risk of multiple pregnancy appears to be less with letrozole, compared to clomiphene citrate.

Clomiphene citrate and metformin

Clomiphene citrate could be used alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and pregnancy rates.

Metformin could be used alone in women with PCOS, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates, although women should be informed that there are more effective ovulation induction agents.

Clomiphene citrate could be used in preference, when considering clomiphene citrate or metformin for ovulation induction in women with PCOS who are obese ($BMI \geq 30 \text{ kg/m}^2$) with anovulatory infertility and no other infertility factors.

If metformin is being used for ovulation induction in women with PCOS who are obese ($BMI \geq 30 \text{ kg/m}^2$) with anovulatory infertility and no other infertility factors, clomiphene citrate could be added to improve ovulation, pregnancy and live birth rates.

Clomiphene citrate could be combined with metformin, rather than persisting with clomiphene citrate alone, in women with PCOS who are clomiphene citrate-resistant, with anovulatory infertility and no other infertility factors, to improve ovulation and pregnancy rates.

The risk of multiple pregnancy is increased with clomiphene citrate use and therefore monitoring needs to be considered.

Gonadotrophins

Gonadotrophins could be used as second line pharmacological agents in women with PCOS who have failed first line oral ovulation induction therapy and are anovulatory and infertile, with no other infertility factors.

Gonadotrophins could be considered as first line treatment, in the presence of ultrasound monitoring, following counselling on cost and potential risk of multiple pregnancy, in women with PCOS with anovulatory infertility and no other infertility factors.

Gonadotrophins, where available and affordable, should be used in preference to clomiphene citrate combined with metformin therapy for ovulation induction, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates.

Gonadotrophins with the addition of metformin, could be used rather than gonadotrophins alone, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates.

Either gonadotrophins or laparoscopic ovarian surgery could be used in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, following counselling on benefits and risks of each therapy.

Where gonadotrophins are prescribed, the following should be considered:

- cost and availability
- expertise required for use in ovulation induction
- degree of intensive ultrasound monitoring required
- lack of difference in clinical efficacy of available gonadotrophin preparations
- low dose gonadotrophin protocols optimise monofollicular development
- risk and implications of potential multiple pregnancy

Gonadotrophin induced ovulation should only be triggered when there are fewer than three mature follicles and should be cancelled if there are more than two mature follicles with the patient advised to avoid unprotected intercourse.

Anti-obesity agents

Pharmacological anti-obesity agents should be considered an experimental therapy for women with PCOS for the purpose of improving fertility, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy.

Laparoscopic ovarian surgery

Laparoscopic ovarian surgery could be second line therapy for women with PCOS, who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors.

Laparoscopic ovarian surgery could potentially be offered as first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors.

Risks should be explained to all women with PCOS considering laparoscopic ovarian surgery.

Where laparoscopic ovarian surgery is to be recommended, the following should be considered:

- comparative cost
- expertise required for use in ovulation induction
- intra-operative and post-operative risks are higher in women who are overweight and obese
- there may be a small associated risk of lower ovarian reserve or loss of ovarian function
- periadnexal adhesion formation may be an associated risk

Bariatric Surgery

Bariatric surgery should be considered an experimental therapy in women with PCOS, for the purpose of having healthy baby, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy.

If bariatric surgery is to be prescribed, the following should be considered:

- comparative cost
- the need for a structured weight management program involving diet, physical activity and interventions to improve psychological, musculoskeletal and cardiovascular health to continue post-operatively
- perinatal risks such as small for gestational age, premature delivery, possibly increased infant mortality
- potential benefits such as reduced incidence of large for gestational age fetus and gestational diabetes
- recommendations for pregnancy avoidance during periods of rapid weight loss and for at least 12 months after bariatric surgery with appropriate contraception

If pregnancy occurs, the following should be considered:

- awareness and preventative management of pre- and post-operative nutritional deficiencies is important, ideally in a specialist interdisciplinary care setting
- monitoring of fetal growth during pregnancy

In-vitro fertilisation (IVF)

In the absence of an absolute indication for IVF ± ICSI, women with PCOS and anovulatory infertility could be offered IVF third line where other ovulation induction therapies have failed.

In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used, multiple pregnancies can be minimised.

Women with PCOS undergoing IVF ± ICSI therapy should be counselled prior to starting treatment, including on:

- availability, cost and convenience
- increased risk of ovarian hyperstimulation syndrome
- options to reduce the risk of ovarian hyperstimulation

Urinary or recombinant follicle stimulation hormone can be used in women with PCOS undergoing controlled ovarian hyperstimulation for IVF ± ICSI, with insufficient evidence to recommend specific FSH preparations.

Exogenous recombinant luteinising hormone treatment should not be routinely used in combination with follicle stimulating hormone therapy in women with PCOS undergoing controlled ovarian hyperstimulation for IVF ± ICSI.

A gonadotrophin releasing hormone antagonist protocol is preferred in women with PCOS undergoing an IVF ± ICSI cycle, over a gonadotrophin releasing hormone agonist long protocol, to reduce the duration of stimulation, total gonadotrophin dose and incidence of ovarian hyperstimulation syndrome (OHSS).

Human chorionic gonadotrophins should be used at the lowest doses to trigger final oocyte maturation in women with PCOS undergoing an IVF ± ICSI cycle to reduce the incidence of OHSS.

Triggering final oocyte maturation with a GnRH agonist and freezing all suitable embryos could be considered in women with PCOS having an IVF/ICSI cycle with a GnRH antagonist protocol and at an increased risk of developing OHSS or where fresh embryo transfer is not planned.

In IVF ± ICSI cycles in women with PCOS, consideration should be given to an elective freeze of all embryos.

Adjunct metformin therapy could be used before and/or during follicle stimulating hormone ovarian stimulation in women with PCOS undergoing IVF ± ICSI therapy with a gonadotrophin releasing hormone agonist protocol, to improve the clinical pregnancy rate and reduce the risk of OHSS.

In a gonadotrophin releasing hormone agonist protocol with adjunct metformin therapy, in women with PCOS undergoing IVF ± ICSI treatment, the following could be considered:

- metformin commencement at the start of gonadotrophin releasing hormone agonist treatment
- metformin use at a dose of between 1000mg to 2550mg daily
- metformin cessation at the time of the pregnancy test or menses (unless the metformin therapy is otherwise indicated)
- metformin side-effects (refer to the International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 available at: www.monash.edu/medicine/sphpm/mchri/pcos)

In IVF ± ICSI cycles, women with PCOS could be counselled on potential benefits of adjunct metformin in a gonadotrophin releasing hormone antagonist protocol to reduce risk of ovarian hyperstimulation syndrome (refer to the International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 available at: www.monash.edu/medicine/sphpm/mchri/pcos).

The term in vitro maturation (IVM) treatment cycle should be applied to “the maturation in vitro of immature cumulus oocyte complexes collected from antral follicles” (encompassing both stimulated and unstimulated cycles, but without the use of a human gonadotrophin trigger).

In units with sufficient expertise, IVM could be offered to achieve pregnancy and live birth rates approaching those of standard IVF ± ICSI treatment without the risk of OHSS for women with PCOS, where an embryo is generated, then vitrified and thawed and transferred in a subsequent cycle.

International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018

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Polycystic Ovary Syndrome: An Evolutionary Adaptation to Lifestyle and the Environment

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Review

Polycystic Ovary Syndrome: An Evolutionary Adaptation to Lifestyle and the Environment

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Abstract: Polycystic ovary syndrome (PCOS) is increasingly recognized as a complex metabolic disorder that manifests in genetically susceptible women following a range of negative exposures to nutritional and environmental factors related to contemporary lifestyle. The hypothesis that PCOS phenotypes are derived from a mismatch between ancient genetic survival mechanisms and modern lifestyle practices is supported by a diversity of research findings. The proposed evolutionary model of the pathogenesis of PCOS incorporates evidence related to evolutionary theory, genetic studies, in-utero developmental epigenetic programming, transgenerational inheritance, metabolic features including insulin resistance, obesity and the apparent paradox of lean phenotypes, reproductive effects and subfertility, the impact of the microbiome and dysbiosis, endocrine disrupting chemical exposure, and the influence of lifestyle factors such as poor quality diet and physical inactivity. Based on these premises, the diverse lines of research are synthesized into a composite evolutionary model of the pathogenesis of PCOS. It is hoped that this model will assist clinicians and patients to understand the importance of lifestyle interventions in the prevention and management of PCOS and provide a conceptual framework for future research. It is appreciated that this theory represents a synthesis of the current evidence and that it is expected to evolve and change over time.

Keywords: polycystic ovary syndrome; evolution; insulin resistance; infertility; toxins, endocrine disrupting chemicals; environment; lifestyle; diet

1. Introduction

It is widely accepted that there is a global epidemic of lifestyle-related chronic diseases, such as obesity and diabetes, that are underpinned by reversible metabolic dysfunction in the majority of individuals affected (1–3). It is also recognized that many of these chronic diseases may share a similar pathogenesis involving the interaction of genetic and environmental factors that manifest in overlapping pathophysiological features (4–6). The revised International Guidelines for the assessment and management of women with PCOS, emphasise that the associated metabolic dysfunction and symptoms should initially be addressed via lifestyle interventions (7).

Evolutionary medicine is an emerging discipline involving the study of evolutionary processes that relate to human traits and diseases and the incorporation of these findings



into the practice of medicine (8). Evolutionary medicine brings together interdisciplinary research to inform clinical medicine based on the influence of evolutionary history on human health and disease (9). Previous utilization of the principles of evolutionary medicine has been limited to monogenetic diseases (cystic fibrosis, sickle cell anaemia, phenylketonuria and many others), drug resistance of microorganisms, tumour growth and chemoresistance (8). Future insights into the application of evolutionary research offers the potential to improve and personalize the established medical and scientific approaches to complex chronic diseases like type 2 diabetes, metabolic syndrome and PCOS (5,9).

The evolutionary origins of complex chronic diseases incorporate considerations of relative reproductive fitness, mismatch between our biological past and modern environment, trade-offs involving combinations of genetic traits, and evolutionary conflicts (8,10). These evolutionary factors are relevant when analysing the contributors to the pathogenesis of PCOS in modern and modernising societies, that result in a mismatch between our rapid cultural evolution with our slow biological evolution (11,12). The unique cultural evolution of humans does not have a plausible analogue in most other species and is increasingly recognised to play a significant role in the pathogenesis of metabolic diseases such as PCOS (5,13–17).

Polycystic ovary syndrome is a complex multisystem condition with metabolic, endocrine, psychological, fertility and pregnancy-related implications at all stages of life (7,18). The majority of women with PCOS manifest multiple metabolic features including obesity, insulin resistance (IR), hyperlipidaemia and hyperandrogenism (19,20). PCOS results in an increased risk of developing metabolic disease (type 2 diabetes, non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome), cardiovascular disease, cancer, a wide array of pregnancy complications (deep venous thrombosis, pre-eclampsia, gestational diabetes, macrosomia, growth restriction, miscarriage, stillbirth and preterm labour) and psychological problems (anxiety, depression) (6,21–25). PCOS is part of a cluster of inter-related metabolic conditions and makes a significant contribution to the chronic disease epidemic.

Extensive research suggests that the aetiology of PCOS involves an interaction between environmental factors and gene variants, although it has been suggested that genetic factors contribute less than 10% to disease susceptibility (26–28). A large number of genetic and genome-wide association studies (GWAS) have identified common gene loci associated with PCOS phenotypes in different ethnic populations (29–31). These appear to be normal gene variants or polymorphisms, given the frequency and type of genes that have been identified. PCOS is therefore viewed as a polygenic trait that results from an interaction between susceptible genomic variants and the environment.

PCOS affects upward of 10% of reproductive-aged women, estimated at over 200 million women worldwide (32,33). PCOS is thought to be increasing in incidence in both developing and developed nations as a result of lifestyle-related changes in diet quality, reduced physical activity, ubiquitous environmental endocrine disrupting chemicals (EDC), altered light exposures, sleep disturbance, heightened levels of stress and other

environmental factors (11,34–38). These factors, and the high prevalence of PCOS, suggest that there could be an evolutionary basis for the syndrome (15,16,39). Evolutionary medicine has changed the paradigm for understanding PCOS, acknowledging many of the contributing lifestyle and environmental factors that facilitate the observed metabolic and clinical features and that are also shared with related metabolic diseases (8). These “mismatch disorders” are estimated to make a significant contribution to chronic disease in developed countries and a growing proportion of disability and death in developing nations (3). According to the Global Burden of Disease Study, the human diet is now the leading risk factor for morbidity and mortality worldwide (3). In keeping with these findings, diet is recognized as one of the major contributors to the growing prevalence of PCOS globally (7,40).

Dietary and environmental factors are hypothesized to have an impact on developmental programming of susceptible gene variants in women with PCOS (41–43). Extensive experimental evidence suggests that prenatal androgen exposure may play a role in the pathogenesis of PCOS-like syndromes in animal models (19,44–46). The discovery of naturally-occurring PCOS phenotypes in non-human primates supports a survival advantage of a hyperandrogenic, insulin resistant phenotype with delayed fertility (47). In humans, the origin of excess androgens may be from maternal, fetal or placental sources. In addition, emerging and concerning evidence suggests that EDC may contribute to altered fetal programming and play a role in the pathogenesis of PCOS (41,48).

In-utero genomic programming of metabolic and endocrine pathways can increase the susceptibility of offspring to develop PCOS following exposure to specific nutritional and environmental conditions (45). This view of the pathogenesis of PCOS is consistent with the Developmental Origins of Health and Disease (DOHaD) model proposed by Neel (49). Postnatal exposure to lifestyle and environmental factors, such as poor-quality diet and EDC, may activate epigenetically programmed pathways that further promote the observed features of PCOS. Dietary and lifestyle interventions have demonstrated that many of the clinical, metabolic and endocrine features of PCOS can be reversed (7,50,51).

Lifestyle-induced changes in the gastrointestinal tract microbiome are another significant factor in the aetiology of PCOS (52,53). Dysbiosis of the gut microbiota has been hypothesised to play a role in increased gastrointestinal permeability, initiating chronic inflammation, IR and hyperandrogenism (40). Numerous studies have reported reduced alpha diversity of the microbiome that has been associated with the metabolic, endocrine and clinical features observed in women with PCOS (54,55). The resulting dysbiosis has been shown to be reversible after interventions aimed at improving diet quality or treatment with probiotics or synbiotics (50,51,56–58).

A unified evolutionary theory of the pathogenesis of PCOS proposes that ancient genetic polymorphisms that were aligned with the environment of that era, resulted in an adaptive survival advantage in offspring in ancestral populations (14–16,28). When these same genetic variants are exposed to modern lifestyle and environmental influences, maladaptive physiological responses occur. The prior advantages of insulin resistance, hyperandrogenism, enhanced energy storage and reduced fertility in ancestral

populations become pathological and result in the observed features of PCOS in contemporary women (figure 1).

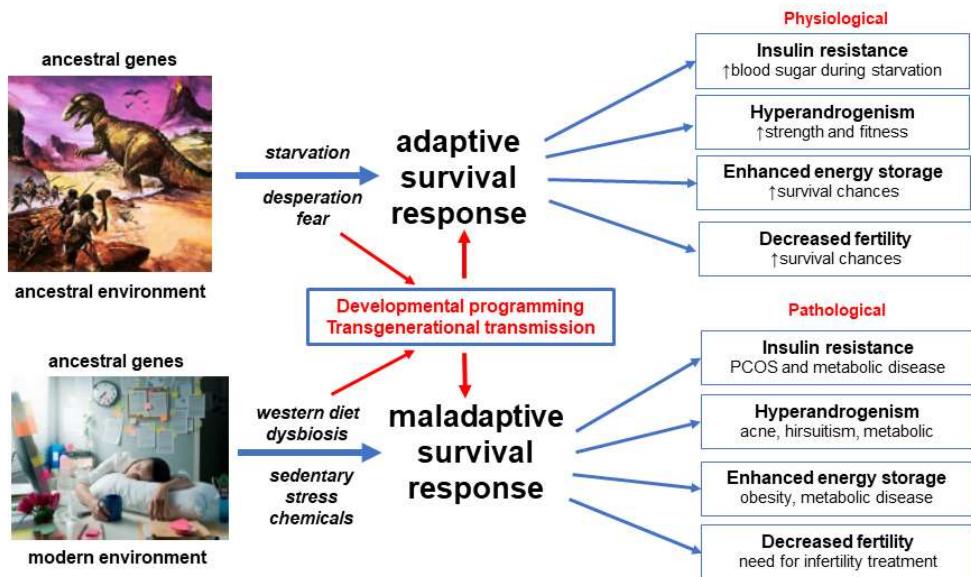


Figure 1. Evolutionary model of the pathogenesis of polycystic ovary syndrome

2. Materials and Methods

The literature search focused on research publications related to the pathogenesis of PCOS using the keywords listed above and related mesh terms for data on the evolutionary aspects of PCOS, genetic studies, in-utero developmental epigenetic programming, transgenerational inheritance, metabolic features including insulin resistance, obese and lean PCOS phenotypes, reproductive changes and subfertility, impact of the microbiome and dysbiosis, possible effects of endocrine disrupting chemical exposure and the influence of lifestyle factors such as diet and physical activity. The databases searched included PubMed, Scopus, Cochrane and Google Scholar. Relevant papers were selected and citation searches were performed.

The present manuscript synthesizes the findings into a unified evolutionary model. The following text is presented as a narrative review of factors involved in the pathogenesis of PCOS and is discussed in ten main subject areas that provide the rationale for the development of a unified model. 1. Evolution 2. Genetics 3. Developmental Epigenetic Programming 4. Microbiome and Dysbiosis 5. Insulin resistance 6. Obesity and the lean paradox 7. Environmental Chemical Exposure 8. Lifestyle Contributors to the Pathogenesis of PCOS 9. Conceptual Framework of a Unified Evolutionary Model 10. Explanation to women diagnosed with PCOS.

3. Pathogenesis of PCOS

3.1. Evolution

The description of PCOS phenotypes can be found in medical records from antiquity and the modern syndrome was described over 80 years ago (17,59). Nevertheless, there is ongoing debate regarding the evolutionary origins of PCOS (15–17,39,60–64). PCOS

susceptibility alleles may have arisen in our phylogenetic ancestors, in the Hunter-gatherer Paleolithic period of the Stone Age, after the Neolithic Agricultural Revolution or following the Industrial Revolution (16,17). From an evolutionary perspective, nearly all genetic variants that influence disease risk have human-specific origins, but the systems they relate to have ancient roots in our evolutionary ancestors (8). Regardless of the precise timing of the origin of PCOS in humans, the complex metabolic and reproductive gene variants identified in women with PCOS relate to ancient evolutionary-conserved metabolic and reproductive survival pathways (15,29). Although evolutionary hypotheses about disease vulnerability are impossible to prove they have the potential to frame medical thinking and direct scientific research for the proximate causes of disease (15,60).

Multiple hypotheses have been proposed regarding the evolutionary origins of PCOS and related metabolic diseases (8,60,63). These hypotheses are focused on the relative importance of metabolic survival adaptations versus improved reproductive success, or a combination of both. A detailed analysis of these hypotheses, and the complexities of the evolutionary considerations, have been reviewed elsewhere and is beyond the scope of the present review (8,60). One common theme is that PCOS may be viewed as a “conditional phenotype” where a specific set of conditions has unmasked normally unexpressed or partly expressed genetic pathways, which then provide a survival advantage under certain environmental conditions (14,16).

All organisms have physiological adaptive responses to deal with changing environmental conditions (starvation, fasting, physical threat, stress and infection) and the varying demands of internal physiological states (pregnancy, lactation and adolescence) (14,65). It has been proposed that the PCOS phenotype may have been invoked in specific environmental conditions in ancestral populations as a short, medium or even long-term adaptive survival mechanism (15–17). The view of PCOS as a conditional phenotype proposes that these physiological responses become pathological in our modern environment due to factors such as food abundance, reduced physical activity, circadian disruption, stress and environmental chemical exposure. The transgenerational evolutionary theory of the pathogenesis of PCOS encompasses all of the above ideas to explain the observed pathophysiological and clinical features of PCOS (28).

It is generally accepted that almost all pre-industrial societies and animal populations experienced seasonal or unpredictable episodes of food shortage that applied evolutionary pressure to develop metabolic and reproductive adaptive survival responses (17,49). It is also appreciated that metabolic and reproductive pathways are interconnected and involve reciprocal feedback control mechanisms (66–68). During periods of starvation, anorexia or excessive weight gain, reproduction is down-regulated and ovulation becomes irregular or ceases (69,70). Similarly, metabolic function is co-ordinated with the menstrual cycle to ensure optimal physiological conditions for fertilisation, implantation, pregnancy, parturition and lactation (71). Recent research has elaborated on the details of how some of these complex regulatory mechanisms interact by using specific hormonal, nutrient sensing and intracellular signalling networks (72–74).

Details of the mechanisms underlying the proposed adaptive survival advantages of IR, hyperandrogenism, enhanced energy storage and sub-fertility have been obtained from paleolithic records, animal models and human populations exposed to adverse environmental conditions such as war and famine-inflicted starvation (14,16,62,63). Multiple lines of evidence support the maladaptive response of human populations to rapidly changing nutritional, physical, psychological and cultural environments, in the modern world (5,11,14,75). These “adaptations” result in pathological responses to IR, hyperandrogenism, enhanced energy storage and ovulation (figure 1).

Theories of evolutionary mismatch have also been advanced to explain all of the cluster of metabolic diseases associated with PCOS (type 2 diabetes, metabolic syndrome, NAFLD and cardiovascular disease) and follow the same set of basic principles and explanations (14,76). This common body of evolutionary evidence is supported by the increasing incidence of metabolic-related disease, such as diabetes and obesity, in developed countries and in developing nations adopting a Western diet and lifestyle (11,77). In addition, the demonstrated reversibility of PCOS and related metabolic and biochemical features following changes in diet, increased physical activity and other lifestyle interventions, adds further support to a transgenerational evolutionary model (50,51).

3.2. Genetics

The heritable nature of PCOS has been proposed since the 1960’s following a range of familial, twin and chromosomal studies (78–80). Cytogenetic studies failed to identify karyotypic abnormalities and genetic studies did not show a monogenic inheritance pattern following examination of candidate genes (81,82). In addition, two or more phenotypes can be present in the same family suggesting that some of the phenotypic differences could be accounted for by variable expression of the same shared genes (81,83).

The mapping of the human genome in 2003 (84) and the publication of the human haplotype map (more than one million single nucleotide polymorphisms of common genetic variants) in 2005 (85), lead to the realisation that most DNA variation is shared by all humans and is inherited as blocks of linked genes (linkage disequilibrium) (86). These advances enabled a revolution in case-control studies and the development of GWAS which map the entire human genome looking for susceptibility genes for complex traits such as obesity, type 2 diabetes and PCOS (81).

The first PCOS GWAS was published in 2010 and demonstrated 11 gene loci associated with PCOS (87). Additional loci have subsequently been found in a number of different ethnic groups (86,88). The first GWAS analysis of quantitative traits was published in 2015 and showed that a variant (rs11031006) was associated with luteinizing hormone levels (88). The largest GWAS included a meta-analysis of 10,074 PCOS cases and 103,164 controls and identified 19 loci that confer risk for PCOS (29). The genes associated with these loci involve gonadotrophin action, ovarian steroidogenesis, insulin resistance and type 2 diabetes susceptibility genes. The first GWAS using electronic health record-linked biobanks has introduced greater investigative power and identified 2 additional loci (89). These variants were associated with polycystic ovaries and hyperandrogenism

(rs17186366 near *SOD2*) and oligomenorrhoea and infertility (rs144248326 near *WWTR1*) (89). In addition to identifying common gene variants for PCOS phenotypes, finding the same signals (*THADA*, *YAP1* and *c9orf3*) in Chinese and European populations suggests that PCOS is an ancient trait that was present before humans migrated out of Africa (81).

More recently Mendelian randomization (MR) studies have been used to explore the potential causative association between gene variants identified in GWAS and PCOS (90,91). Many of the gene variants identified in GWAS are located in non-coding regions of DNA (92). The genes or functional DNA elements through which these variants exert their effects are often unknown. Mendelian randomization is a statistical methodology used to jointly analyse GWAS and quantitative gene loci to test for association between gene expression and a trait, due to a shared or potentially causal variant at a specific locus (93). A detailed analysis of MR methodology and the limitations of this statistical tool is beyond the scope of the present review. Although MR studies have the potential to infer causation it is recognised that they also have limitations in PCOS research (90). Nevertheless, preliminary evidence suggests that a number of genes related to obesity, metabolic and reproductive function, may play a causal role in the pathogenesis of PCOS (90,91).

Decades of genetic research has therefore characterised PCOS as a polygenic trait that results from interactions between the environment and susceptible genomic traits (27,29,79,88). The failure to identify a qualitative or monogenic inheritance pattern and the findings from GWAS, MR, familial and twin studies, suggests that the heritability of PCOS is likely to be due to the combination of multiple genes having small effect size, as has been found with obesity and type 2 diabetes (79,80,94–96). Polygenic traits are the result of gene variants that represent one end of the bell-shaped normal distribution curve of continuous variation in a population (97). From an evolutionary perspective, women with PCOS may represent the “metabolic elite” end of the normal distribution curve, being able to efficiently store energy in periods of food abundance and down-regulate fertility in times of food scarcity, or even in anticipation of reduced seasonal food availability as a predictive adaptive response (16,17,60).

The realisation that PCOS is a quantitative trait (phenotype determined by multiple genes and environmental factors) has far-reaching implications for the diagnosis, treatment and prevention of symptoms and pathology associated with PCOS. The implications require a shift in thinking about PCOS as a “disease” to a variation of normal metabolic and reproductive function. This shift invites a change in vocabulary from talking about “disorder” and “risk” to talking about “expression” and “variability” (97). This new understanding supports and reinforces an evolutionary model of the pathogenesis of PCOS. In keeping with this model, multiple lines of evidence suggest that inherited PCOS gene variants are developmentally programmed in a way that primes them for activation by nutritional and environmental factors in postnatal life (41,42,98).

3.3. Developmental epigenetic programming

The developmental programming of PCOS represents changes in gene expression that occur during critical periods of fetal development (99). Following fertilisation, most

parental epigenetic programming is erased and dramatic epigenomic reprogramming occurs (100). This results in transformation of the parental epigenome to the zygote epigenome and determines personalised gene function. Compelling evidence shows that a wide range of maternal, nutritional and environmental factors can effect fetal development during these critical periods of programming (44,98,99,101,102). These include hormones, vitamins, diet-derived metabolites and environmental chemicals (48,98,103,104). In addition, epigenetic reprogramming of germ-line cells can lead to transgenerational inheritance resulting in phenotypic variation or pathology in the absence of continued direct exposure (98).

Experimental studies in primates, sheep, rats and mice show that PCOS-like syndromes can be induced by a range of treatments including androgens, anti-Mullerian hormone and letrozole (19,44,46). Nevertheless, there is significant debate regarding when an animal model qualifies as PCOS-like (105). The model used and the method of induction of PCOS phenotypes therefore needs to be carefully scrutinised when generalising findings from animal research to women with PCOS. The vast majority of animal and human research on the developmental origins of PCOS has focussed on the role of prenatal androgen exposure. This has been extensively reviewed in numerous previous publications (41,46). This research has resulted in a proposed “two hit” hypothesis for the development of PCOS phenotypes (43,45). The “first hit” involves developmental programming of inherited susceptibility genes and the “second hit” arises due to lifestyle and environmental influences in childhood, adolescence and adulthood (41,106).

If PCOS is a quantitative trait involving normal gene variants, as suggested by the evolutionary considerations and findings from genetic research, then the “first hit” may result from normal developmental programming events as occurs with other gene variants (102). According to this hypothesis, the polygenic susceptibility genes would be normally “activated” and “primed” to respond to future maternal and environmental conditions and exposures, as would be the case with many other normal genes (28). In addition, the susceptibility alleles may be “activated” or “functionally enhanced” by a range of maternal and environmental factors, as is usually presumed to be the case in PCOS (5,14,102). This developmental plasticity would provide a mechanism for a predictive adaptive response, based on inputs from the maternal environment that could be used to programme metabolic and reproductive survival pathways, to better prepare the offspring for the future world in which they may be expected to live (107).

Parental lifestyle factors including diet, obesity, smoking and endocrine disrupting chemicals, have all been shown to modulate disease risk later in life (104,108,109). The original description of the fetal origin’s hypothesis proposed that poor maternal nutrition would increase fetal susceptibility to the effects of a Western-style diet later in life (49). Subsequent studies have confirmed that maternal exposure to either nutrient excess or deficit, can have long-term consequences for the health of the progeny (104). Evidence from human and animal studies suggests that maternal obesity programs the offspring for increased risk of developing obesity, hyperglycaemia, diabetes, hypertension and metabolic syndrome (108).

The developmental origins of PCOS may have been due to different factors in ancestral and modern populations (17,60). It has been hypothesised that environmental stress, infection, nutrient deprivation, fetal growth restriction and stress hormone responses may have resulted in maternally-mediated modulation of gene expression in ancestral offspring (17,110). Some of these factors have been investigated and confirmed in modern populations subject to starvation and extreme environmental conditions (111). In contrast, altered fetal programming in modern societies may be secondary to maternal overnutrition, sedentary behaviour, obesity, emotional stress, circadian rhythm disruption, poor gut health or environmental chemical exposure (35,101,112,113). The preconception and pregnancy periods therefore provide a unique opportunity for lifestyle interventions that promote optimal future health for both the mother and the offspring (figure 2).

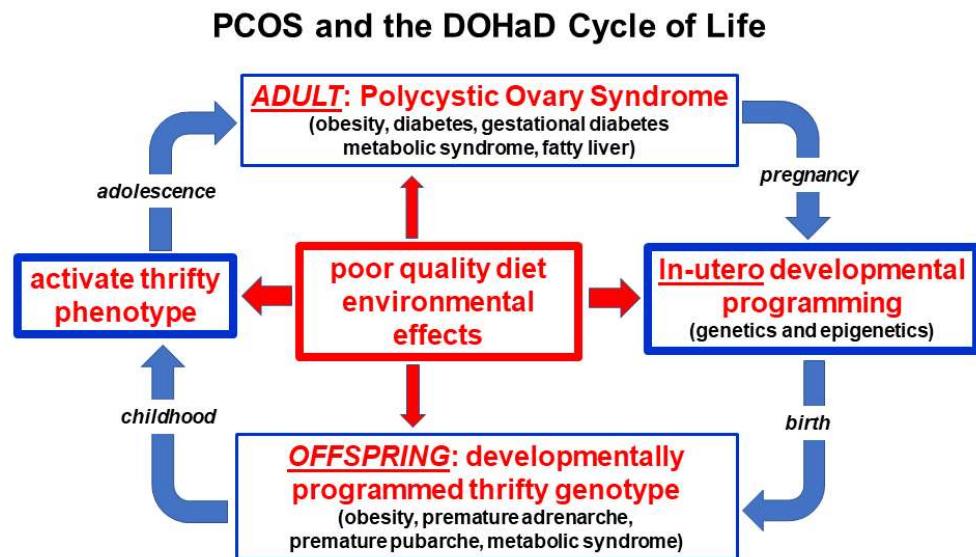


Figure 2. Nutritional and environmental influences throughout the life course and the perpetuation of the transgenerational inheritance of polycystic ovary syndrome

3.4. Microbiome and Dysbiosis

The gastrointestinal microbiome is now appreciated to play a central role in human health and disease (114,115). The microbiome is known to co-regulate many physiological functions involving the immune, neuroendocrine and metabolic systems via complex reciprocal feedback mechanisms that operate between the microbial ecosystem and the host (116,117). Evidence from studies in Western populations, Hunter-gatherer societies and phylogenetic studies in other species, have attempted to place the human microbiome into an evolutionary context (118). Although microbes clearly impact host physiology and have changed along branches of the evolutionary tree, there is ongoing debate regarding whether the microbiome can evolve according to the usual evolutionary forces (119,120). Nevertheless, it has been argued that focusing on functional pathways and metabolic roles of microbial communities, rather than on specific microbes, provides a better model for

understanding evolutionary fitness (118). The co-evolution of the microbiome and human physiology may therefore be important in understanding the differences between ancient adaptive physiological survival mechanisms and modern lifestyle-related pathological responses, in women with PCOS (figure 1).

Twin studies and GWAS show that host genetics can influence the microbiome composition, and microbes can exert effects on the host genome, although the environment has an important role (121,122). Humans are constantly adapting to the gut microbiome to try to determine which microorganisms are beneficial or harmful. Immune genes involved in this process are the most rapidly evolving protein-encoding genes in the mammalian genome (123,124). Diversification of microbes allows humans to access dietary niches and nutritional components they otherwise wouldn't be able to access, which may be beneficial and ultimately lead to the integration of specific microbes into the ecosystem (125). Although no living population today carries an ancestral microbiome, comparison studies of non-Western and Western populations show significant differences in the relative abundances of common phyla and a much greater species diversity in non-Western populations (126,127). A review of non-human primate and human gut microbiome datasets, revealed a changing microbiome in response to host habitat, season and diet, although there appear to be common species-specific symbiotic communities (118).

Rapid human cultural changes have resulted in significant dietary modifications in urban-industrialised communities and shifted the microbiome at an unprecedented rate. The result has been the development of a mismatch between human metabolic genes and bacteria that enhance fat storage (128). In our evolutionary past, when nutrients were scarce, it has been theorized that host selection led to the maintenance of microbes that enhance nutrient uptake or host energy storage. However, in the modern environment where a high fat, high sugar, low fibre diet has become common and easily accessible, integration of these microbes leads to maladaptive physiological responses (40). For metabolically thrifty individuals with PCOS, harbouring microbes that enhance energy storage escalates the evolutionary conflict, furthering the development of insulin resistance and thereby progression to obesity and type 2 diabetes (12,129). Further compounding this maladaptive response is the loss of microbes that are required to access other dietary niches. One example is the loss of symbiotic species of *Treponema* in individuals living in urban-industrialised communities (130). A change from the ancestral hunter-gatherer diet, where foods consumed changed seasonally and a wide variety of food components were eaten, to a diet that is similar across seasons and significantly less varied, is another likely contributor to reduced diversity of the microbiomes of individuals living in urbanised-industrialised communities (131).

The majority of women with PCOS are overweight or obese and evidence indicates that the microbiome of obese individuals is capable of extracting more energy from the host diet compared with the microbiome of lean individuals (132). This is thought to be driven by an expansion in pro-inflammatory species of bacteria, such as *E. coli*, and a depletion of anti-inflammatory bacteria such as *Faecalibacterium prausnitzii* (133,134).

Chronic low-grade ‘metabolic’ inflammation, or meta-inflammation, is a result of an imbalanced gut microbiome that promotes the development of insulin resistance and type 2 diabetes (135–137).

The dysbiosis of gut microbiota theory of PCOS, proposed by Tremellen in 2012, accounts for the development of all of the components of PCOS (multiple ovarian follicles, anovulation or menstrual irregularity and hyperandrogenism) (40). The theory proposes that a poor-quality diet and resulting imbalanced microbiome, induces intestinal permeability and endotoxaemia, exacerbating hyperinsulinaemia. Increased insulin levels promotes higher androgen production by the ovaries and disrupts normal follicle development. Metabolic, endocrine and environmental factors associated with PCOS are not mutually exclusive, and therefore their relative contributions to dysbiosis in PCOS remains uncertain (138). Consuming a balanced diet that is low in fat and high in fibre, can also restore balance to the ecosystem (termed eubiosis) (50). A recent study showed that dietary intake of fibre and vitamin D was significantly decreased in both lean and obese women with PCOS, compared to healthy controls, and correlated with lower diversity of the gut microbiome (139). Dysbiosis is reversible with improvement in diet quality augmented by the addition of probiotics or synbiotics (51,56–58).

Dysbiosis is a consistent finding when looking at the microbiome of women with PCOS (140–143). Although most studies are small, dysbiosis has consistently been found to correlate with different physiological parameters, such as obesity, sex hormones and metabolic defects (140,141,143). Similar to microbiomes associated with obesity, the microbiomes of individuals with PCOS have generally been found to have lower alpha diversity (lower numbers of bacterial taxa) than controls, and most studies describe an altered composition of taxa relative to controls (140,143). However, the bacterial taxa observed to be either increased, depleted or absent in PCOS differs from study to study. This is likely due to both the immense inter-individual variation in microbiotas, as well the fact that PCOS is a quantitative trait with women having various degrees and levels of obesity and sex hormones.

In keeping with the developmental origins hypothesis previously discussed, maternal androgens may alter the composition and function of the microbiome, thereby facilitating the pathogenesis of PCOS (140). One study showed that beta diversity, which is used to measure differences between groups, was negatively correlated with hyperandrogenism, suggesting that androgens play a significant role in dysbiosis (140). The ‘first hit’ in utero may therefore combine with vertical transmission of a dysbiotic microbiome from a mother with PCOS, resulting in dysbiosis in the offspring. Preconception and pregnancy provide a unique opportunities for lifestyle and dietary interventions aimed at restoring eubiosis, to enable the transference of a balanced ecosystem to the offspring, via vertical transmission (118).

The accumulating scientific evidence strongly supports the significant role played by the microbiome in the pathogenesis and maintenance of PCOS, consistent with research in other related metabolic conditions. Dysbiosis is a significant factor in the pathogenesis of PCOS and an important component of a unified evolutionary model. Dysbiosis represents

a maladaptive response of the microbiome to modern lifestyle influences and is a modifiable factor in the treatment of women with PCOS.

3.5. *Insulin Resistance*

There are a number of dilemmas when assessing the role of IR in women with PCOS. There is no consensus on the definition of IR (144,145), measurement is difficult (146,147), whole-body IR is usually measured although it is recognized that IR can be selective being either tissue-specific or pathway-specific within cells (148–150), normal values are categorical and determined by arbitrary cut-offs (4.45 mg/kg/min) (144), testing is not recommended in clinical practice (38), reported prevalence rates in obese and lean women vary widely (146,151), and the significance of IR as a pathognomonic component of PCOS is an area of debate (152–154).

Despite these limitations, it is hypothesised that IR is a significant proximate cause of PCOS and is intrinsic to the underlying pathophysiology (44,155). In addition, it is recognized that IR plays a major role in the pathophysiology of all of the metabolic diseases, cardiovascular disease, some neurodegenerative diseases, and selected cancers (22,156). Insulin resistance is therefore considered to be the main driver for many diseases and makes a significant contribution to the chronic disease epidemic (157). Nevertheless, being able to vary the sensitivity and physiological action of insulin is thought to have conferred a significant adaptive survival role in many animals throughout evolutionary history (145,158). It has been proposed that IR may have evolved as a switch in reproductive and metabolic strategies, since the development of IR can result in anovulation and reduced fertility, in addition to differential energy repartitioning to specific tissues (158).

Insulin receptors are located on the cell membranes of most tissues in the body (159). Ligand binding to the alpha-subunit induces autophosphorylation of specific tyrosine residues on the cytoplasmic side of the membrane (159,160). The activated insulin receptor initiates signal transduction via the phosphatidylinositol-3 kinase (PI-3K) metabolic pathway and the mitogen-activated protein kinase pathway (MAPK) which is involved in cell growth and proliferation (160). Insulin is an anabolic hormone that facilitates glucose removal from the blood, enhances fat storage and inhibits lipolysis in adipose tissue, stimulates glycogen synthesis in muscle and liver and inhibits hepatic glucose output (160). IR can be defined as a state where higher circulating insulin levels are necessary to achieve an integrated glucose-lowering response (145). IR results from alterations to cellular membrane insulin-receptor function or intracellular signaling, enzyme, metabolic or gene function (145,159,160).

Insulin resistance can be caused by a wide variety of mechanisms that have the ability to disrupt any part of this metabolic signaling system (53,160). These include autoantibodies, receptor agonists and antagonists, hormones, inflammatory cytokines, oxidative stress, nutrient sensors and metabolic intermediates (159–162). Physiological regulation of insulin function can be viewed as an adaptive mechanism to regulate the metabolic pathway of insulin signaling (PI-3K), in response to changing environmental conditions (starvation, fear, stress) (163,164) or during normal alterations of internal states (pregnancy, lactation, adolescence) (65,145,151).

The physiological activation of IR allows the organism to switch from an anabolic energy storage state to a catabolic or energy mobilizing state. This allows free fatty acids to be mobilized from adipose tissue, which are then converted to glucose in the liver and released into the circulation (160). As a result of this metabolic change, blood sugar levels are maintained for vital metabolic processes and brain function (14). This adaptive protective mechanism can be pathway specific during periods of growth, such as pregnancy, lactation and adolescence, so that only the metabolic signaling (PI-3K) is inhibited and not the mitogenic pathway (MAPK), which may even be upregulated (30,65,159).

When the physiology of insulin function is considered as a quantitative or continuous variable from an evolutionary perspective, it is likely that all women with PCOS, whether obese or lean, have reduced insulin sensitivity (151,154,165). A systematic review and meta-analysis of euglycemic-hyperinsulinaemic clamp studies found that women with PCOS have a 27% reduction in insulin sensitivity compared to body mass index (BMI) and age-matched controls (154). In evolutionary terms, women with a PCOS metabolic phenotype would have increased survival chances during times of environmental or physiological demand for altered energy metabolism, but be more vulnerable to the pathological effects of IR when exposed to modern lifestyle factors (14,17,158). In particular, a poor-quality, high glycaemic, high fat, low fibre diet has been shown to cause IR (40,166). As discussed in the dysbiosis section, diet-related changes in the gastrointestinal microbiome have also been shown to cause IR in women with PCOS (53,55). Numerous studies have shown that dietary modification (167–169), or treatment with probiotics or synbiotics, has the potential to restore normal insulin function (57,170).

Consumption of a high glycaemic load diet results in rapid increases in blood sugar levels that cause compensatory hyperinsulinaemia (166,171). Excessive dietary intake of glucose and fructose are converted to fatty acids by de novo lipogenesis in the liver, transported to adipocytes via lipoproteins, released as fatty acids to adipocytes and stored in fat globules as triglycerides (160). As a result of nutrient overload, diacylglycerol, the penultimate molecule in the synthesis of triglyceride, accumulates in the cytoplasm and binds with the threonine amino acid in the 1160 position of the insulin receptor. This inhibits autophosphorylation and down-regulates the metabolic PI-3K pathway and causes IR (160). This process has the potential to be reversible following changes in diet quantity and quality, as has been shown to occur with calorie restriction, fasting, time-restricted eating, gastric bypass surgery, low saturated fat and low glycaemic diets (167,169,172). Diets high in animal protein or saturated fat can also cause IR independent of BMI (173,174). These mechanisms provide the rationale for the principal recommendation of the International Guidelines, that women with PCOS should be advised about dietary modification as the first-line of management in all symptom presentations (38).

3.6. Obesity and the lean PCOS paradox

Insight can be obtained into the role of obesity in women with PCOS by examining the evolutionary history, genetic studies and pathological disorders of adipose tissue

(150,175,176). The ability to store energy is a basic function of life beginning with unicellular organisms (175). In multicellular organisms, from yeast to humans, the largest source of stored energy is as triglycerides in lipid droplets in order to provide energy during periods when energy demands exceed caloric intake (175). Understanding the biological functions of adipose tissue has progressed from energy storage and thermal insulation to that of a complex endocrine organ with immune and inflammatory effects and important reproductive and metabolic implications (175,177).

Adipose tissue is organized into brown adipose tissue (BAT) and white adipose tissue (WAT), both with different functions (177). While the evolutionary origins of BAT and WAT are the subject of ongoing debate (175), BAT is located in the supraclavicular and thoracic prevertebral areas and is primarily involved in cold thermogenesis and regulation of basal metabolic rate (178). WAT is distributed in multiple anatomical areas such as visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) and functions as a fat storage depot and an endocrine organ (177,178). An additional layer of SAT is thought to have evolved as insulation against cool night temperatures in the Pleistocene open Savanah (179). The lower body distribution of SAT in women is hypothesised to have evolved to provide additional calorie storage for pregnancy and lactation and is unique to human females (14). Lower body SAT has a metabolic programme that makes it less readily available for every-day energy needs, but it can be mobilized during pregnancy and lactation (14). In addition, excess accumulation of SAT is much less likely to cause IR and metabolic dysfunction and explains why IR is not observed in all obese individuals (150,180). Visceral WAT is associated with IR in women with PCOS leading to both metabolic and reproductive problems (181).

Multiple lines of evidence from evolutionary history, genetic and twin studies, support a genetic basis for obesity and differences in obese and lean phenotypes in women with PCOS (182–185). The majority of women with PCOS are overweight or obese, with reports ranging from 38–88% (151,185). Studies comparing obese and lean women with PCOS have a number of methodological problems including small sample size, overlap of PCOS characteristics with normal pubertal changes, non-standardized diagnostic criteria, and limited generalizability to the entire population due to a focus on a specific ethnic group (165,181). In addition, most of the studies examining body composition in PCOS have relied on anthropomorphic measurements (BMI, waist circumference, waist-to-hip ratio) which are considered inaccurate compared with the current gold-standard of magnetic resonance imaging (181). Consequently, there is wide heterogeneity in reports examining the relationship between body composition measures, including extent of VAT and metabolic changes such as IR (185).

In humans, there is large individual variation in the fat storage capability and expandability of different adipose tissue depots (150). It has been hypothesised that once the genetically determined limit of expandability of SAT is reached, there is expansion of VAT and excess lipid accumulation in muscle, liver and other organs, resulting in IR, inflammation and metabolic dysregulation (150). We hypothesize that lean women with PCOS have a genetically determined limited ability to store excess lipid in SAT, but

develop increased lipid deposition in VAT and organs such as the liver, resulting in metabolic dysregulation and IR in a similar manner to what occurs in obese women with PCOS. The wide variation in the genetic limitation of SAT expansion is also supported by studies in individuals with lipodystrophy.

Lipodystrophies are a heterogenous group of rare inherited and acquired disorders characterized by a selective loss of adipose tissue (176,186). They are classified on the basis of the extent of fat loss as generalized, partial or localized (186). Patients with congenital generalised lipodystrophy have a generalized deficiency of fat from birth, usually have severe IR and develop diabetes at puberty. As a consequence of genetically limited ability for SCT lipid storage, lipids can only be stored ectopically in non-adipocytes resulting in major health consequences including IR, fatty liver, diabetes and PCOS (187). In contrast to generalised lipodystrophy, patients with familial partial lipodystrophy have normal fat distribution at birth but loose SAT in the limbs, buttocks and hips, at puberty. Fifty percent of women develop diabetes and 20-35% develop irregular periods and polycystic ovaries (176) . Despite the rare nature of these syndromes much has been learned about the underlying genetic variants involved (186).

Elucidation of clinical subtypes and the genetic background of patients with lipodystrophies may pave the way to new insights into the role of fat partitioning and obesity, and has implications for understanding the pathogenesis of insulin resistance, diabetes and PCOS (176). Lean women with PCOS may have a genetic predisposition for limited SCT fat storage, coupled with underlying metabolic predispositions, that result in deposition of excess lipid in VAT and liver and the observed metabolic features of IR, fatty liver and diabetes. If the extent of IR and ectopic fat deposition is excessive, the resulting hormonal changes may be sufficient to cause oligomenorrhoea and sub-fertility as occurs with secondary familial partial lipodystrophy type 2 (187,188). If this underlying mechanism is confirmed in future studies, the main difference between women with lean or obese PCOS may be the combined effects of metabolic programming and the genetically-determined extent of SCT fat deposition. This would explain why lean women have all the same clinical, biochemical and endocrine features, although possibly less severe, than overweight and obese women with PCOS (185).

3.7. Environmental chemical exposure

Anthropomorphic chemical exposure is ubiquitous in the environment and has possible effects on many aspects related to women's health (36,189–191). Historically, many environmental chemicals have resulted in large-scale health disasters in human populations including diethylstilbestrol (DES), dichlorodiphenyltrichloroethane (DDT), asbestos, lead, mercury and nicotine (191). There over 191 million organic and inorganic chemicals registered on the Chemical Abstract Service Registry (192). Detailed analysis of risks is extremely limited and regulation relies on animal toxicology, in-vitro assays, and epidemiological studies that retrospectively examine adverse effects after population exposure (193,194). More recently, toxogenetic testing of chemical-gene interactions have been employed to identify molecular pathways involved in causing toxicity (193). These

studies have concluded that the majority of endocrine and metabolic pathways are sensitive to the effects of environmental chemicals (193).

The identification of more than 1000 EDC in food, air, water, pesticides, plastics, personal care products, and other consumer goods, raises specific concerns for pregnant women and women with increased susceptibility to metabolic diseases like PCOS (36,171,191,195,196). Endocrine disrupting chemicals may be involved in the pathogenesis of PCOS given their known and potential hormonal and metabolic effects (36,189,197). This includes many of the areas that have been considered in the unified evolutionary model, such as developmental epigenetic programming, microbiome composition and function, metabolic processes such IR, and regulation of body weight.

3.7.1. EDC and DOHaD

Many observational studies have demonstrated the presence of EDC in maternal and fetal serum and urine, amniotic fluid, cord blood and breast milk (198–200). Six classes of EDC have been shown to cross the placenta confirming that the fetus is exposed at all stages of development (109,198). Although it is impossible to perform experimental studies in humans, evidence from epidemiological, molecular toxicology and animal studies provide compelling evidence of adverse developmental effects and transgenerational toxicity (171,189,191,201,202). The realisation of the tragic effects of DES in the 1970's was first example of an in-utero exposure causing serious transgenerational health effects (191). This was followed by increasing interest in identifying the properties of environmental oestrogens (36).

Several oestrogenic EDC have been associated with birth outcomes that are thought to be associated with the development of PCOS (189). These include decreased birthweight (perfluoroalkyl substances [PFAS], perfluorooctanoic acid) and preterm birth (di-2-ethylhexyl phthalate) (201). Prenatal exposure to androgenic EDC (triclosan, glyphosate, tributyltin, nicotine) is of increasing concern, given the suspected epigenetic role of in-utero androgen exposure in the pathogenesis of PCOS (48,203,204). EDC can act at any stage of the human lifespan, including preconception and prenatally, and are increasingly becoming a priority in PCOS research (205).

3.7.2. EDC and the microbiome

As discussed above, the microbiome is increasingly considered to make a significant contribution to many human diseases, including PCOS (40,206). EDC that disrupts the composition or function of the microbiome have been termed "microbiota disrupting chemicals" (207). In turn, any disruption of the microbiome from EDC can impact crucial metabolic and endocrine physiology and homeostasis (36,208). A number of studies have reviewed the effect of EDC in invertebrate and vertebrate species, animal models and humans. These studies have found that BPA, phthalates, artificial sweeteners, heavy metals, fungicides, pesticides and microplastics can all affect the gut microbiome, and have metabolic and obesogenic effects (202,209,210). They have concluded that EDC exert their effects in a variety of species via a range of mechanisms, including modification of

epigenetic, cell signalling and metabolomic pathways, in addition to their effects on the microbiome.

Human exposure to the herbicide glyphosate, through diet and drinking water, has also been reported to alter gut microbial communities (211). Glyphosate-mediated inhibition of 5-enolpyruvylshikimate-3-phosphate synthase in intestinal microbiota has been shown to alter composition and enrich potentially pathogenic bacteria (212–214). In addition, microbiota exposure to glyphosate has been shown to alter mucosal-associated T-cells and promote a pro-inflammatory immune response (211). Taken together, EDC have been found to alter microbial composition and diversity (207,213), disrupt gastrointestinal barrier integrity (202,215), increase systemic endotoxin levels and inflammatory cytokines (216,217), alter the production of metabolites and influence metabolomic patterns (210), all of which have been proposed to be involved in the pathogenesis of PCOS (40).

3.7.3. EDC, insulin resistance and diabetes

Kahn et al reviewed six cohort studies and 2 case-control studies that raise concerns about exposure to PFAS in pregnancy and increased risk of impaired glucose tolerance and gestational diabetes in different ethnic groups (189). They also identified 4 studies showing similar increased risk with phthalate exposure during pregnancy, and one study that did not identify an association with gestational diabetes. Animal studies have found that some EDC target alpha and beta cells in the pancreas, adipose cells and hepatocytes, and contribute to insulin resistance (218). As a result of these and many other concerning studies the Endocrine Society issued a scientific statement cautioning that emerging evidence ties EDC exposure to two of the biggest public health threats facing society, diabetes and obesity (219,220).

3.7.4. EDC and obesity

A large number of EDC are now classified as “obesogens” due to their suspected role in promoting weight-gain and contributing to the global rise in obesity (202,203,221). So far, about 50 obesogens have been recognized including tributyltin, parabins, DDT, cadmium, persistent organic pollutants and many others (202,222,223). Three of the most studied compounds are BPA, phthalates and PFAS (200,201,221). Evidence from multiple birth cohort studies have shown an association between prenatal exposure to PFAS and childhood obesity (200,201). A number of reports have suggested that exposure to PFAS and phthalates also contribute to weight gain in adults (224). Two trials have identified an association between weight gain (Diabetes Prevention Trial Program Lifestyle Trial) (225) and reduced resting metabolic rate (the POUNDS Lost trial) (226), with serum PFAS concentrations. In recognition of the suspected significant risk, the International Federation of Obstetrics and Gynecology (FIGO) recommended a full global phase out of PFAS (227).

3.7.5. EDC and PCOS

A large number of cross-sectional studies have identified associations between EDC and PCOS, including PFAS, phthalates, bisphenol-A, triclosan and nicotine (196,208,228,229). Experimental animal studies have shown that exposure to androgenic EDC in pregnancy can result in significantly increased androgen levels in female offspring (36,48). Other androgenic EDC have been found to alter surrogate markers of developmental programming, such as anogenital distance (224). Although there are no specific toxicogenetic studies in women with PCOS, many EDC have been found to activate signalling pathways thought to be involved in the pathogenesis of PCOS (193,208). Taken together, the available evidence suggests EDC are likely to have a role in the pathogenesis of PCOS.

3.7.6. EDC recommendations

There is a significant global imperative to implement a multifaceted global programme to address the effects of EDC on human health using a hazard-based approach in preference to the current risk-based regulatory framework (230). As a result, implementation of the precautionary principle is a high priority in counselling women with PCOS (231). International professional bodies (The Royal College of Obstetricians and Gynaecologists, Endocrine Society, FIGO) have recommended that all pregnant women should be advised of the possible risks of EDC and that education programmes be developed to inform health professionals (220,232,233). An explanation of the pathogenesis of PCOS (discussed below), should include reference to environmental chemical exposure and open the way for more detailed discussion of specific personalised advice and lifestyle recommendations.

3.8. *Lifestyle Contributors to the Pathogenesis of PCOS*

It has been recognized that a variety of lifestyle factors contribute to the pathogenesis of PCOS for many decades (234,235). As a result, a number of lifestyle factors have been investigated for their role in the pathogenesis of PCOS. These include diet, exercise, stress, sleep disturbance and exposure to environmental chemicals (28,41,236). A large number of animal studies have provided experimental evidence supporting a causative role for many of these factors either individually, or in combination (44). Human research investigating causation is limited to observational and epidemiological studies, as many experimental protocols would be unethical. As a result, proving causation in humans will be extremely difficult. In addition, proving causation in evolutionary models also has a number of significant challenges (8,9,60). Nevertheless, developing a unified evolutionary model based on the large number of available human and animal studies may provide a useful evidenced-based framework for counselling women and informing future research.

Despite the limitations in proving causation, recent advances in genomics, epigenetics, metabolomics, nutrigenomics, evolutionary biology, computer technology and artificial intelligence, are providing many insights into the mechanisms of how lifestyle factors impact the pathogenesis of PCOS (9,90,235,237). We have attempted to integrate the research findings supporting an evolutionary model into the respective sections outlined

in this paper. It has not been our aim to comprehensively review all aspects of the role of lifestyle in the pathogenesis of PCOS. We have tried to highlight the evolutionary aspects of how diet in particular, may impact the pathogenesis of PCOS, as components of the human diet have effects on many areas of the proposed unified evolutionary model. A large body of evidence from studies in women with PCOS, and a range of other metabolic diseases, supports the view that a Western-style high glycaemic, high saturated fat, high calorie, low nutrient-dense, and low fibre diet that contains a high proportion of processed rather than whole food, contributes to the pathogenesis of PCOS (28,40,235). This is likely to be exacerbated by the additional adverse effects of multiple other lifestyle factors such as EDC, stress, circadian disruption and reduced physical activity.

The dysbiosis theory of the pathogenesis of PCOS highlights the role of a poor-quality diet in the pathogenesis of PCOS and is supported by over 30 proof-of-concept studies (40,238). International Guidelines for the assessment and management of PCOS recommend lifestyle management, with diet and exercise as first-line treatment for all women with PCOS, and provide a comprehensive review of the literature (7). Nutritional studies based on diet indices, diet composition and metabolomics have identified dietary components that contribute to a healthy eating pattern (51,237,239,240). Healthy diet patterns, or wholefood diets, have been found to be effective in controlling and reversing many of the symptoms and metabolic alterations associated with PCOS, and have also previously been reviewed (50). Two components of a healthy wholefood diet that appear to be important from an evolutionary perspective, in addition to the requirement for fundamental macronutrients (protein, fat and carbohydrate) and essential micronutrients (vitamins and minerals), are dietary fibre and polyphenols.

Throughout evolutionary history, humans have obtained nutrients from a wide variety of plant and animal food sources (241). These foods provided macronutrients, micronutrients and contingent nutrient factors that contain a range of bioactive components. Contingent nutrients include a variety of compounds that are not essential but may be beneficial to human health (242). Polyphenols are an important contingent nutrient, and comprise a large collection of plant-derived secondary metabolites that have been found to have beneficial biological and metabolic effects when consumed (243). Dietary polyphenols improve microbiota diversity and undergo extensive biotransformation by a variety of microbial species (244). It is estimated that less than 5% of ingested polyphenols reach the circulation intact (245). A large number of microbially-derived polyphenol metabolites can be detected in plasma compared with low levels of the parent compounds (246). Polyphenols have potent anti-inflammatory and antioxidant effects and are the most abundant antioxidant in the human diet (246). Not surprisingly, there has been significant interest in investigating the possible beneficial effects of polyphenols in PCOS, since the pathophysiology involves oxidative stress, chronic inflammation and alterations in the microbiome (247–250).

Polyphenol-rich foods have historically made up a considerable proportion of the dietary intake in many Hunter-gatherer societies and post-agricultural communities, and until recently, in Western nations (251–253). Polyphenols are present in fruits, vegetables,

legumes, nuts, and whole grains, as well as plant-derived foods and drinks like green tea, red wine, and chocolate (50). Women with PCOS have been noted to consume diets lower in polyphenol-containing foods (236). Consumption of polyphenols and polyphenol-rich foods and drinks have been found to improve a number of important outcome measures in women with PCOS, such as body weight, metabolic abnormalities, and serum androgen levels (50). Some polyphenols can act as selective oestrogen receptor modulators and may provide unique benefits to women with PCOS due to estrogen-related effects (254). Polyphenols are therefore an important part of a healthy diet and have been investigated for their potential role in the pathogenesis of PCOS (50). A healthy wholefood diet contains a wide variety of polyphenols coupled with the necessary dietary fibre required for optimal microbiome and metabolic function.

As previously discussed, the modern Western diet and lifestyle is at odds with our evolutionary background. In general, our traditional hunter-gatherer ancestors consumed significantly more fibre than modern populations. Studies that have investigated the dietary patterns of remaining contemporary Hunter-gatherer societies, have found their dietary fibre intake to be around 80-150 grams per day (255). This contrasts with the contemporary Western diet, where the average fibre intake is 18.2 grams per day in children and 20.7 grams per day in adults (256). Adequate dietary fibre consumption is important as it has a number of benefits, such as improved insulin sensitivity, reduced blood glucose levels, decreased systemic inflammation, lower serum levels of androgens and LPS, all of which have been linked to the pathogenesis of PCOS (257-260).

Recent systematic reviews of observational studies and randomized controlled trials have found dietary fibre consumption to be inversely related to risk of obesity, type 2 diabetes, and cardiovascular disease (261,262). A recent cohort study from Canada found that obese women with PCOS consumed significantly less dietary fibre than normal weight women without PCOS (263). In addition, fibre intake of women with PCOS was negatively correlated with IR, fasting insulin, glucose tolerance and serum androgens (263). Hence, the mismatch between the amount of fibre traditionally consumed and the fibre content of Western diets, may be an important dietary component contributing to the increased rates of PCOS seen in developed and developing nations.

The current low level of fibre consumption in Western nations also contributes to a lack of microbial diversity in the microbiota. The amount and variety of fibre in the diet is one of the main determinants of ecosystem diversity (264). Lack of microbial diversity has been associated with obesity, IR, and systemic inflammation (136,265,266). As previously discussed, low diversity is one of the key microbiota patterns observed in women with PCOS, and has been positively associated with hyperandrogenism, total testosterone levels, and hirsutism in this population (267). Conversely, ecosystem diversity and richness are hallmarks of Hunter-gatherer microbiotas who consume a high-fibre, more diverse plant-based diet (255,268). A shift towards a more wholefood diet therefore provides a variety of phytonutrients, polyphenols and fibre, in addition to the other essential macronutrients and micronutrients, and is likely to make a significant difference to metabolic and symptomatic outcomes in women with PCOS.

Although discussion of specific details related to lifestyle counselling are beyond the scope of this review, it is clear that improving outcomes in PCOS will require a multifaceted population-based approach that includes public health measures (269,270), improved compliance-aiding strategies, inclusion of nutrition training in medical education (271), implementation of current best-practice management strategies, and further development of the International Guidelines for the Assessment and Management of PCOS (7).

3.9. Conceptual framework of the unified evolutionary theory

Comprehensive International Guidelines have made 166 recommendations for the assessment and management of PCOS (38). We believe the current unified evolutionary theory of the pathogenesis of PCOS provides a conceptual framework that may help practitioners and patients understand the development of PCOS symptoms and pathology in the context of our modern lifestyle and environment. It will hopefully contribute to improved communication, result in improved feelings of empowerment over the personal manifestations of PCOS, improve compliance, reduce morbidity, increase quality of life and inform future research (figure 3).

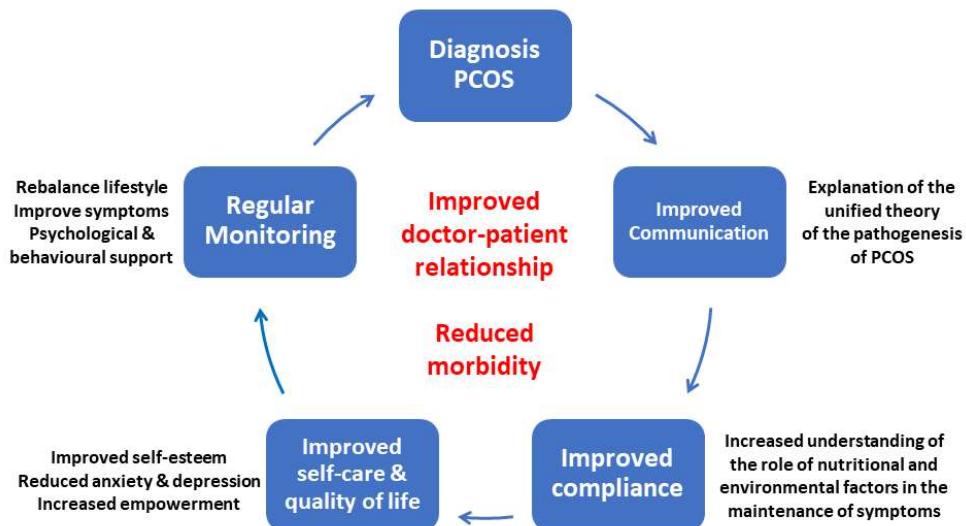


Figure 3. Impact of the unified theory on the management of polycystic ovary syndrome

3.10. Explanation to Women Diagnosed with PCOS

"Polycystic ovary syndrome is a problem that is inherited from both of your parents. The inherited genes are activated by a range of dietary and environmental factors that can cause a number of symptoms. These include weight gain, irregular periods, acne, excess hair growth, hair loss, anxiety and depression. Women with PCOS are also at risk of developing a range of other problems throughout their lifetime if they are not adequately treated. These include gestational diabetes, type 2 diabetes, heart disease and fertility problems. All of these symptoms and problems can be treated, controlled and reversed with appropriate lifestyle changes. These include a healthy

diet, exercise, avoiding environmental chemicals, stress management techniques, sleep and support from friends, family and health professionals. In addition, there are a range of medical and natural treatments that can also be used. Women with PCOS can have healthy, active lives with normal fertility”.

4. Conclusions

Substantial evidence and discussion support an evolutionary basis for the pathogenesis of polycystic ovary syndrome, although many of the mechanistic details are yet to be determined. Nevertheless, multiple lines of evidence from evolutionary theory, comparative biology, genetics, epigenetics, metabolism research, and cell biology, provide supportive evidence and hypothesis-generating data. The ability of animals to synchronize internal physiology, metabolism and reproductive function, with our changing external environment and habitat, are a necessary requirement for individual and species survival. The co-operative and sometimes competitive evolution of metabolism and reproduction provided adaptive survival mechanisms in ancestral environments that appear to be maladaptive in modern environments.

Lifestyle and environmental influences such as food abundance, altered food quality, chemical exposure, circadian disruption, chronic stress and sedentary behaviour, combine to redirect previously beneficial adaptations into adverse symptoms and disease. A unified evolutionary model provides a conceptual framework that considers the role of genetics, developmental programming, the microbiome, dysbiosis, environmental chemical exposure, metabolism, reproduction, and lifestyle factors that are involved in the initiation, treatment and prevention of PCOS. Mechanistic studies of the relative contributions of these and other ultimate and proximate causes are the subject of ongoing research and discussion. An evolutionary model therefore provides a framework to enhance practitioner and patient understanding, improve compliance with lifestyle interventions, reduce morbidity, improve quality of life and will evolve and change over time.

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Review

Polycystic Ovarian Syndrome: Diagnosis and Management

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ABSTRACT

Polycystic ovarian syndrome (PCOS) affects 4% to 12% of women of reproductive age. The lack of well-defined diagnostic criteria makes identification of this common disease confusing to many clinicians. Also, with the varied manifestations of the disorder a patient may present to any one of several providers: an internist, family practitioner, nurse practitioner, pediatrician, gynecologist, dermatologist, or endocrinologist. Furthermore, the most distressing aspect of PCOS for any given patient may change over time, from hirsutism as a teenager to infertility as a young adult—potentially requiring several different providers along the way. It is important, therefore, that those caring for these patients understand not only the management issues pertinent to their specialty, but also appreciate the other potential health risks in these women. Recent insights into the pathophysiology of PCOS have shown insulin resistance to play a substantial role and as such have brought the long-term issues of type 2 diabetes mellitus and its resultant increased risk of coronary artery disease to the forefront. No longer can irregular menses and/or hirsutism be thought of as benign nuisances.

This review will focus on the two most confusing aspects of PCOS for the practicing provider—diagnosis/differential diagnosis and treatment options. Special attention is given to the role of insulin resistance and the potential utility of insulin sensitizers in management. The benefit and utmost importance of lifestyle modification for the long-term health of these women is stressed as well. It is hoped that some clarity in this regard will allow more women to not only be diagnosed and managed properly for their presenting symptoms (hirsutism, irregular menses, etc.), but also to be educated and managed for the continuing health risk of insulin resistance throughout their lives.

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an extremely common disorder affecting 4% to 12% of women of reproductive age.^{1,2} Despite being heterogeneous in nature, the hallmarks of the disease are hyperandrogenism and chronic anovulation. Since its description in 1935 by Stein and Leventhal,³ much has been learned about the pathophysiology of PCOS from its neuroendocrine underpinnings⁴ to an ever-growing understanding of the link between obesity, insulin resistance (IR) and PCOS.⁵ Based on this current understanding of PCOS, it is important that the patient and medical provider approach management not only toward improving the often troublesome hirsutism and infertility but also toward the long-term risks associated with IR. Indeed, the management of the PCOS patient often will vary over time as the patient enters different stages of life with different goals. In contrast, because of the long-term health implications of IR, the importance of lifestyle modification toward weight management and maintaining adequate physical activity should be the one constant in the management of these patients.

Despite the high prevalence of PCOS, the diagnosis and differential diagnosis remains confusing. This is in part due to the lack of a specific diagnostic test for the disorder. Oftentimes the clinical history and a few laboratory tests are enough to make the diagnosis and exclude other entities that may present in much the same way. Once the diagnosis is made, the management options can seem daunting at first. This has become especially true since the link between PCOS and IR has been made (i.e., adding the issue of if/when insulin sensitizers should be used). However, if approached from the standpoint of what the patient and/or medical provider is concerned about at any given time, the options seem more manageable. Generally there are but four issues which arise in the management of PCOS patients: regulation of menses, control of hirsutism, fertility issues, and the management of the IR syndrome and its associated risks (type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease). This review aims to not only clarify the diagnosis of PCOS and the management of its manifestations, but also to stress the importance of taking a life-long approach to the management of the IR syndrome in these often young patients.

CLINICAL FEATURES AND HISTORY

Often the first step in the diagnosis of any disorder lies in the recognition of historical and physical manifestations of the disease process. These clues may be brought to the attention of the medical provider by the patient (i.e., the complaint of hair growth under the chin) or during a routine history and physical examination (i.e., a history of irregular menstrual cycles or the discovery of acanthosis nigricans). No matter how these issues come to light, the crucial next step is to further pursue the findings through a more detailed history and examination targeted at the diagnosis and differential diagnosis. This is extremely important in the evaluation of PCOS because, again, there is not one specific test that makes the diagnosis.

PCOS is most simply defined as the presence of hyperandrogenism (clinically and/or biochemically) and/or chronic anovulation in the absence of specific adrenal and/or pituitary disease.⁶ Table 1 outlines the clinical features of PCOS. Hyperandrogenism may present clinically as hirsutism, acne, and/or male pattern alopecia. Hirsutism can be defined as the growth of coarse hair on a woman in a male pattern (upper lip, chin, chest, upper abdomen, back etc.). This is to be distinguished from hypertrichosis that involves a more uniform, whole body distribution of fine hair. Acne related to hyperandrogenism may be difficult to distinguish from normal pubertal acne in an adolescent with PCOS though pubertal acne in general is twice as prevalent in adolescent males versus females and males are more likely to have severe disease.⁷ Thus, an adolescent female with moderate to severe acne should be investigated for PCOS. Furthermore, the development or persistence of acne into adulthood is unusual and should raise attention. The severity of any of these manifestations is highly variable and may depend on genetic and ethnic differences in the sensitivity to the effects of androgens. The presence of virilization (clitoromegaly, deepening voice, increased musculature, or rapidly progressive hirsutism or alopecia), however, is not a feature of PCOS, but instead of more severe hyperandrogenism. Chronic anovulation often presents as oligomenorrhea, amenorrhea, dysfunctional uterine bleeding, and/or infertility. Interestingly, however, around 20% of patients with PCOS may describe normal menstrual cycles.⁸ Often, but not always, menstrual abnormalities are long-standing, even since menarche. Other women may only develop menstrual problems later in life, perhaps after significant weight gain. Furthermore, primary amenorrhea is possible although not common.

When clinically evaluating a patient for the possibility of PCOS, it is also important to search for signs of IR. Upper-body obesity is a key component of the IR syndrome.⁹ However, obesity is not required for the diagnosis of PCOS with perhaps only 35% to 50% of these patients being obese.^{1,10} Acanthosis nigricans on physical examination is a sign of IR. A personal or family history of type 2 diabetes mellitus or gestational diabetes mellitus, or the presence of hypertension should also be sought in the evaluation. Overall, the criteria for diagnosis of the IR syndrome in women should be evaluated in all patients (table 2).

Table 1. Clinical features of polycystic ovary syndrome.

Oligomenorrhea/amenorrhea

Infertility/first trimester miscarriage

Obesity

Hirsutism

Acne

Acanthosis nigricans

Male pattern alopecia

Sheehan

DIAGNOSIS AND DIFFERENTIAL DIAGNOSES

As noted previously, the diagnosis of PCOS is based on hyperandrogenism or chronic anovulation in the absence of specific pituitary and/or adrenal disease. The differential diagnoses of PCOS are listed in table 3 along with the tests needed to adequately assess for these possibilities. As is apparent, these disorders may cause some, but not all, features of PCOS. For instance, pregnancy, hypothyroidism, and hyperprolactinemia may all cause secondary amenorrhea but do not cause hirsutism; however, they need to be ruled-out.

A careful history and physical examination, looking for other signs of those disorders that may not be a part of PCOS, must be performed. Symptoms of cold intolerance, dry skin, and increased fatigue (among others) may signify hypothyroidism, as would the presence of a goiter. Galactorrhea may or may not be present in women with hyperprolactinemia. Signs of virilization signify more significantly elevated androgen levels than those seen in PCOS (see below) and may indicate an ovarian or adrenal tumor. Patients with Cushing's syndrome may be more apt to have hypertension, purple abdominal striae, prominent dorsal cervical fat pads, and a rounded, plethoric face.

Late-onset congenital adrenal hyperplasia, even though relatively rare, deserves mention as it can mimic PCOS in all regards clinically. Congenital adrenal hyperplasia is due to one of a variety of enzymatic defects in adrenal steroidogenesis (which leads to increased levels of precursor hormones that have androgenic properties). The classic forms of these disorders involve complete enzymatic defects and present in newborn girls as ambiguous genitalia. More recently partial enzymatic defects in these same pathways have been shown to not present until menarche and then with irregular menses and hirsutism mimicking PCOS. Measurement of the hormone preceding the enzymatic block is used to definitively diagnose these disorders. The most common form of late-onset congenital adrenal hyperplasia is due to

Table 2. Diagnostic criteria for the insulin resistance syndrome in women.

Any three or more of the following:

Waist circumference >88 cm

Triglycerides \geq 150 mg/dL^a

HDL-cholesterol <50 mg/dL^b

Blood pressure \geq 130/85

Fasting glucose \geq 110 mg/dL^c

^a To convert triglycerides to mmol/L multiply by 0.0112.

^b To convert HDL-cholesterol to mmol/L multiply by 0.0256.

^c To convert glucose to mmol/L multiply by 0.055.

HDL, high density lipoprotein. Adapted from reference 9.

21-hydroxylase deficiency and, as such, is often the only type tested for in the differential diagnosis of PCOS. The interested reader is referred to the review by Azziz and colleagues for a more complete discussion of these disorders.¹¹

LABORATORY EVALUATION

Biochemical evaluations should look for supporting evidence of PCOS (hyperandrogenism and IR) and rule out the other disorders described above. All of the tests in table 3 (with the exception of the 24-hour urine free cortisol) should be performed in every patient. Tests helpful in evaluating for IR are listed in table 4. It should be noted that direct testing for IR is fraught with difficulties and there are many methods in use.¹² Only the simplest, fasting glucose-to-insulin ratio is mentioned for simplicity. It should be noted that the use of the fasting glucose-to-insulin ratio to measure IR has been studied primarily in obese and lean euglycemic, non-Hispanic white adult women and in obese and lean euglycemic, Hispanic adolescents.¹³⁻¹⁵ It is likely not a valid marker in patients with impaired fasting glucose or impaired glucose tolerance, and assessing for IR in patients who are not euglycemic is likely a moot point. Furthermore, none of the tests for IR are extremely sensitive or specific, and the argument can be made that none are needed. On the contrary, assessment of fasting lipids and glucose may be enough (table 2). Lastly, a 2-hour oral glucose tolerance test may be a better predictor of IR than fasting glucose,¹⁶ and it is extremely useful in categorizing patients' risk of type 2 diabetes mellitus, which may affect therapeutic decisions.

There are a variety of nuances in the interpretation of these laboratory tests that can greatly affect further decision-making:

Table 3. Differential diagnoses and screening tests.

Diagnosis	Laboratory test
Pregnancy	Pregnancy test
Hypothyroidism	TSH
Hyperprolactinemia	Prolactin
Late-onset CAH	17-hydroxyprogesterone ^a
Ovarian tumor	Total testosterone ^b
Hyperthecosis	Total testosterone
Adrenal tumor	DHEA-S ^b
Cushing's syndrome	24-hour urine free cortisol

^a Only assesses for 21-hydroxylase deficiency (most common form of CAH).

^b Degree of elevation helpful.

TSH, thyroid stimulating hormone; CAH, congenital adrenal hyperplasia; DHEA-S, dehydroepiandrosterone-sulfate.

Testosterone

- A total testosterone is likely to be more reliable than a free testosterone given the difficulties seen with many of the assays used for the latter.¹⁷
- Testosterone values may be normal in PCOS.
- Oral contraceptives will lower total testosterone, and interpretation in this setting is difficult (3 months off oral contraceptives is best to get a “true” testosterone value).
- Most testosterone values in PCOS will be ≤ 150 ng/dL (≤ 5.2 nmol/L).
- Testosterone values of ≥ 200 ng/dL (≥ 6.9 nmol/L) warrant consideration of an ovarian or adrenal tumor.¹⁸

Dehydroepiandrosterone-sulfate (DHEA-S)

- DHEA-S values may be normal or slightly elevated in PCOS.
- DHEA-S values ≥ 800 $\mu\text{g}/\text{dL}$ (21.7 $\mu\text{mol}/\text{L}$) warrant consideration of an adrenal tumor.¹⁸

Prolactin

- Mild hyperprolactinemia has been reported in 5% to 30% of patients with PCOS.^{19,20} Prolactin is generally only 50% above the upper limit of normal.²¹ Furthermore, hyperprolactinemia is most often transient, with perhaps only 3% to 7% of hyperprolactinemic PCOS patients having persistently elevated prolactin levels.²² Thus, it is now felt that PCOS and hyperprolactinemia are independent disorders. If normalization on re-sampling does not occur, then an assessment for other causes should be undertaken (including pituitary magnetic resonance imaging).
- Patients with prolactinomas may have polycystic ovaries on ultrasound.²³

17-hydroxyprogesterone

- A morning, fasting, unstimulated level of <200 ng/dL (<6 nmol/L) in the follicular phase reliably excludes late-onset 21-hydroxylase deficiency.
- Further evaluation of levels ≥ 200 ng/dL involves adrenocorticotrophic hormone (ACTH)-stimulation with an intravenous 250 μg dose and a 30 minute value (stimulated values $\geq 1,000$ ng/dL (≥ 30 nmol/L) confirm the diagnosis).¹¹
- Oral contraceptives and glucocorticoids can affect values.

24-hour urine free cortisol

- Mild elevations can be seen in PCOS with values ≥ 2 times the upper limit of normal more consistent with Cushing's syndrome.
- For mild elevations a dexamethasone-suppression, corticotropin-releasing hormone stimulation test is needed to distinguish mild Cushing's syndrome from pseudo-Cushing's.²⁴
- Interpretation of serum (but not urine) cortisol levels in patients on oral contraceptives is problematic as cortisol-binding globulin may be increased falsely elevating the values (it is especially important that oral contraceptives be discontinued before dynamic testing is performed).

Luteinizing hormone/follicle stimulating hormone (LH/FSH) ratio

- A ratio ≥ 2.0 is suggestive of PCOS but is not highly sensitive or specific.
- Gonadotropin levels are affected by oral contraceptives.

Pelvic ultrasonography may be very helpful in the evaluation as well, but polycystic ovaries are not specific for PCOS with over 20% of “normal” women having this finding.²⁵ The number of follicles and ovary volume are both important in the ultrasound evaluation. The criteria for PCOS put forth by Adams et al. are the most often cited: the presence of ≥ 10 cysts measuring 2-8 mm around a dense core of stroma or scattered within an increased amount of stroma.²⁶ A recent proposal to modify these criteria has been put forth by Jonard et al.: “increased ovarian area ($>5.5\text{cm}^2$) or volume (>11 mL) and/or presence of ≥ 12 follicles measuring 2 to 9 mm in diameter (mean of both ovaries).”²⁷ These criteria had a specificity of 99% and a sensitivity of 75% for the diagnosis of PCOS.

The approach to laboratory and ultrasound evaluations in the diagnosis of PCOS varies widely without any consensus even among experts in the field. Indeed, the diagnosis of PCOS in Europe does not require any hormonal testing, with great importance placed on the finding of polycystic ovaries on ultrasound.²⁸ This is in stark contrast to the National Institute of Health conference in 1990 which did not include ultrasound evidence of polycystic ovaries in the diagnostic criteria.⁶ What is needed is a simple consensus that is easy to implement for the clinician trying to diagnose this highly prevalent disorder with important health consequences.

Table 4. Laboratory evaluation for insulin resistance/glucose intolerance.

Test	Interpretation
Fasting glucose/insulin ratio	<4.5 in obese, euglycemic, non-Hispanic white adult polycystic ovarian syndrome patients ¹⁴ (<7.0 in adolescents ¹³) consistent with insulin resistance
75 g oral glucose tolerance test	Normal: 2 hour glucose <140 mg/dL Impaired glucose tolerance: 2 hour glucose 140-199 mg/dL Diabetes: 2 hour glucose ≥ 200 mg/dL

Perhaps this 'clinical' consensus should be different than that used in the research setting. An extremely practical proposal has recently been put forth for the diagnosis of PCOS by Homburg.²⁸ In this proposal any one of four classic symptoms of PCOS (menstrual disturbance, hirsutism, acne or anovulatory infertility) should lead to an ultrasound evaluation of the ovaries. If polycystic ovaries are found, the diagnosis is confirmed. If the ovarian morphology is normal, then biochemical testing is undertaken. If any one or more of the following are noted, the diagnosis is confirmed: elevated LH, fasting glucose/insulin <4.5, and/or elevated testosterone or free androgen index (in the absence of late-onset congenital adrenal hyperplasia). The argument could be made, however, that the exclusion of the other conditions listed in table 3 should be a part of such guidelines. That said, proposals such as the one put forward by Homburg are the first steps toward a much needed, simple, and unified set of diagnostic guidelines for the clinician.

MANAGEMENT FOR PCOS

The medical management of PCOS can be broken down into four components, three of which are "acute" issues (control of irregular menses, treatment of hirsutism and management of infertility) and one that is more "chronic." This latter issue may be the most important but least remembered by patients and providers alike—management of the IR syndrome. "Acute" issues that need management may change, however, a continuous life-long management approach is important for the IR of PCOS.

CONTROL OF IRREGULAR MENSES

This cardinal feature of PCOS can be both a nuisance and a significant health risk to patients. Irregular menses can be embarrassing because of unpredictability and painful because the infrequent occurrence often leads to increased cramping with the heavier flow. Infrequent menstrual cycles also carry a 3-fold increased risk of endometrial carcinoma.²⁹ In general, four menses per year are required to control this increased risk. Four common management options in this regard are listed in table 5.

The mainstay for decades has been oral contraceptives, which are nearly always effective at normalizing menstrual cycles. The newer formulations are generally safer than those of years past, although recently their use in PCOS is coming under greater scrutiny in regard to their potentially detrimental effect on insulin sensitivity.³⁰ Oral contraceptives should not be used in those with a history of hypercoagulable state or deep venous thrombosis or in women over the age of 35 who smoke. A fasting lipid profile should be assessed before initiating therapy as oral contraceptives can worsen hypertriglyceridemia. For those women who might prefer not to cycle every month, periodic progesterone withdrawal is an option. A 7- to 10-day course of medroxyprogesterone 10 mg daily every 3 months will often result in four menses annually. One appealing aspect of this is that women can often plan their menses to avoid vacations, etc. A cycle should occur a week after the course of therapy has been completed.

Because of the central role IR plays in PCOS, it is understandable that improving insulin sensitivity can restore normal menstrual function. This might be looked at as treating the "root cause" of the problem rather than simply using oral contraceptives to regulate the cycles. Weight loss itself can result in improvement in menses. Kiddy et al. showed improvement in menstrual function in 9 of 11 patients (82%) with oligomenorrhea who lost >5% initial body weight (range 5.9 to 22%) on a 1000 kcal/day, low-fat diet over 6 to 7 months, whereas only 1 of 11 patients (9%) losing <5% body weight demonstrated such improvement.³¹ Metformin therapy has been shown to induce resumption of normal, ovulatory menstrual cycles in 40% to 90% of patients studied.³²⁻³⁵ Doses used varied from 500 to 1000 mg twice daily. Table 6 lists dosing/titration information, as well as safety issues with metformin use. The response to metformin is predictable based on higher levels of testosterone^{33,36,37} and in those patients with less severe menstrual irregularities at baseline.³⁷ The degree of hyperinsulinemia may³⁷ or may not^{33,36} be predictive. It is not clear how long metformin should be tried before it is deemed ineffective at improving menstrual function. However, a 6 month trial seems reasonable.

Overall, the option chosen at present to regulate menses should depend on factors such as the degree of weight excess or IR/glucose intolerance, the presence of other PCOS issues requiring management (hirsutism or infertility), and patient and/or physician preferences based on a careful discussion. Insulin sensitizers and/or weight loss may be most effective in patients in which this is a greater problem. However, recent data have shown that lean PCOS patients also respond to metformin.³⁸ In the future perhaps certain patient characteristics and/or laboratory parameters will be found to be predictive of the response to various interventions that will help guide the clinician.

TREATMENT OF HIRsutISM

Hirsutism can be measured and quantified by a variety of methods. However, the decision of if and when to treat should be based on the patient's perception of the excess terminal hair growth. A similar degree of hirsutism in two different patients may result in vastly different degrees of distress. When thought of simply, hirsutism can be managed in two ways: through medical means by decreasing the amount or blocking the action of androgens or by mechanical means (i.e., shaving, etc.). These options are summarized in table 5.

Table 5. Management options for polycystic ovarian syndrome.

Control of irregular menses
Oral contraceptives
Periodic progesterone withdrawal
Lifestyle modification/weight loss
Metformin
Treatment of hirsutism
Biochemical
Decreasing testosterone production
Oral contraceptives
Lifestyle modification/weight loss
Metformin
Decreasing testosterone action
Anti-androgens (spironolactone)
Lifestyle modification/weight loss
Metformin
Mechanical
Plucking/shaving/electrolysis/laser
Vaniqa cream (eflornithine hydrochloride 13.9%) (Bristol Myers-Squibb/Gillette Co, Princeton, NJ)
Management of infertility
Clomiphene citrate
Lifestyle modification/weight loss
Metformin
Thiazolidinediones
Management of insulin resistance/type 2 diabetes mellitus risk
Lifestyle modification/weight loss
Metformin

Table 6. Dose titration and safety issues with the use of metformin.

Dose titration example		
Breakfast	Supper	Duration
X	500 mg	1 week
500 mg	500 mg	1 week
500 mg	1000 mg	1 week
1000 mg	1000 mg	Thereafter
Side effects	Gastrointestinal intolerance in 30% (nausea, abdominal pain and/or diarrhea)	
Precautions	Hold for 48 hours prior to and after surgery and/or administration of radiocontrast materials	
Contraindications	Creatinine ≥ 1.4 mg/dL (for women) Liver disease (or risk thereof: alcohol abuse/binge drinking) Other risks for lactic acidosis: pulmonary disease, congestive heart failure	

MEDICAL

Decreasing testosterone production

Excess testosterone production is predominantly ovarian in nature and is caused by both increased luteinizing hormone stimulation from the pituitary and the effect of hyperinsulinemia at the ovary. By decreasing gonadotropin production and increasing sex hormone binding globulin (SHBG), oral contraceptives generally decrease bioavailable testosterone levels by 40% to 60%.³⁹ By improving insulin sensitivity (and thus lowering insulin levels), both metformin and lifestyle modification/weight loss also lower testosterone, although to a lesser degree.⁴⁰ Overall hirsutism scores improve by approximately 33% with the use of second or third generation oral contraceptives.⁴¹ Only 50% of patients respond to oral contraceptives, however.⁴² Targeting IR seems to have less pronounced improvements on hirsutism scores: metformin (3% to 13%)⁴³⁻⁴⁵ and troglitazone (17%).⁴⁶ Insulin sensitizers are not yet well studied in this area, however, and as such should not be the initial therapeutic option for the management of hirsutism unless there are contraindications to more established therapies.

Decreasing testosterone action

As none of the above therapies will fully suppress testosterone levels, the additional method of blocking testosterone action is useful. There are several anti-androgens available, but only spironolactone will be discussed further since many of the others have poor side effect profiles, are expensive, or are unavailable in the United States. Spironolactone is an aldosterone antagonist that was initially introduced as an antihypertensive agent. It also, however, has a 67% relative affinity for the testosterone receptor (versus dihydrotestosterone).⁴⁷ Spironolactone reduces hirsutism scores by ~40%^{48,49} and is effective in ~50% of patients when used alone.⁵⁰ When combined with oral contraceptives, the response rate increases to 75%⁵⁰ with a reduction in hirsutism scores of about 45%.⁵¹ Fifty milligrams twice daily is a reasonable starting dose working up to 100 mg twice daily if needed after 6 to 12 months. The most common side effect is menstrual irregularity, but nausea may also occur. Due to its effect on menses, its unknown safety during pregnancy, and the theoretical risk of preventing normal masculinization of a male fetus, the use of spironolactone in combination with oral contraceptives may be preferred. For monitoring, potassium can be checked 1 to 2 weeks after initiation or after a dose increase.

The effect of metformin and lifestyle modification/weight loss on testosterone action involves the increase in SHBG that occurs with improvement in insulin sensitivity. With an increase in SHBG, bioavailable (free) testosterone decreases, thus lowering testosterone action. The effect of these treatments on hirsutism, then, is due in part to decreased testosterone action (in addition to lowering testosterone as noted earlier). In the previously mentioned study by Kiddy et al., >5% weight loss resulted in a 40% reduction in hirsutism.³¹

Whatever biochemical option is used for hirsutism, the patient should be informed that a trial of 6 to 12 months is needed before any given therapy and/or dose can be deemed ineffective. Also, as noted, not all patients will respond to treatment, and any response is likely to be incomplete. Thus, mechanical measures will often be needed, although at a lesser frequency than would otherwise be required.

MECHANICAL

Plucking/shaving/electrolysis/laser

Many women have already used one or a combination of these methods to control hirsutism by the time they present for medical evaluation. Others have and may continue to avoid them for fear of worsening hair growth, although this does not occur.⁵² Plucking is best avoided, as it can lead to folliculitis and scarring in some women. Shaving is likely to be the cheapest and simplest way to remove unwanted hair but may not be acceptable to some women. Electrolysis involves electrocoagulation of the hair follicle, which may or may not be permanent and generally does not result in scarring.²¹ Laser treatment of hirsutism involves causing selective thermal damage to the hair follicle while avoiding surrounding tissue and thus works best in fair-skinned patients with darker unwanted hairs.⁵³ Laser treatment may lead to erythema, edema, blistering and/or temporary hyper- or hypopigmentation.⁵⁴

Eflornithine hydrochloride 13.9% cream

Vaniqa (Bristol Myers-Squibb/Gillette Co., San Diego, CA) is approved for the treatment of unwanted facial hair. Its mechanism of action is to inhibit the enzyme L-ornithine decarboxylase, which is involved in hair growth. Through this mechanism, Vaniqa slows the growth of, but does not remove hair. In a 24-week trial, 58% of treated subjects had some improvement in facial hirsutism versus 34% in the placebo group, while 32% and 8%, respectively were deemed to have marked improvement.⁵⁵ Continued use is required, however, as hair growth rates returned to baseline after 8 weeks off therapy. Adverse events more common than in the placebo group were limited to skin irritation (burning, stinging, and/or tingling). Because Vaniqa is often not covered by insurance, it may be less appealing.

MANAGEMENT OF INFERTILITY

PCOS accounts for 75% of anovulatory infertility. Additionally, if/when pregnancies do occur, the first trimester miscarriage rate is as high as 30% to 50%.⁵⁶ Successful medical management of infertility in these patients can be extremely rewarding to patients and physicians alike. Management of infertility can be difficult, however, and a team approach between the endocrinologist, gynecologist and, perhaps, reproductive endocrinologist should be stressed. An extensive review of the intricacies of infertility management of the patient with PCOS is beyond the scope of this review. Instead, a brief discussion of the relative resistance to clomiphene therapy in PCOS will be

undertaken followed by a more in depth look at the potential utility of methods aimed at improving insulin sensitivity (with a focus on metformin).

CLOMIPHENE CITRATE

Obese women with PCOS often do not respond to low doses of clomiphene, with only a 20% ovulation rate at the 50 mg dose seen in women weighing more than 91 kg.⁵⁷ Indeed, the degree of obesity correlates with the dose of clomiphene needed to induce ovulation.⁵⁸ The higher doses of clomiphene often required may cause side effects and can increase the rate of multiple gestations.⁵⁹ Clomiphene has been extensively studied in combination with metformin (see below).

LIFESTYLE MODIFICATION/WEIGHT LOSS

As mentioned in previous discussions, weight loss reduces hyperinsulinemia and subsequently hyperandrogenism. In the study by Kiddy et al. discussed earlier, about 40% of obese women with PCOS (mean body mass index [BMI] ~34 kg/m²) who lost >5% of initial body weight with caloric restriction achieved spontaneous pregnancy.³¹ A more recent trial compared the effects of an energy-restricted diet (~1400 kcal/day) through either a low or high protein diet in 28 obese (mean BMI ~ 37 kg/m²) PCOS subjects over 12 weeks.⁶⁰ Subjects were also advised to increase exercise to a minimum of 3 times weekly though no information was reported as to the actual duration and/or intensity achieved. Average weight loss was 7.5% (with abdominal fat decreasing 12.5%), and 3 of the 20 subjects actively trying to conceive did so (two in the high and one in the low-protein group) for a rate of 15%. Thus, lifestyle modification needs to be stressed in the treatment of infertility. A 3 to 6 month trial of aggressive lifestyle modification may be a prudent first step before considering an insulin sensitizer. However, many patients will have difficulty in achieving weight loss (see later).

METFORMIN

The initial report of metformin in the treatment of PCOS by Velazquez et al. in 1994 described three spontaneous pregnancies (~11% of subjects).⁶¹ Since that time, a number of other studies have been completed assessing metformin's role in the treatment of PCOS. The primary outcomes of these studies were the effects on parameters of IR, hyperandrogenemia, and improvements in menstrual function and ovulation. Many of these studies were small, involving approximately 20 patients each, but in the five trials describing spontaneous pregnancies, the rate was between 5% and 18%.^{33,62-65} A recent study by Heard et al. involved 48 anovulatory PCOS patients (mean age of 29.9 years and BMI of 28.7 kg/m²) enrolled for 15 months.³⁴ Metformin was started at 500 mg twice daily and increased to three times daily if ovulation did not occur by 6 weeks, and clomiphene was added 6 weeks later as needed.

Normalization of menstrual cycles and ovulation occurred in 19/48 subjects (40%) on metformin alone, and 15 of them (79%) became pregnant. Nearly 75% of these pregnancies

on metformin alone occurred within 3 months of starting the medication. The addition of low dose clomiphene (50 mg) resulted in five additional pregnancies.³⁴ Similar rates of ovulation (40%) were seen with metformin alone in obese subjects (mean BMI ~32 kg/m²), while the addition of clomiphene increased that rate to 89%.³² The use of clomiphene alone resulted in only an 11.5% ovulation rate. Pregnancies were not reported. Lastly, in clomiphene-resistant PCOS patients, metformin pre-treatment increased conception rates from 7% to 55%.⁶⁶ The use of metformin also improves the outcome of more advanced infertility therapies. When used for 1 month prior to ovulation induction with FSH, metformin reduced the risk of ovarian hyperstimulation.⁶⁷ As well, metformin improves fertilization and pregnancy rates in women with PCOS undergoing *in vitro* fertilization.⁶⁸ Thus, in the setting of infertility, metformin therapy should likely be continued for as long as fertility efforts are ongoing, even if it "fails" initially.

As mentioned, once pregnancy is achieved in PCOS patients, the first-trimester miscarriage rate is 3-fold higher than that of normal women.⁵⁶ Recently, metformin therapy continued throughout pregnancy has been shown to reduce this risk of early pregnancy loss. In a retrospective study of women who became pregnant on metformin and continued it throughout pregnancy, the rate of early pregnancy loss was 8.8% compared to 41.9% of women who were not on the drug.⁶⁹ In a prospective pilot study, Glueck et al. have reported on 19 women receiving metformin during their pregnancy to date.⁷⁰ Fifty-eight percent have had normal live births, 32% have ongoing pregnancies beyond the first trimester, and 10.5% had first-trimester miscarriages. No birth defects occurred.⁷⁰ This study will eventually include 125 women with PCOS. However, metformin is not approved for use in ovulation induction or during pregnancy. It is pregnancy category B.

THIAZOLIDINEDIONES (TZDs)

Several studies evaluating ovulation induction with troglitazone were completed before it was removed from the market in 2000.^{46,71,72} Troglitazone alone resulted in ovulatory rates of >40%, and the success rate of clomiphene increased from 35% to 75% with troglitazone pretreatment.⁷¹ Also, the use of troglitazone in clomiphene-resistant patients resulted in ovulation and pregnancy rates of 83% and 39%, respectively.⁷² In the largest trial involving a TZD, Azziz et al. evaluated the effect of troglitazone in 305 obese PCOS patients.⁴⁶ At the highest dose of troglitazone (600 mg daily), 57% of the patients ovulated >50% of the time compared with just 12% of the placebo group. Although pregnancy was not an outcome measure of the study, troglitazone-treated subjects had a 4-fold greater fertility rate compared to the placebo group (18% versus 4%).⁴⁶ Recently, data using the currently available TZDs was published. Pre-treatment with rosiglitazone 4 mg twice daily was used with placebo or clomiphene on cycle days 5-9 in 25 PCOS patients previously resistant to clomiphene (mean BMI >35 kg/m²).⁷³ Rosiglitazone alone resulted in ovulation

in 33% of subjects versus 77% in the combination group. One patient in the rosiglitazone-only group (8%) and two in the rosiglitazone-clomiphene group (15%) conceived.⁷³ TZDs are not approved for use in ovulation induction or during pregnancy. They are pregnancy category C.

DIABETES RISK AND LONG-TERM MANAGEMENT OF IR IN PCOS

Most PCOS patients are inherently IR with the obesity seen in many, only adding to this problem. Perhaps not surprisingly then a substantial proportion of PCOS patients have abnormalities on the oral glucose tolerance testing at the time of diagnosis. When assessed overall (obese and lean together), PCOS patients had a 31% rate of impaired glucose tolerance and 7.5% met the criteria for type 2 diabetes mellitus.⁷⁴ These results were confirmed in another United States study,⁷⁵ but a European study found only a 6.4% rate of impaired glucose tolerance and no cases of type 2 diabetes mellitus.⁷⁶ This discrepancy may be related to a significant difference in the severity of obesity between studies.⁷⁷ In the United States, even non-obese PCOS patients have a prevalence of these disorders 3 times that of the general population (10.3% impaired glucose tolerance and 1.5% type 2 diabetes mellitus).⁷⁴ Also, Norman et al. followed 67 women with PCOS (54 with normal glucose tolerance and 13 with impaired glucose tolerance) for a mean of 6.2 years.⁷⁸ In those with normal glucose tolerance at baseline 17% had developed impaired glucose tolerance or type 2 diabetes mellitus over time, while 54% of those with impaired glucose tolerance at baseline had progressed to type 2 diabetes mellitus. Further support for the high prevalence of abnormal glucose tolerance in PCOS is the 10-fold increased risk of developing gestational diabetes mellitus compared to the general population (baseline risk ~3%).⁷⁹ Lastly, Cibula et al. noted a 4-fold increased prevalence of type 2 diabetes mellitus in women with PCOS who had undergone ovarian wedge resection for polycystic ovaries some 20 to 40 years earlier compared to a closely matched control population.⁸⁰

With the high prevalence of abnormalities in glucose tolerance in PCOS and the significant impact this might have on patients' health, much has been done to evaluate the effects of insulin sensitizers in this regard. Metformin is perhaps the most widely studied agent thus far and most,^{62,64,81} but not all⁸² uncontrolled studies have shown a significant improvement in insulin sensitivity. A review of controlled trials showed similar findings with 5 of 7 studies showing improvements in insulin sensitivity.⁴⁰ Troglitazone has similar effects in PCOS patients.^{83,84} Also, metformin use throughout pregnancy in women with PCOS decreases the rate of gestational diabetes mellitus from ~30% to ~3%.⁷⁹

With these results, there may be potential utility in using insulin sensitizers to prevent or delay the onset of type 2 diabetes mellitus in PCOS patients. Perhaps the closest data available to deal with such an issue comes from the Diabetes Prevention Program where the effect of metformin or

lifestyle modification was compared to placebo in obese patients with impaired glucose tolerance (68% of whom were women). Metformin resulted in a 31% reduction in the development of type 2 diabetes mellitus over 2.8 years versus placebo, while lifestyle modification reduced the risk to a greater extent (58%).⁸⁵ It is important to note that the lifestyle intervention was modest involving approximately a 7% weight loss and 20 minutes of brisk walking daily. Metformin plus lifestyle modification was not studied. It is apparent that a strong emphasis needs to be placed on lifestyle modification in the management of the long-term health risks of PCOS. The results of the Diabetes Prevention Program should be discussed at length with all PCOS patients. If metformin is used for the prevention of type 2 diabetes mellitus, it is unclear how long it should be continued, as the risk is lifelong and the effectiveness of this agent wanes after it is discontinued. Further research is needed in this area.

Information on the effectiveness of various therapies on two of the cornerstones of 'acute' PCOS management (hirsutism and irregular menses) and their effect on testosterone levels is spread throughout this discussion. Therefore, table 7 is included as a concise summary.

OTHER ISSUES

Cardiovascular Risk Factors and Disease in PCOS

Aside from the increased risk of type 2 diabetes mellitus in PCOS patients, there are multiple other metabolic abnormalities that put them at higher risk for cardiovascular disease. Many,⁸⁶⁻⁸⁹ but not all^{90,91} studies have shown either a greater prevalence of diagnosed hypertension or higher ambulatory blood pressure in PCOS. The pattern of dyslipidemia in PCOS is in keeping with IR, increased triglycerides, and low HDL-cholesterol.⁹²⁻⁹⁵ Women with PCOS may also have higher levels of small, dense LDL-cholesterol,⁹⁶ homocysteine,⁹⁷ plasminogen activator inhibitor type 1,⁸¹ decreased insulin-induced vascular relaxation,⁹⁸ and endothelial dysfunction.⁹⁹ As an extension of these data on risk factors, two retrospective studies of patients undergoing coronary angiography found women with a significant history of hirsutism to be more likely to have coronary artery disease.^{100,101} Also, women with polycystic ovaries on ultrasound had more extensive coronary artery disease at catheterization than those without such ultrasound findings.¹⁰¹ Lastly, PCOS patients have been shown to have increased carotid intimal media thickness¹⁰² and an almost 6-fold increased prevalence of coronary artery calcification¹⁰³ versus age-matched control subjects.

Based on the increased prevalence of risk factors in patients with PCOS, Dahlgren and colleagues estimated a 7-fold increased risk of myocardial infarction in these women.¹⁰⁴ While there is evidence emerging showing increased cardiovascular and cerebrovascular event rates in these patients, the burden of disease does not seem to be as great as initially predicted. The Nurses' Health Study cohort revealed that women with "usually irregular" or "very irregular"

Table 7. Effects of various therapies on serum testosterone, hirsutism, and menstrual function in PCOS.

Intervention	Hirsutism			
	Decreased T	Response rate	Degree of improvement	Rate of improved menses/ovulation
Weight loss ($\geq 5\%$)	31% ³¹	50% ¹²⁶	40% ³¹	40% to 81% ^{31,126,127}
Metformin ^a	16% to 70% ^{38,40,63,128}	50% ¹²⁹	3% to 25% ^{43-45,129}	40% to 90% ³²⁻³⁵
TZD	25% to 35% ¹²⁸	Not reported	17% ⁴⁶	33% to 83% ^{46,71,73,130}
OCP	40% to 60% ³⁹	50% ⁴²	33% ⁴¹	Not applicable
Spironolactone	Not applicable	50% ⁵⁰	40% ^{48,49}	Not applicable ^b
OCP + spironolactone	Not applicable	75% ⁵⁰	45% ⁵¹	Not applicable
Clomiphene	Not applicable	Not applicable	Not applicable	11% to 48% ^{32,66,131}
Metformin + clomiphene	Not applicable	Not applicable	Not applicable	75% to 89% ^{32,66}
TZD + clomiphene	Not applicable	Not applicable	Not applicable	72% to 75% ^{71,73,131}

^a Includes data from lean and obese patients with regard to decreased T and menses/ovulation (see references for details).

^b Spironolactone alone may cause/worsen menstrual irregularities.

T, total or free testosterone (see specific reference for details); TZD, thiazolidinediones; OCP, oral contraceptive pills.

menstrual cycles had an increased risk of coronary artery disease events of approximately 20% and 60%, respectively versus those with “very regular” cycles.¹⁰⁵ There was a non-significant increased risk of cerebrovascular events of ~30%. Wild et al. found a significantly increased risk of stroke (odds ratio, 2.8) but no difference in coronary artery disease in a retrospective cohort of PCOS patients followed for 30 years,¹⁰⁶ while Cibula et al. reported a 4-fold increased risk of coronary artery disease in PCOS patients followed 20 to 40 years.⁸⁰ Further study into this crucial aspect of long-term risk/care of PCOS patients is desperately needed.

PCOS in Adolescents

Premature pubarche (appearance of pubic hair before age 8) may be an early expression of PCOS and is associated with ovarian hyperandrogenism¹⁰⁷ and the development of chronic anovulation.¹⁰⁸ Increased awareness of PCOS by physicians has and will continue to lead to diagnosis at an earlier age. Many previously mentioned diagnostic and therapeutic issues apply to adolescents with PCOS. Perhaps most alarming is the aspect of IR. It is well known that the increase in type 2 diabetes mellitus in the United States has paralleled the increase in overweight individuals and obesity.¹⁰⁹ Furthermore, the incidence of type 2 diabetes mellitus in children is increasing dramatically.¹¹⁰ Palment and colleagues performed oral glucose tolerance tests in adolescents with PCOS (mean age 16.7 years) and found the prevalence of impaired glucose tolerance to be 30% and that of type 2 diabetes mellitus 3.7%.¹¹¹ A glucose-to-insulin ratio may also be used in adolescents to help determine IR¹³ (see table 4).

Several small studies have been completed using metformin in adolescents with PCOS. Similar to the results in adult women, these studies have shown benefits in hirsutism,¹¹² dyslipidemia,¹¹² hyperandrogenism,¹¹²⁻¹¹⁴ menstrual function,^{112,113} and glucose intolerance.¹¹⁴ Overall, experience is very limited, however, and many questions are as yet unanswered. More data are needed before metformin can be routinely used in the management of adolescents with PCOS.

PCOS, Seizure Disorders, and Valproic Acid

There is an increased prevalence of reproductive endocrine disorders in patients with epilepsy. The reason for this overrepresentation is debatable but likely multifactorial, ranging from the influence of epilepsy itself on the hypothalamic-pituitary axis to various effects of anti-epileptic drugs on hormone secretion and action both directly and indirectly through changes in weight and body composition.^{115,116} Valproic acid has received particular attention in this regard. Some evidence suggests that some women on this therapy have higher levels of insulin, testosterone, and triglycerides than those on another agent (lamotrigine), although few actually had a clear biochemical suggestion of PCOS.¹¹⁷ Further study into this complex issue is needed, but in the meantime women with seizure disorders, perhaps especially those on valproic acid, deserve careful monitoring of their menstrual function clinically and potentially biochemically (i.e., assessment for hyperandrogenism).

Difficulties in Lifestyle Modification/Weight Loss

Mention has been made earlier as to the effectiveness of weight loss as an intervention to every aspect of PCOS. Weight loss, however, is difficult to achieve and maintain as is evidenced by the millions of overweight/obese children and adults. While a complete discussion of the options/strategies to attain and maintain weight loss is beyond the scope of this article, several basic points deserve mention. For summaries on the effect and role of lifestyle modification in PCOS, the interested reader is referred to the excellent reviews by Hoeger¹¹⁸ and Norman et al.,¹¹⁹ respectively.

Increased physical activity and dietary modification are the cornerstones to successful weight loss and cardiovascular risk reduction. Unfortunately, few patients attempting to lose weight are actually implementing both of these strategies simultaneously. Indeed, one report demonstrated only ~20% of men and women actively trying to lose weight were employing both.¹²⁰ One misconception that perhaps limits many patients' ability to achieve and maintain weight loss is that increased physical activity means vigorous exercise. On the contrary, moderate exercise is as efficacious as vigorous exercise.¹²¹ Also, moderate-intensity lifestyle activity has proven equal to structured aerobic exercise with regard to weight loss in obese women.¹²² Lastly, reducing sedentary behaviors may be extremely important in weight loss efforts. In a 1997 survey, adult women spent an average of 34 hours per week watching television.¹²³ In one study, each 2 hour/day increment in television watching was associated with a 23% increase in obesity and a 14% increase in the risk of type 2 diabetes mellitus over 6 years.¹²⁴ Clinicians should be stressing a 3 point approach to increasing physical activity: decreasing sedentary behaviors, increasing lifestyle activity and initiating moderate exercise.

The National Institutes of Health clinical guidelines for the treatment of overweight and obesity¹²⁵ should be followed in the management of PCOS patients who require weight loss. These guidelines focus not only on diet and activity, but also on the importance of behavior modification, reduction of psychosocial stressors, social support from family and peers, and smoking cessation.^{119,125}

SUMMARY

Much has been learned of the pathophysiology of PCOS since its first description in 1935. Yet, despite a better understanding of the disease itself (and the passage of nearly 70 years), it still lacks specific diagnostic criteria making identification of patients difficult. With appreciation of the role IR plays in PCOS, proper identification has become more important than ever before. There are several other disease states that may present in much the same way as PCOS, and evaluation to rule out these is crucial to apply appropriate management options. Further research into proper identification of patients with PCOS and perhaps updated diagnostic criteria are needed.

Management of any three "acute" concerns of the PCOS patient (control of irregular menses and/or hirsutism and/or infertility management) can be a challenge, and some guidance is offered in this review. Treatment for PCOS will change over time based on what issue is most important to the patient at that stage of her life. That said, it is imperative to not lose sight of the crucial, life-long importance of managing the IR syndrome. There are several approaches to quantifying the degree of IR (glucose to insulin ratio, etc.), but just simply evaluating for the presence of dyslipidemia and impaired glucose tolerance test or type 2 diabetes mellitus may be a better approach.

If diagnosed early and managed properly with lifestyle modification (and/or insulin sensitizers), the onset of type 2 diabetes mellitus and its resultant risk of coronary artery disease may be delayed or prevented. PCOS is a varied and complex entity requiring much knowledge and skill both for proper diagnosis and management over time. It is hoped that this review will add to the growing knowledge base that providers in many areas of medicine seek in regard to the management of these challenging patients.

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Review

Polycystic Ovary Syndrome: An Evolutionary Adaptation to Lifestyle and the Environment

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Abstract: Polycystic ovary syndrome (PCOS) is increasingly recognized as a complex metabolic disorder that manifests in genetically susceptible women following a range of negative exposures to nutritional and environmental factors related to contemporary lifestyle. The hypothesis that PCOS phenotypes are derived from a mismatch between ancient genetic survival mechanisms and modern lifestyle practices is supported by a diversity of research findings. The proposed evolutionary model of the pathogenesis of PCOS incorporates evidence related to evolutionary theory, genetic studies, in-utero developmental epigenetic programming, transgenerational inheritance, metabolic features including insulin resistance, obesity and the apparent paradox of lean phenotypes, reproductive effects and subfertility, the impact of the microbiome and dysbiosis, endocrine disrupting chemical exposure, and the influence of lifestyle factors such as poor quality diet and physical inactivity. Based on these premises, the diverse lines of research are synthesized into a composite evolutionary model of the pathogenesis of PCOS. It is hoped that this model will assist clinicians and patients to understand the importance of lifestyle interventions in the prevention and management of PCOS and provide a conceptual framework for future research. It is appreciated that this theory represents a synthesis of the current evidence and that it is expected to evolve and change over time.

Keywords: polycystic ovary syndrome; evolution; insulin resistance; infertility; toxins, endocrine disrupting chemicals; environment; lifestyle; diet

1. Introduction

It is widely accepted that there is a global epidemic of lifestyle-related chronic diseases, such as obesity and diabetes, that are underpinned by reversible metabolic dysfunction in the majority of individuals affected (1–3). It is also recognized that many of these chronic diseases may share a similar pathogenesis involving the interaction of genetic and environmental factors that manifest in overlapping pathophysiological features (4–6). The revised International Guidelines for the assessment and management of women with PCOS, emphasise that the associated metabolic dysfunction and symptoms should initially be addressed via lifestyle interventions (7).

Evolutionary medicine is an emerging discipline involving the study of evolutionary processes that relate to human traits and diseases and the incorporation of these findings



into the practice of medicine (8). Evolutionary medicine brings together interdisciplinary research to inform clinical medicine based on the influence of evolutionary history on human health and disease (9). Previous utilization of the principles of evolutionary medicine has been limited to monogenetic diseases (cystic fibrosis, sickle cell anaemia, phenylketonuria and many others), drug resistance of microorganisms, tumour growth and chemoresistance (8). Future insights into the application of evolutionary research offers the potential to improve and personalize the established medical and scientific approaches to complex chronic diseases like type 2 diabetes, metabolic syndrome and PCOS (5,9).

The evolutionary origins of complex chronic diseases incorporate considerations of relative reproductive fitness, mismatch between our biological past and modern environment, trade-offs involving combinations of genetic traits, and evolutionary conflicts (8,10). These evolutionary factors are relevant when analysing the contributors to the pathogenesis of PCOS in modern and modernising societies, that result in a mismatch between our rapid cultural evolution with our slow biological evolution (11,12). The unique cultural evolution of humans does not have a plausible analogue in most other species and is increasingly recognised to play a significant role in the pathogenesis of metabolic diseases such as PCOS (5,13–17).

Polycystic ovary syndrome is a complex multisystem condition with metabolic, endocrine, psychological, fertility and pregnancy-related implications at all stages of life (7,18). The majority of women with PCOS manifest multiple metabolic features including obesity, insulin resistance (IR), hyperlipidaemia and hyperandrogenism (19,20). PCOS results in an increased risk of developing metabolic disease (type 2 diabetes, non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome), cardiovascular disease, cancer, a wide array of pregnancy complications (deep venous thrombosis, pre-eclampsia, gestational diabetes, macrosomia, growth restriction, miscarriage, stillbirth and preterm labour) and psychological problems (anxiety, depression) (6,21–25). PCOS is part of a cluster of inter-related metabolic conditions and makes a significant contribution to the chronic disease epidemic.

Extensive research suggests that the aetiology of PCOS involves an interaction between environmental factors and gene variants, although it has been suggested that genetic factors contribute less than 10% to disease susceptibility (26–28). A large number of genetic and genome-wide association studies (GWAS) have identified common gene loci associated with PCOS phenotypes in different ethnic populations (29–31). These appear to be normal gene variants or polymorphisms, given the frequency and type of genes that have been identified. PCOS is therefore viewed as a polygenic trait that results from an interaction between susceptible genomic variants and the environment.

PCOS affects upward of 10% of reproductive-aged women, estimated at over 200 million women worldwide (32,33). PCOS is thought to be increasing in incidence in both developing and developed nations as a result of lifestyle-related changes in diet quality, reduced physical activity, ubiquitous environmental endocrine disrupting chemicals (EDC), altered light exposures, sleep disturbance, heightened levels of stress and other

environmental factors (11,34–38). These factors, and the high prevalence of PCOS, suggest that there could be an evolutionary basis for the syndrome (15,16,39). Evolutionary medicine has changed the paradigm for understanding PCOS, acknowledging many of the contributing lifestyle and environmental factors that facilitate the observed metabolic and clinical features and that are also shared with related metabolic diseases (8). These “mismatch disorders” are estimated to make a significant contribution to chronic disease in developed countries and a growing proportion of disability and death in developing nations (3). According to the Global Burden of Disease Study, the human diet is now the leading risk factor for morbidity and mortality worldwide (3). In keeping with these findings, diet is recognized as one of the major contributors to the growing prevalence of PCOS globally (7,40).

Dietary and environmental factors are hypothesized to have an impact on developmental programming of susceptible gene variants in women with PCOS (41–43). Extensive experimental evidence suggests that prenatal androgen exposure may play a role in the pathogenesis of PCOS-like syndromes in animal models (19,44–46). The discovery of naturally-occurring PCOS phenotypes in non-human primates supports a survival advantage of a hyperandrogenic, insulin resistant phenotype with delayed fertility (47). In humans, the origin of excess androgens may be from maternal, fetal or placental sources. In addition, emerging and concerning evidence suggests that EDC may contribute to altered fetal programming and play a role in the pathogenesis of PCOS (41,48).

In-utero genomic programming of metabolic and endocrine pathways can increase the susceptibility of offspring to develop PCOS following exposure to specific nutritional and environmental conditions (45). This view of the pathogenesis of PCOS is consistent with the Developmental Origins of Health and Disease (DOHaD) model proposed by Neel (49). Postnatal exposure to lifestyle and environmental factors, such as poor-quality diet and EDC, may activate epigenetically programmed pathways that further promote the observed features of PCOS. Dietary and lifestyle interventions have demonstrated that many of the clinical, metabolic and endocrine features of PCOS can be reversed (7,50,51).

Lifestyle-induced changes in the gastrointestinal tract microbiome are another significant factor in the aetiology of PCOS (52,53). Dysbiosis of the gut microbiota has been hypothesised to play a role in increased gastrointestinal permeability, initiating chronic inflammation, IR and hyperandrogenism (40). Numerous studies have reported reduced alpha diversity of the microbiome that has been associated with the metabolic, endocrine and clinical features observed in women with PCOS (54,55). The resulting dysbiosis has been shown to be reversible after interventions aimed at improving diet quality or treatment with probiotics or synbiotics (50,51,56–58).

A unified evolutionary theory of the pathogenesis of PCOS proposes that ancient genetic polymorphisms that were aligned with the environment of that era, resulted in an adaptive survival advantage in offspring in ancestral populations (14–16,28). When these same genetic variants are exposed to modern lifestyle and environmental influences, maladaptive physiological responses occur. The prior advantages of insulin resistance, hyperandrogenism, enhanced energy storage and reduced fertility in ancestral

populations become pathological and result in the observed features of PCOS in contemporary women (figure 1).

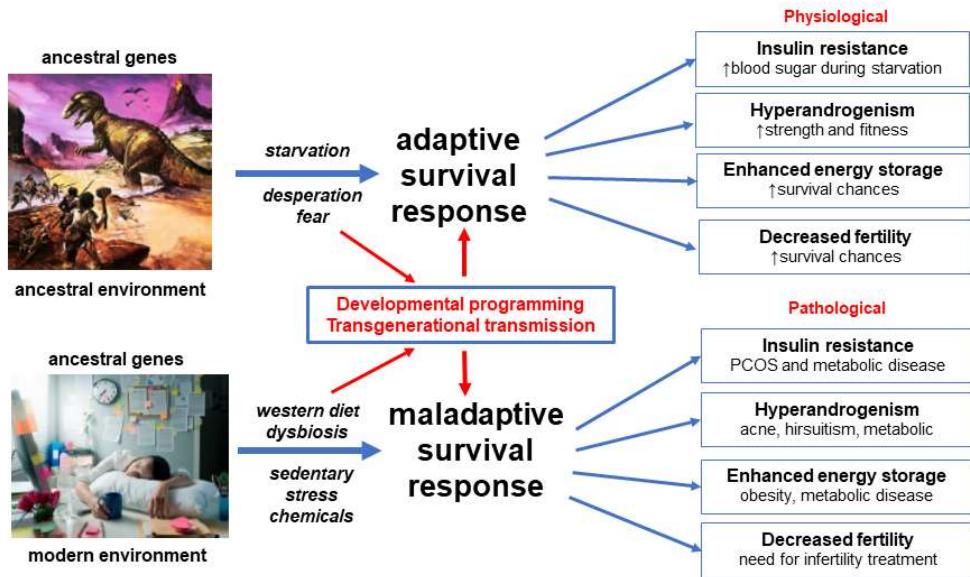


Figure 1. Evolutionary model of the pathogenesis of polycystic ovary syndrome

2. Materials and Methods

The literature search focused on research publications related to the pathogenesis of PCOS using the keywords listed above and related mesh terms for data on the evolutionary aspects of PCOS, genetic studies, in-utero developmental epigenetic programming, transgenerational inheritance, metabolic features including insulin resistance, obese and lean PCOS phenotypes, reproductive changes and subfertility, impact of the microbiome and dysbiosis, possible effects of endocrine disrupting chemical exposure and the influence of lifestyle factors such as diet and physical activity. The databases searched included PubMed, Scopus, Cochrane and Google Scholar. Relevant papers were selected and citation searches were performed.

The present manuscript synthesizes the findings into a unified evolutionary model. The following text is presented as a narrative review of factors involved in the pathogenesis of PCOS and is discussed in ten main subject areas that provide the rationale for the development of a unified model. 1. Evolution 2. Genetics 3. Developmental Epigenetic Programming 4. Microbiome and Dysbiosis 5. Insulin resistance 6. Obesity and the lean paradox 7. Environmental Chemical Exposure 8. Lifestyle Contributors to the Pathogenesis of PCOS 9. Conceptual Framework of a Unified Evolutionary Model 10. Explanation to women diagnosed with PCOS.

3. Pathogenesis of PCOS

3.1. Evolution

The description of PCOS phenotypes can be found in medical records from antiquity and the modern syndrome was described over 80 years ago (17,59). Nevertheless, there is ongoing debate regarding the evolutionary origins of PCOS (15–17,39,60–64). PCOS

susceptibility alleles may have arisen in our phylogenetic ancestors, in the Hunter-gatherer Paleolithic period of the Stone Age, after the Neolithic Agricultural Revolution or following the Industrial Revolution (16,17). From an evolutionary perspective, nearly all genetic variants that influence disease risk have human-specific origins, but the systems they relate to have ancient roots in our evolutionary ancestors (8). Regardless of the precise timing of the origin of PCOS in humans, the complex metabolic and reproductive gene variants identified in women with PCOS relate to ancient evolutionary-conserved metabolic and reproductive survival pathways (15,29). Although evolutionary hypotheses about disease vulnerability are impossible to prove they have the potential to frame medical thinking and direct scientific research for the proximate causes of disease (15,60).

Multiple hypotheses have been proposed regarding the evolutionary origins of PCOS and related metabolic diseases (8,60,63). These hypotheses are focused on the relative importance of metabolic survival adaptations versus improved reproductive success, or a combination of both. A detailed analysis of these hypotheses, and the complexities of the evolutionary considerations, have been reviewed elsewhere and is beyond the scope of the present review (8,60). One common theme is that PCOS may be viewed as a “conditional phenotype” where a specific set of conditions has unmasked normally unexpressed or partly expressed genetic pathways, which then provide a survival advantage under certain environmental conditions (14,16).

All organisms have physiological adaptive responses to deal with changing environmental conditions (starvation, fasting, physical threat, stress and infection) and the varying demands of internal physiological states (pregnancy, lactation and adolescence) (14,65). It has been proposed that the PCOS phenotype may have been invoked in specific environmental conditions in ancestral populations as a short, medium or even long-term adaptive survival mechanism (15–17). The view of PCOS as a conditional phenotype proposes that these physiological responses become pathological in our modern environment due to factors such as food abundance, reduced physical activity, circadian disruption, stress and environmental chemical exposure. The transgenerational evolutionary theory of the pathogenesis of PCOS encompasses all of the above ideas to explain the observed pathophysiological and clinical features of PCOS (28).

It is generally accepted that almost all pre-industrial societies and animal populations experienced seasonal or unpredictable episodes of food shortage that applied evolutionary pressure to develop metabolic and reproductive adaptive survival responses (17,49). It is also appreciated that metabolic and reproductive pathways are interconnected and involve reciprocal feedback control mechanisms (66–68). During periods of starvation, anorexia or excessive weight gain, reproduction is down-regulated and ovulation becomes irregular or ceases (69,70). Similarly, metabolic function is co-ordinated with the menstrual cycle to ensure optimal physiological conditions for fertilisation, implantation, pregnancy, parturition and lactation (71). Recent research has elaborated on the details of how some of these complex regulatory mechanisms interact by using specific hormonal, nutrient sensing and intracellular signalling networks (72–74).

Details of the mechanisms underlying the proposed adaptive survival advantages of IR, hyperandrogenism, enhanced energy storage and sub-fertility have been obtained from paleolithic records, animal models and human populations exposed to adverse environmental conditions such as war and famine-inflicted starvation (14,16,62,63). Multiple lines of evidence support the maladaptive response of human populations to rapidly changing nutritional, physical, psychological and cultural environments, in the modern world (5,11,14,75). These “adaptations” result in pathological responses to IR, hyperandrogenism, enhanced energy storage and ovulation (figure 1).

Theories of evolutionary mismatch have also been advanced to explain all of the cluster of metabolic diseases associated with PCOS (type 2 diabetes, metabolic syndrome, NAFLD and cardiovascular disease) and follow the same set of basic principles and explanations (14,76). This common body of evolutionary evidence is supported by the increasing incidence of metabolic-related disease, such as diabetes and obesity, in developed countries and in developing nations adopting a Western diet and lifestyle (11,77). In addition, the demonstrated reversibility of PCOS and related metabolic and biochemical features following changes in diet, increased physical activity and other lifestyle interventions, adds further support to a transgenerational evolutionary model (50,51).

3.2. Genetics

The heritable nature of PCOS has been proposed since the 1960’s following a range of familial, twin and chromosomal studies (78–80). Cytogenetic studies failed to identify karyotypic abnormalities and genetic studies did not show a monogenic inheritance pattern following examination of candidate genes (81,82). In addition, two or more phenotypes can be present in the same family suggesting that some of the phenotypic differences could be accounted for by variable expression of the same shared genes (81,83).

The mapping of the human genome in 2003 (84) and the publication of the human haplotype map (more than one million single nucleotide polymorphisms of common genetic variants) in 2005 (85), lead to the realisation that most DNA variation is shared by all humans and is inherited as blocks of linked genes (linkage disequilibrium) (86). These advances enabled a revolution in case-control studies and the development of GWAS which map the entire human genome looking for susceptibility genes for complex traits such as obesity, type 2 diabetes and PCOS (81).

The first PCOS GWAS was published in 2010 and demonstrated 11 gene loci associated with PCOS (87). Additional loci have subsequently been found in a number of different ethnic groups (86,88). The first GWAS analysis of quantitative traits was published in 2015 and showed that a variant (rs11031006) was associated with luteinizing hormone levels (88). The largest GWAS included a meta-analysis of 10,074 PCOS cases and 103,164 controls and identified 19 loci that confer risk for PCOS (29). The genes associated with these loci involve gonadotrophin action, ovarian steroidogenesis, insulin resistance and type 2 diabetes susceptibility genes. The first GWAS using electronic health record-linked biobanks has introduced greater investigative power and identified 2 additional loci (89). These variants were associated with polycystic ovaries and hyperandrogenism

(rs17186366 near *SOD2*) and oligomenorrhoea and infertility (rs144248326 near *WWTR1*) (89). In addition to identifying common gene variants for PCOS phenotypes, finding the same signals (*THADA*, *YAP1* and *c9orf3*) in Chinese and European populations suggests that PCOS is an ancient trait that was present before humans migrated out of Africa (81).

More recently Mendelian randomization (MR) studies have been used to explore the potential causative association between gene variants identified in GWAS and PCOS (90,91). Many of the gene variants identified in GWAS are located in non-coding regions of DNA (92). The genes or functional DNA elements through which these variants exert their effects are often unknown. Mendelian randomization is a statistical methodology used to jointly analyse GWAS and quantitative gene loci to test for association between gene expression and a trait, due to a shared or potentially causal variant at a specific locus (93). A detailed analysis of MR methodology and the limitations of this statistical tool is beyond the scope of the present review. Although MR studies have the potential to infer causation it is recognised that they also have limitations in PCOS research (90). Nevertheless, preliminary evidence suggests that a number of genes related to obesity, metabolic and reproductive function, may play a causal role in the pathogenesis of PCOS (90,91).

Decades of genetic research has therefore characterised PCOS as a polygenic trait that results from interactions between the environment and susceptible genomic traits (27,29,79,88). The failure to identify a qualitative or monogenic inheritance pattern and the findings from GWAS, MR, familial and twin studies, suggests that the heritability of PCOS is likely to be due to the combination of multiple genes having small effect size, as has been found with obesity and type 2 diabetes (79,80,94–96). Polygenic traits are the result of gene variants that represent one end of the bell-shaped normal distribution curve of continuous variation in a population (97). From an evolutionary perspective, women with PCOS may represent the “metabolic elite” end of the normal distribution curve, being able to efficiently store energy in periods of food abundance and down-regulate fertility in times of food scarcity, or even in anticipation of reduced seasonal food availability as a predictive adaptive response (16,17,60).

The realisation that PCOS is a quantitative trait (phenotype determined by multiple genes and environmental factors) has far-reaching implications for the diagnosis, treatment and prevention of symptoms and pathology associated with PCOS. The implications require a shift in thinking about PCOS as a “disease” to a variation of normal metabolic and reproductive function. This shift invites a change in vocabulary from talking about “disorder” and “risk” to talking about “expression” and “variability” (97). This new understanding supports and reinforces an evolutionary model of the pathogenesis of PCOS. In keeping with this model, multiple lines of evidence suggest that inherited PCOS gene variants are developmentally programmed in a way that primes them for activation by nutritional and environmental factors in postnatal life (41,42,98).

3.3. Developmental epigenetic programming

The developmental programming of PCOS represents changes in gene expression that occur during critical periods of fetal development (99). Following fertilisation, most

parental epigenetic programming is erased and dramatic epigenomic reprogramming occurs (100). This results in transformation of the parental epigenome to the zygote epigenome and determines personalised gene function. Compelling evidence shows that a wide range of maternal, nutritional and environmental factors can effect fetal development during these critical periods of programming (44,98,99,101,102). These include hormones, vitamins, diet-derived metabolites and environmental chemicals (48,98,103,104). In addition, epigenetic reprogramming of germ-line cells can lead to transgenerational inheritance resulting in phenotypic variation or pathology in the absence of continued direct exposure (98).

Experimental studies in primates, sheep, rats and mice show that PCOS-like syndromes can be induced by a range of treatments including androgens, anti-Mullerian hormone and letrozole (19,44,46). Nevertheless, there is significant debate regarding when an animal model qualifies as PCOS-like (105). The model used and the method of induction of PCOS phenotypes therefore needs to be carefully scrutinised when generalising findings from animal research to women with PCOS. The vast majority of animal and human research on the developmental origins of PCOS has focussed on the role of prenatal androgen exposure. This has been extensively reviewed in numerous previous publications (41,46). This research has resulted in a proposed “two hit” hypothesis for the development of PCOS phenotypes (43,45). The “first hit” involves developmental programming of inherited susceptibility genes and the “second hit” arises due to lifestyle and environmental influences in childhood, adolescence and adulthood (41,106).

If PCOS is a quantitative trait involving normal gene variants, as suggested by the evolutionary considerations and findings from genetic research, then the “first hit” may result from normal developmental programming events as occurs with other gene variants (102). According to this hypothesis, the polygenic susceptibility genes would be normally “activated” and “primed” to respond to future maternal and environmental conditions and exposures, as would be the case with many other normal genes (28). In addition, the susceptibility alleles may be “activated” or “functionally enhanced” by a range of maternal and environmental factors, as is usually presumed to be the case in PCOS (5,14,102). This developmental plasticity would provide a mechanism for a predictive adaptive response, based on inputs from the maternal environment that could be used to programme metabolic and reproductive survival pathways, to better prepare the offspring for the future world in which they may be expected to live (107).

Parental lifestyle factors including diet, obesity, smoking and endocrine disrupting chemicals, have all been shown to modulate disease risk later in life (104,108,109). The original description of the fetal origin’s hypothesis proposed that poor maternal nutrition would increase fetal susceptibility to the effects of a Western-style diet later in life (49). Subsequent studies have confirmed that maternal exposure to either nutrient excess or deficit, can have long-term consequences for the health of the progeny (104). Evidence from human and animal studies suggests that maternal obesity programs the offspring for increased risk of developing obesity, hyperglycaemia, diabetes, hypertension and metabolic syndrome (108).

The developmental origins of PCOS may have been due to different factors in ancestral and modern populations (17,60). It has been hypothesised that environmental stress, infection, nutrient deprivation, fetal growth restriction and stress hormone responses may have resulted in maternally-mediated modulation of gene expression in ancestral offspring (17,110). Some of these factors have been investigated and confirmed in modern populations subject to starvation and extreme environmental conditions (111). In contrast, altered fetal programming in modern societies may be secondary to maternal overnutrition, sedentary behaviour, obesity, emotional stress, circadian rhythm disruption, poor gut health or environmental chemical exposure (35,101,112,113). The preconception and pregnancy periods therefore provide a unique opportunity for lifestyle interventions that promote optimal future health for both the mother and the offspring (figure 2).

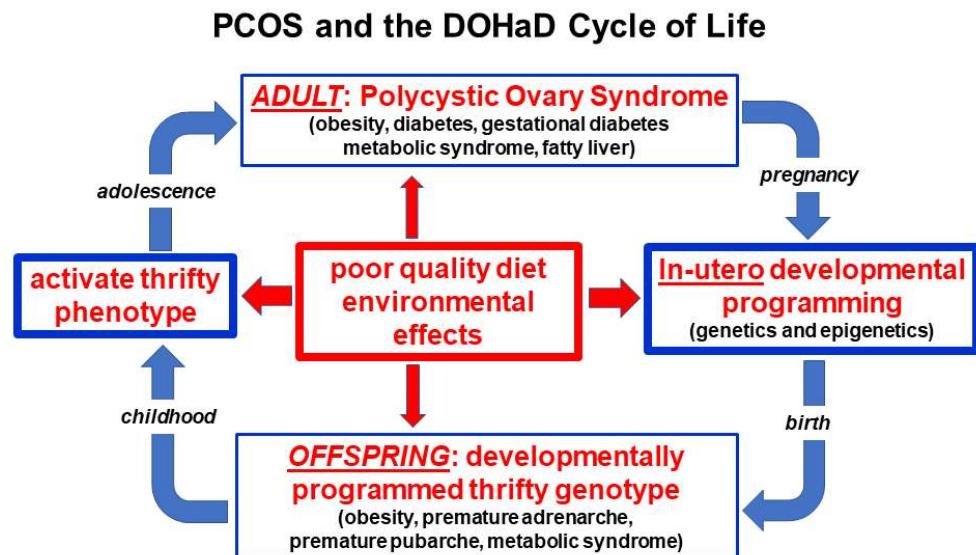


Figure 2. Nutritional and environmental influences throughout the life course and the perpetuation of the transgenerational inheritance of polycystic ovary syndrome

3.4. Microbiome and Dysbiosis

The gastrointestinal microbiome is now appreciated to play a central role in human health and disease (114,115). The microbiome is known to co-regulate many physiological functions involving the immune, neuroendocrine and metabolic systems via complex reciprocal feedback mechanisms that operate between the microbial ecosystem and the host (116,117). Evidence from studies in Western populations, Hunter-gatherer societies and phylogenetic studies in other species, have attempted to place the human microbiome into an evolutionary context (118). Although microbes clearly impact host physiology and have changed along branches of the evolutionary tree, there is ongoing debate regarding whether the microbiome can evolve according to the usual evolutionary forces (119,120). Nevertheless, it has been argued that focusing on functional pathways and metabolic roles of microbial communities, rather than on specific microbes, provides a better model for

understanding evolutionary fitness (118). The co-evolution of the microbiome and human physiology may therefore be important in understanding the differences between ancient adaptive physiological survival mechanisms and modern lifestyle-related pathological responses, in women with PCOS (figure 1).

Twin studies and GWAS show that host genetics can influence the microbiome composition, and microbes can exert effects on the host genome, although the environment has an important role (121,122). Humans are constantly adapting to the gut microbiome to try to determine which microorganisms are beneficial or harmful. Immune genes involved in this process are the most rapidly evolving protein-encoding genes in the mammalian genome (123,124). Diversification of microbes allows humans to access dietary niches and nutritional components they otherwise wouldn't be able to access, which may be beneficial and ultimately lead to the integration of specific microbes into the ecosystem (125). Although no living population today carries an ancestral microbiome, comparison studies of non-Western and Western populations show significant differences in the relative abundances of common phyla and a much greater species diversity in non-Western populations (126,127). A review of non-human primate and human gut microbiome datasets, revealed a changing microbiome in response to host habitat, season and diet, although there appear to be common species-specific symbiotic communities (118).

Rapid human cultural changes have resulted in significant dietary modifications in urban-industrialised communities and shifted the microbiome at an unprecedented rate. The result has been the development of a mismatch between human metabolic genes and bacteria that enhance fat storage (128). In our evolutionary past, when nutrients were scarce, it has been theorized that host selection led to the maintenance of microbes that enhance nutrient uptake or host energy storage. However, in the modern environment where a high fat, high sugar, low fibre diet has become common and easily accessible, integration of these microbes leads to maladaptive physiological responses (40). For metabolically thrifty individuals with PCOS, harbouring microbes that enhance energy storage escalates the evolutionary conflict, furthering the development of insulin resistance and thereby progression to obesity and type 2 diabetes (12,129). Further compounding this maladaptive response is the loss of microbes that are required to access other dietary niches. One example is the loss of symbiotic species of *Treponema* in individuals living in urban-industrialised communities (130). A change from the ancestral hunter-gatherer diet, where foods consumed changed seasonally and a wide variety of food components were eaten, to a diet that is similar across seasons and significantly less varied, is another likely contributor to reduced diversity of the microbiomes of individuals living in urbanised-industrialised communities (131).

The majority of women with PCOS are overweight or obese and evidence indicates that the microbiome of obese individuals is capable of extracting more energy from the host diet compared with the microbiome of lean individuals (132). This is thought to be driven by an expansion in pro-inflammatory species of bacteria, such as *E. coli*, and a depletion of anti-inflammatory bacteria such as *Faecalibacterium prausnitzii* (133,134).

Chronic low-grade ‘metabolic’ inflammation, or meta-inflammation, is a result of an imbalanced gut microbiome that promotes the development of insulin resistance and type 2 diabetes (135–137).

The dysbiosis of gut microbiota theory of PCOS, proposed by Tremellen in 2012, accounts for the development of all of the components of PCOS (multiple ovarian follicles, anovulation or menstrual irregularity and hyperandrogenism) (40). The theory proposes that a poor-quality diet and resulting imbalanced microbiome, induces intestinal permeability and endotoxaemia, exacerbating hyperinsulinaemia. Increased insulin levels promotes higher androgen production by the ovaries and disrupts normal follicle development. Metabolic, endocrine and environmental factors associated with PCOS are not mutually exclusive, and therefore their relative contributions to dysbiosis in PCOS remains uncertain (138). Consuming a balanced diet that is low in fat and high in fibre, can also restore balance to the ecosystem (termed eubiosis) (50). A recent study showed that dietary intake of fibre and vitamin D was significantly decreased in both lean and obese women with PCOS, compared to healthy controls, and correlated with lower diversity of the gut microbiome (139). Dysbiosis is reversible with improvement in diet quality augmented by the addition of probiotics or synbiotics (51,56–58).

Dysbiosis is a consistent finding when looking at the microbiome of women with PCOS (140–143). Although most studies are small, dysbiosis has consistently been found to correlate with different physiological parameters, such as obesity, sex hormones and metabolic defects (140,141,143). Similar to microbiomes associated with obesity, the microbiomes of individuals with PCOS have generally been found to have lower alpha diversity (lower numbers of bacterial taxa) than controls, and most studies describe an altered composition of taxa relative to controls (140,143). However, the bacterial taxa observed to be either increased, depleted or absent in PCOS differs from study to study. This is likely due to both the immense inter-individual variation in microbiotas, as well the fact that PCOS is a quantitative trait with women having various degrees and levels of obesity and sex hormones.

In keeping with the developmental origins hypothesis previously discussed, maternal androgens may alter the composition and function of the microbiome, thereby facilitating the pathogenesis of PCOS (140). One study showed that beta diversity, which is used to measure differences between groups, was negatively correlated with hyperandrogenism, suggesting that androgens play a significant role in dysbiosis (140). The ‘first hit’ in utero may therefore combine with vertical transmission of a dysbiotic microbiome from a mother with PCOS, resulting in dysbiosis in the offspring. Preconception and pregnancy provide a unique opportunities for lifestyle and dietary interventions aimed at restoring eubiosis, to enable the transference of a balanced ecosystem to the offspring, via vertical transmission (118).

The accumulating scientific evidence strongly supports the significant role played by the microbiome in the pathogenesis and maintenance of PCOS, consistent with research in other related metabolic conditions. Dysbiosis is a significant factor in the pathogenesis of PCOS and an important component of a unified evolutionary model. Dysbiosis represents

a maladaptive response of the microbiome to modern lifestyle influences and is a modifiable factor in the treatment of women with PCOS.

3.5. *Insulin Resistance*

There are a number of dilemmas when assessing the role of IR in women with PCOS. There is no consensus on the definition of IR (144,145), measurement is difficult (146,147), whole-body IR is usually measured although it is recognized that IR can be selective being either tissue-specific or pathway-specific within cells (148–150), normal values are categorical and determined by arbitrary cut-offs (4.45 mg/kg/min) (144), testing is not recommended in clinical practice (38), reported prevalence rates in obese and lean women vary widely (146,151), and the significance of IR as a pathognomonic component of PCOS is an area of debate (152–154).

Despite these limitations, it is hypothesised that IR is a significant proximate cause of PCOS and is intrinsic to the underlying pathophysiology (44,155). In addition, it is recognized that IR plays a major role in the pathophysiology of all of the metabolic diseases, cardiovascular disease, some neurodegenerative diseases, and selected cancers (22,156). Insulin resistance is therefore considered to be the main driver for many diseases and makes a significant contribution to the chronic disease epidemic (157). Nevertheless, being able to vary the sensitivity and physiological action of insulin is thought to have conferred a significant adaptive survival role in many animals throughout evolutionary history (145,158). It has been proposed that IR may have evolved as a switch in reproductive and metabolic strategies, since the development of IR can result in anovulation and reduced fertility, in addition to differential energy repartitioning to specific tissues (158).

Insulin receptors are located on the cell membranes of most tissues in the body (159). Ligand binding to the alpha-subunit induces autophosphorylation of specific tyrosine residues on the cytoplasmic side of the membrane (159,160). The activated insulin receptor initiates signal transduction via the phosphatidylinositol-3 kinase (PI-3K) metabolic pathway and the mitogen-activated protein kinase pathway (MAPK) which is involved in cell growth and proliferation (160). Insulin is an anabolic hormone that facilitates glucose removal from the blood, enhances fat storage and inhibits lipolysis in adipose tissue, stimulates glycogen synthesis in muscle and liver and inhibits hepatic glucose output (160). IR can be defined as a state where higher circulating insulin levels are necessary to achieve an integrated glucose-lowering response (145). IR results from alterations to cellular membrane insulin-receptor function or intracellular signaling, enzyme, metabolic or gene function (145,159,160).

Insulin resistance can be caused by a wide variety of mechanisms that have the ability to disrupt any part of this metabolic signaling system (53,160). These include autoantibodies, receptor agonists and antagonists, hormones, inflammatory cytokines, oxidative stress, nutrient sensors and metabolic intermediates (159–162). Physiological regulation of insulin function can be viewed as an adaptive mechanism to regulate the metabolic pathway of insulin signaling (PI-3K), in response to changing environmental conditions (starvation, fear, stress) (163,164) or during normal alterations of internal states (pregnancy, lactation, adolescence) (65,145,151).

The physiological activation of IR allows the organism to switch from an anabolic energy storage state to a catabolic or energy mobilizing state. This allows free fatty acids to be mobilized from adipose tissue, which are then converted to glucose in the liver and released into the circulation (160). As a result of this metabolic change, blood sugar levels are maintained for vital metabolic processes and brain function (14). This adaptive protective mechanism can be pathway specific during periods of growth, such as pregnancy, lactation and adolescence, so that only the metabolic signaling (PI-3K) is inhibited and not the mitogenic pathway (MAPK), which may even be upregulated (30,65,159).

When the physiology of insulin function is considered as a quantitative or continuous variable from an evolutionary perspective, it is likely that all women with PCOS, whether obese or lean, have reduced insulin sensitivity (151,154,165). A systematic review and meta-analysis of euglycemic-hyperinsulinaemic clamp studies found that women with PCOS have a 27% reduction in insulin sensitivity compared to body mass index (BMI) and age-matched controls (154). In evolutionary terms, women with a PCOS metabolic phenotype would have increased survival chances during times of environmental or physiological demand for altered energy metabolism, but be more vulnerable to the pathological effects of IR when exposed to modern lifestyle factors (14,17,158). In particular, a poor-quality, high glycaemic, high fat, low fibre diet has been shown to cause IR (40,166). As discussed in the dysbiosis section, diet-related changes in the gastrointestinal microbiome have also been shown to cause IR in women with PCOS (53,55). Numerous studies have shown that dietary modification (167–169), or treatment with probiotics or synbiotics, has the potential to restore normal insulin function (57,170).

Consumption of a high glycaemic load diet results in rapid increases in blood sugar levels that cause compensatory hyperinsulinaemia (166,171). Excessive dietary intake of glucose and fructose are converted to fatty acids by de novo lipogenesis in the liver, transported to adipocytes via lipoproteins, released as fatty acids to adipocytes and stored in fat globules as triglycerides (160). As a result of nutrient overload, diacylglycerol, the penultimate molecule in the synthesis of triglyceride, accumulates in the cytoplasm and binds with the threonine amino acid in the 1160 position of the insulin receptor. This inhibits autophosphorylation and down-regulates the metabolic PI-3K pathway and causes IR (160). This process has the potential to be reversible following changes in diet quantity and quality, as has been shown to occur with calorie restriction, fasting, time-restricted eating, gastric bypass surgery, low saturated fat and low glycaemic diets (167,169,172). Diets high in animal protein or saturated fat can also cause IR independent of BMI (173,174). These mechanisms provide the rationale for the principal recommendation of the International Guidelines, that women with PCOS should be advised about dietary modification as the first-line of management in all symptom presentations (38).

3.6. Obesity and the lean PCOS paradox

Insight can be obtained into the role of obesity in women with PCOS by examining the evolutionary history, genetic studies and pathological disorders of adipose tissue

(150,175,176). The ability to store energy is a basic function of life beginning with unicellular organisms (175). In multicellular organisms, from yeast to humans, the largest source of stored energy is as triglycerides in lipid droplets in order to provide energy during periods when energy demands exceed caloric intake (175). Understanding the biological functions of adipose tissue has progressed from energy storage and thermal insulation to that of a complex endocrine organ with immune and inflammatory effects and important reproductive and metabolic implications (175,177).

Adipose tissue is organized into brown adipose tissue (BAT) and white adipose tissue (WAT), both with different functions (177). While the evolutionary origins of BAT and WAT are the subject of ongoing debate (175), BAT is located in the supraclavicular and thoracic prevertebral areas and is primarily involved in cold thermogenesis and regulation of basal metabolic rate (178). WAT is distributed in multiple anatomical areas such as visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) and functions as a fat storage depot and an endocrine organ (177,178). An additional layer of SAT is thought to have evolved as insulation against cool night temperatures in the Pleistocene open Savanah (179). The lower body distribution of SAT in women is hypothesised to have evolved to provide additional calorie storage for pregnancy and lactation and is unique to human females (14). Lower body SAT has a metabolic programme that makes it less readily available for every-day energy needs, but it can be mobilized during pregnancy and lactation (14). In addition, excess accumulation of SAT is much less likely to cause IR and metabolic dysfunction and explains why IR is not observed in all obese individuals (150,180). Visceral WAT is associated with IR in women with PCOS leading to both metabolic and reproductive problems (181).

Multiple lines of evidence from evolutionary history, genetic and twin studies, support a genetic basis for obesity and differences in obese and lean phenotypes in women with PCOS (182–185). The majority of women with PCOS are overweight or obese, with reports ranging from 38–88% (151,185). Studies comparing obese and lean women with PCOS have a number of methodological problems including small sample size, overlap of PCOS characteristics with normal pubertal changes, non-standardized diagnostic criteria, and limited generalizability to the entire population due to a focus on a specific ethnic group (165,181). In addition, most of the studies examining body composition in PCOS have relied on anthropomorphic measurements (BMI, waist circumference, waist-to-hip ratio) which are considered inaccurate compared with the current gold-standard of magnetic resonance imaging (181). Consequently, there is wide heterogeneity in reports examining the relationship between body composition measures, including extent of VAT and metabolic changes such as IR (185).

In humans, there is large individual variation in the fat storage capability and expandability of different adipose tissue depots (150). It has been hypothesised that once the genetically determined limit of expandability of SAT is reached, there is expansion of VAT and excess lipid accumulation in muscle, liver and other organs, resulting in IR, inflammation and metabolic dysregulation (150). We hypothesize that lean women with PCOS have a genetically determined limited ability to store excess lipid in SAT, but

develop increased lipid deposition in VAT and organs such as the liver, resulting in metabolic dysregulation and IR in a similar manner to what occurs in obese women with PCOS. The wide variation in the genetic limitation of SAT expansion is also supported by studies in individuals with lipodystrophy.

Lipodystrophies are a heterogenous group of rare inherited and acquired disorders characterized by a selective loss of adipose tissue (176,186). They are classified on the basis of the extent of fat loss as generalized, partial or localized (186). Patients with congenital generalised lipodystrophy have a generalized deficiency of fat from birth, usually have severe IR and develop diabetes at puberty. As a consequence of genetically limited ability for SCT lipid storage, lipids can only be stored ectopically in non-adipocytes resulting in major health consequences including IR, fatty liver, diabetes and PCOS (187). In contrast to generalised lipodystrophy, patients with familial partial lipodystrophy have normal fat distribution at birth but loose SAT in the limbs, buttocks and hips, at puberty. Fifty percent of women develop diabetes and 20-35% develop irregular periods and polycystic ovaries (176) . Despite the rare nature of these syndromes much has been learned about the underlying genetic variants involved (186).

Elucidation of clinical subtypes and the genetic background of patients with lipodystrophies may pave the way to new insights into the role of fat partitioning and obesity, and has implications for understanding the pathogenesis of insulin resistance, diabetes and PCOS (176). Lean women with PCOS may have a genetic predisposition for limited SCT fat storage, coupled with underlying metabolic predispositions, that result in deposition of excess lipid in VAT and liver and the observed metabolic features of IR, fatty liver and diabetes. If the extent of IR and ectopic fat deposition is excessive, the resulting hormonal changes may be sufficient to cause oligomenorrhoea and sub-fertility as occurs with secondary familial partial lipodystrophy type 2 (187,188). If this underlying mechanism is confirmed in future studies, the main difference between women with lean or obese PCOS may be the combined effects of metabolic programming and the genetically-determined extent of SCT fat deposition. This would explain why lean women have all the same clinical, biochemical and endocrine features, although possibly less severe, than overweight and obese women with PCOS (185).

3.7. Environmental chemical exposure

Anthropomorphic chemical exposure is ubiquitous in the environment and has possible effects on many aspects related to women's health (36,189–191). Historically, many environmental chemicals have resulted in large-scale health disasters in human populations including diethylstilbestrol (DES), dichlorodiphenyltrichloroethane (DDT), asbestos, lead, mercury and nicotine (191). There over 191 million organic and inorganic chemicals registered on the Chemical Abstract Service Registry (192). Detailed analysis of risks is extremely limited and regulation relies on animal toxicology, in-vitro assays, and epidemiological studies that retrospectively examine adverse effects after population exposure (193,194). More recently, toxogenetic testing of chemical-gene interactions have been employed to identify molecular pathways involved in causing toxicity (193). These

studies have concluded that the majority of endocrine and metabolic pathways are sensitive to the effects of environmental chemicals (193).

The identification of more than 1000 EDC in food, air, water, pesticides, plastics, personal care products, and other consumer goods, raises specific concerns for pregnant women and women with increased susceptibility to metabolic diseases like PCOS (36,171,191,195,196). Endocrine disrupting chemicals may be involved in the pathogenesis of PCOS given their known and potential hormonal and metabolic effects (36,189,197). This includes many of the areas that have been considered in the unified evolutionary model, such as developmental epigenetic programming, microbiome composition and function, metabolic processes such IR, and regulation of body weight.

3.7.1. EDC and DOHaD

Many observational studies have demonstrated the presence of EDC in maternal and fetal serum and urine, amniotic fluid, cord blood and breast milk (198–200). Six classes of EDC have been shown to cross the placenta confirming that the fetus is exposed at all stages of development (109,198). Although it is impossible to perform experimental studies in humans, evidence from epidemiological, molecular toxicology and animal studies provide compelling evidence of adverse developmental effects and transgenerational toxicity (171,189,191,201,202). The realisation of the tragic effects of DES in the 1970's was first example of an in-utero exposure causing serious transgenerational health effects (191). This was followed by increasing interest in identifying the properties of environmental oestrogens (36).

Several oestrogenic EDC have been associated with birth outcomes that are thought to be associated with the development of PCOS (189). These include decreased birthweight (perfluoroalkyl substances [PFAS], perfluorooctanoic acid) and preterm birth (di-2-ethylhexyl phthalate) (201). Prenatal exposure to androgenic EDC (triclosan, glyphosate, tributyltin, nicotine) is of increasing concern, given the suspected epigenetic role of in-utero androgen exposure in the pathogenesis of PCOS (48,203,204). EDC can act at any stage of the human lifespan, including preconception and prenatally, and are increasingly becoming a priority in PCOS research (205).

3.7.2. EDC and the microbiome

As discussed above, the microbiome is increasingly considered to make a significant contribution to many human diseases, including PCOS (40,206). EDC that disrupts the composition or function of the microbiome have been termed "microbiota disrupting chemicals" (207). In turn, any disruption of the microbiome from EDC can impact crucial metabolic and endocrine physiology and homeostasis (36,208). A number of studies have reviewed the effect of EDC in invertebrate and vertebrate species, animal models and humans. These studies have found that BPA, phthalates, artificial sweeteners, heavy metals, fungicides, pesticides and microplastics can all affect the gut microbiome, and have metabolic and obesogenic effects (202,209,210). They have concluded that EDC exert their effects in a variety of species via a range of mechanisms, including modification of

epigenetic, cell signalling and metabolomic pathways, in addition to their effects on the microbiome.

Human exposure to the herbicide glyphosate, through diet and drinking water, has also been reported to alter gut microbial communities (211). Glyphosate-mediated inhibition of 5-enolpyruvylshikimate-3-phosphate synthase in intestinal microbiota has been shown to alter composition and enrich potentially pathogenic bacteria (212–214). In addition, microbiota exposure to glyphosate has been shown to alter mucosal-associated T-cells and promote a pro-inflammatory immune response (211). Taken together, EDC have been found to alter microbial composition and diversity (207,213), disrupt gastrointestinal barrier integrity (202,215), increase systemic endotoxin levels and inflammatory cytokines (216,217), alter the production of metabolites and influence metabolomic patterns (210), all of which have been proposed to be involved in the pathogenesis of PCOS (40).

3.7.3. EDC, insulin resistance and diabetes

Kahn et al reviewed six cohort studies and 2 case-control studies that raise concerns about exposure to PFAS in pregnancy and increased risk of impaired glucose tolerance and gestational diabetes in different ethnic groups (189). They also identified 4 studies showing similar increased risk with phthalate exposure during pregnancy, and one study that did not identify an association with gestational diabetes. Animal studies have found that some EDC target alpha and beta cells in the pancreas, adipose cells and hepatocytes, and contribute to insulin resistance (218). As a result of these and many other concerning studies the Endocrine Society issued a scientific statement cautioning that emerging evidence ties EDC exposure to two of the biggest public health threats facing society, diabetes and obesity (219,220).

3.7.4. EDC and obesity

A large number of EDC are now classified as “obesogens” due to their suspected role in promoting weight-gain and contributing to the global rise in obesity (202,203,221). So far, about 50 obesogens have been recognized including tributyltin, parabins, DDT, cadmium, persistent organic pollutants and many others (202,222,223). Three of the most studied compounds are BPA, phthalates and PFAS (200,201,221). Evidence from multiple birth cohort studies have shown an association between prenatal exposure to PFAS and childhood obesity (200,201). A number of reports have suggested that exposure to PFAS and phthalates also contribute to weight gain in adults (224). Two trials have identified an association between weight gain (Diabetes Prevention Trial Program Lifestyle Trial) (225) and reduced resting metabolic rate (the POUNDS Lost trial) (226), with serum PFAS concentrations. In recognition of the suspected significant risk, the International Federation of Obstetrics and Gynecology (FIGO) recommended a full global phase out of PFAS (227).

3.7.5. EDC and PCOS

A large number of cross-sectional studies have identified associations between EDC and PCOS, including PFAS, phthalates, bisphenol-A, triclosan and nicotine (196,208,228,229). Experimental animal studies have shown that exposure to androgenic EDC in pregnancy can result in significantly increased androgen levels in female offspring (36,48). Other androgenic EDC have been found to alter surrogate markers of developmental programming, such as anogenital distance (224). Although there are no specific toxicogenetic studies in women with PCOS, many EDC have been found to activate signalling pathways thought to be involved in the pathogenesis of PCOS (193,208). Taken together, the available evidence suggests EDC are likely to have a role in the pathogenesis of PCOS.

3.7.6. EDC recommendations

There is a significant global imperative to implement a multifaceted global programme to address the effects of EDC on human health using a hazard-based approach in preference to the current risk-based regulatory framework (230). As a result, implementation of the precautionary principle is a high priority in counselling women with PCOS (231). International professional bodies (The Royal College of Obstetricians and Gynaecologists, Endocrine Society, FIGO) have recommended that all pregnant women should be advised of the possible risks of EDC and that education programmes be developed to inform health professionals (220,232,233). An explanation of the pathogenesis of PCOS (discussed below), should include reference to environmental chemical exposure and open the way for more detailed discussion of specific personalised advice and lifestyle recommendations.

3.8. *Lifestyle Contributors to the Pathogenesis of PCOS*

It has been recognized that a variety of lifestyle factors contribute to the pathogenesis of PCOS for many decades (234,235). As a result, a number of lifestyle factors have been investigated for their role in the pathogenesis of PCOS. These include diet, exercise, stress, sleep disturbance and exposure to environmental chemicals (28,41,236). A large number of animal studies have provided experimental evidence supporting a causative role for many of these factors either individually, or in combination (44). Human research investigating causation is limited to observational and epidemiological studies, as many experimental protocols would be unethical. As a result, proving causation in humans will be extremely difficult. In addition, proving causation in evolutionary models also has a number of significant challenges (8,9,60). Nevertheless, developing a unified evolutionary model based on the large number of available human and animal studies may provide a useful evidenced-based framework for counselling women and informing future research.

Despite the limitations in proving causation, recent advances in genomics, epigenetics, metabolomics, nutrigenomics, evolutionary biology, computer technology and artificial intelligence, are providing many insights into the mechanisms of how lifestyle factors impact the pathogenesis of PCOS (9,90,235,237). We have attempted to integrate the research findings supporting an evolutionary model into the respective sections outlined

in this paper. It has not been our aim to comprehensively review all aspects of the role of lifestyle in the pathogenesis of PCOS. We have tried to highlight the evolutionary aspects of how diet in particular, may impact the pathogenesis of PCOS, as components of the human diet have effects on many areas of the proposed unified evolutionary model. A large body of evidence from studies in women with PCOS, and a range of other metabolic diseases, supports the view that a Western-style high glycaemic, high saturated fat, high calorie, low nutrient-dense, and low fibre diet that contains a high proportion of processed rather than whole food, contributes to the pathogenesis of PCOS (28,40,235). This is likely to be exacerbated by the additional adverse effects of multiple other lifestyle factors such as EDC, stress, circadian disruption and reduced physical activity.

The dysbiosis theory of the pathogenesis of PCOS highlights the role of a poor-quality diet in the pathogenesis of PCOS and is supported by over 30 proof-of-concept studies (40,238). International Guidelines for the assessment and management of PCOS recommend lifestyle management, with diet and exercise as first-line treatment for all women with PCOS, and provide a comprehensive review of the literature (7). Nutritional studies based on diet indices, diet composition and metabolomics have identified dietary components that contribute to a healthy eating pattern (51,237,239,240). Healthy diet patterns, or wholefood diets, have been found to be effective in controlling and reversing many of the symptoms and metabolic alterations associated with PCOS, and have also previously been reviewed (50). Two components of a healthy wholefood diet that appear to be important from an evolutionary perspective, in addition to the requirement for fundamental macronutrients (protein, fat and carbohydrate) and essential micronutrients (vitamins and minerals), are dietary fibre and polyphenols.

Throughout evolutionary history, humans have obtained nutrients from a wide variety of plant and animal food sources (241). These foods provided macronutrients, micronutrients and contingent nutrient factors that contain a range of bioactive components. Contingent nutrients include a variety of compounds that are not essential but may be beneficial to human health (242). Polyphenols are an important contingent nutrient, and comprise a large collection of plant-derived secondary metabolites that have been found to have beneficial biological and metabolic effects when consumed (243). Dietary polyphenols improve microbiota diversity and undergo extensive biotransformation by a variety of microbial species (244). It is estimated that less than 5% of ingested polyphenols reach the circulation intact (245). A large number of microbially-derived polyphenol metabolites can be detected in plasma compared with low levels of the parent compounds (246). Polyphenols have potent anti-inflammatory and antioxidant effects and are the most abundant antioxidant in the human diet (246). Not surprisingly, there has been significant interest in investigating the possible beneficial effects of polyphenols in PCOS, since the pathophysiology involves oxidative stress, chronic inflammation and alterations in the microbiome (247–250).

Polyphenol-rich foods have historically made up a considerable proportion of the dietary intake in many Hunter-gatherer societies and post-agricultural communities, and until recently, in Western nations (251–253). Polyphenols are present in fruits, vegetables,

legumes, nuts, and whole grains, as well as plant-derived foods and drinks like green tea, red wine, and chocolate (50). Women with PCOS have been noted to consume diets lower in polyphenol-containing foods (236). Consumption of polyphenols and polyphenol-rich foods and drinks have been found to improve a number of important outcome measures in women with PCOS, such as body weight, metabolic abnormalities, and serum androgen levels (50). Some polyphenols can act as selective oestrogen receptor modulators and may provide unique benefits to women with PCOS due to estrogen-related effects (254). Polyphenols are therefore an important part of a healthy diet and have been investigated for their potential role in the pathogenesis of PCOS (50). A healthy wholefood diet contains a wide variety of polyphenols coupled with the necessary dietary fibre required for optimal microbiome and metabolic function.

As previously discussed, the modern Western diet and lifestyle is at odds with our evolutionary background. In general, our traditional hunter-gatherer ancestors consumed significantly more fibre than modern populations. Studies that have investigated the dietary patterns of remaining contemporary Hunter-gatherer societies, have found their dietary fibre intake to be around 80-150 grams per day (255). This contrasts with the contemporary Western diet, where the average fibre intake is 18.2 grams per day in children and 20.7 grams per day in adults (256). Adequate dietary fibre consumption is important as it has a number of benefits, such as improved insulin sensitivity, reduced blood glucose levels, decreased systemic inflammation, lower serum levels of androgens and LPS, all of which have been linked to the pathogenesis of PCOS (257-260).

Recent systematic reviews of observational studies and randomized controlled trials have found dietary fibre consumption to be inversely related to risk of obesity, type 2 diabetes, and cardiovascular disease (261,262). A recent cohort study from Canada found that obese women with PCOS consumed significantly less dietary fibre than normal weight women without PCOS (263). In addition, fibre intake of women with PCOS was negatively correlated with IR, fasting insulin, glucose tolerance and serum androgens (263). Hence, the mismatch between the amount of fibre traditionally consumed and the fibre content of Western diets, may be an important dietary component contributing to the increased rates of PCOS seen in developed and developing nations.

The current low level of fibre consumption in Western nations also contributes to a lack of microbial diversity in the microbiota. The amount and variety of fibre in the diet is one of the main determinants of ecosystem diversity (264). Lack of microbial diversity has been associated with obesity, IR, and systemic inflammation (136,265,266). As previously discussed, low diversity is one of the key microbiota patterns observed in women with PCOS, and has been positively associated with hyperandrogenism, total testosterone levels, and hirsutism in this population (267). Conversely, ecosystem diversity and richness are hallmarks of Hunter-gatherer microbiotas who consume a high-fibre, more diverse plant-based diet (255,268). A shift towards a more wholefood diet therefore provides a variety of phytonutrients, polyphenols and fibre, in addition to the other essential macronutrients and micronutrients, and is likely to make a significant difference to metabolic and symptomatic outcomes in women with PCOS.

Although discussion of specific details related to lifestyle counselling are beyond the scope of this review, it is clear that improving outcomes in PCOS will require a multifaceted population-based approach that includes public health measures (269,270), improved compliance-aiding strategies, inclusion of nutrition training in medical education (271), implementation of current best-practice management strategies, and further development of the International Guidelines for the Assessment and Management of PCOS (7).

3.9. Conceptual framework of the unified evolutionary theory

Comprehensive International Guidelines have made 166 recommendations for the assessment and management of PCOS (38). We believe the current unified evolutionary theory of the pathogenesis of PCOS provides a conceptual framework that may help practitioners and patients understand the development of PCOS symptoms and pathology in the context of our modern lifestyle and environment. It will hopefully contribute to improved communication, result in improved feelings of empowerment over the personal manifestations of PCOS, improve compliance, reduce morbidity, increase quality of life and inform future research (figure 3).

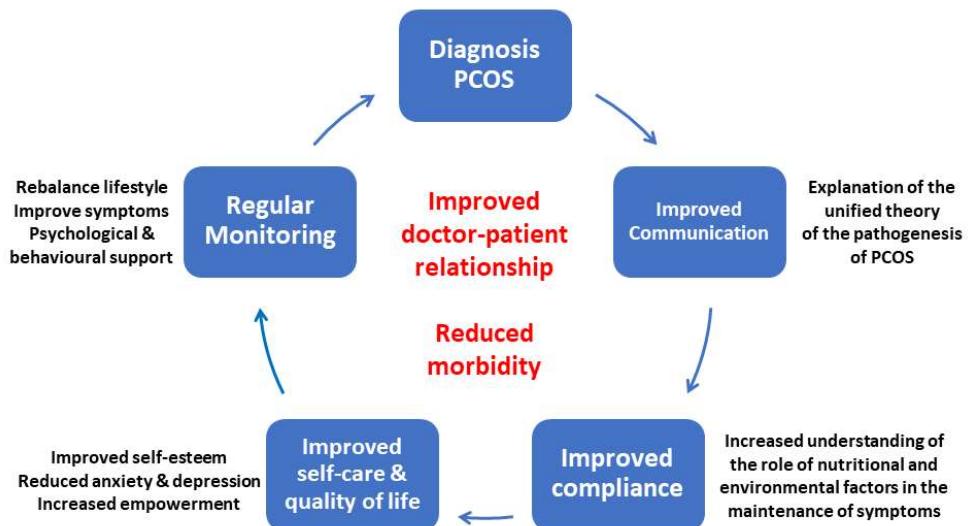


Figure 3. Impact of the unified theory on the management of polycystic ovary syndrome

3.10. Explanation to Women Diagnosed with PCOS

"Polycystic ovary syndrome is a problem that is inherited from both of your parents. The inherited genes are activated by a range of dietary and environmental factors that can cause a number of symptoms. These include weight gain, irregular periods, acne, excess hair growth, hair loss, anxiety and depression. Women with PCOS are also at risk of developing a range of other problems throughout their lifetime if they are not adequately treated. These include gestational diabetes, type 2 diabetes, heart disease and fertility problems. All of these symptoms and problems can be treated, controlled and reversed with appropriate lifestyle changes. These include a healthy

diet, exercise, avoiding environmental chemicals, stress management techniques, sleep and support from friends, family and health professionals. In addition, there are a range of medical and natural treatments that can also be used. Women with PCOS can have healthy, active lives with normal fertility”.

4. Conclusions

Substantial evidence and discussion support an evolutionary basis for the pathogenesis of polycystic ovary syndrome, although many of the mechanistic details are yet to be determined. Nevertheless, multiple lines of evidence from evolutionary theory, comparative biology, genetics, epigenetics, metabolism research, and cell biology, provide supportive evidence and hypothesis-generating data. The ability of animals to synchronize internal physiology, metabolism and reproductive function, with our changing external environment and habitat, are a necessary requirement for individual and species survival. The co-operative and sometimes competitive evolution of metabolism and reproduction provided adaptive survival mechanisms in ancestral environments that appear to be maladaptive in modern environments.

Lifestyle and environmental influences such as food abundance, altered food quality, chemical exposure, circadian disruption, chronic stress and sedentary behaviour, combine to redirect previously beneficial adaptations into adverse symptoms and disease. A unified evolutionary model provides a conceptual framework that considers the role of genetics, developmental programming, the microbiome, dysbiosis, environmental chemical exposure, metabolism, reproduction, and lifestyle factors that are involved in the initiation, treatment and prevention of PCOS. Mechanistic studies of the relative contributions of these and other ultimate and proximate causes are the subject of ongoing research and discussion. An evolutionary model therefore provides a framework to enhance practitioner and patient understanding, improve compliance with lifestyle interventions, reduce morbidity, improve quality of life and will evolve and change over time.

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Review

Polycystic Ovary Syndrome: An Evolutionary Adaptation to Lifestyle and the Environment

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Abstract: Polycystic ovary syndrome (PCOS) is increasingly recognized as a complex metabolic disorder that manifests in genetically susceptible women following a range of negative exposures to nutritional and environmental factors related to contemporary lifestyle. The hypothesis that PCOS phenotypes are derived from a mismatch between ancient genetic survival mechanisms and modern lifestyle practices is supported by a diversity of research findings. The proposed evolutionary model of the pathogenesis of PCOS incorporates evidence related to evolutionary theory, genetic studies, in utero developmental epigenetic programming, transgenerational inheritance, metabolic features including insulin resistance, obesity and the apparent paradox of lean phenotypes, reproductive effects and subfertility, the impact of the microbiome and dysbiosis, endocrine-disrupting chemical exposure, and the influence of lifestyle factors such as poor-quality diet and physical inactivity. Based on these premises, the diverse lines of research are synthesized into a composite evolutionary model of the pathogenesis of PCOS. It is hoped that this model will assist clinicians and patients to understand the importance of lifestyle interventions in the prevention and management of PCOS and provide a conceptual framework for future research. It is appreciated that this theory represents a synthesis of the current evidence and that it is expected to evolve and change over time.

Keywords: polycystic ovary syndrome; evolution; insulin resistance; infertility; toxins; endocrine-disrupting chemicals; environment; lifestyle; diet



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1. Introduction

Polycystic ovary syndrome is a reversible metabolic condition that makes a significant contribution to the global epidemic of lifestyle-related chronic disease [1–3]. Many of these chronic diseases share a similar pathogenesis involving the interaction of genetic and environmental factors [4–6]. The revised International Guidelines for the assessment and management of women with PCOS emphasize that the associated metabolic dysfunction and symptoms should initially be addressed via lifestyle interventions [7]. A unified evolutionary model proposes that PCOS represents a mismatch between our ancient biology and modern lifestyle.

Evolutionary medicine is an emerging discipline involving the study of evolutionary processes that relate to human traits and diseases and the incorporation of these findings into the practice of medicine [8]. Evolutionary medicine brings together interdisciplinary research to inform clinical medicine based on the influence of evolutionary history on human health and disease [9]. Previous utilization of the principles of evolutionary medicine has been limited to monogenetic diseases (cystic fibrosis, sickle cell anemia, phenylketonuria and many others), drug resistance of microorganisms, tumor growth and chemoresistance [8]. Future insights into the application of evolutionary research offers the potential

to improve and personalize the established medical and scientific approaches to complex chronic diseases such as type 2 diabetes, metabolic syndrome and PCOS [5,9].

The evolutionary origins of complex chronic diseases incorporate considerations of relative reproductive fitness, mismatch between our biological past and modern environment, trade-offs involving combinations of genetic traits, and evolutionary conflicts [8,10]. These evolutionary factors are relevant when analyzing the contributors to the pathogenesis of PCOS in modern and modernizing societies that result in a mismatch between our rapid cultural evolution with our slow biological evolution [11,12]. The unique cultural evolution of humans does not have a plausible analogue in most other species and is increasingly recognized to play a significant role in the pathogenesis of metabolic diseases such as PCOS [5,13–17].

Polycystic ovary syndrome is a complex multisystem condition with metabolic, endocrine, psychological, fertility and pregnancy-related implications at all stages of life [7,18]. The majority of women with PCOS manifest multiple metabolic features including obesity, insulin resistance (IR), hyperlipidemia and hyperandrogenism [19,20]. PCOS results in an increased risk of developing metabolic disease (type 2 diabetes, non-alcoholic fatty liver disease [NAFLD] and metabolic syndrome), cardiovascular disease, cancer, a wide array of pregnancy complications (deep venous thrombosis, pre-eclampsia, gestational diabetes [GDM], macrosomia, growth restriction, miscarriage, stillbirth and preterm labor) and psychological problems (anxiety, depression) [6,21–25]. PCOS is part of a cluster of inter-related metabolic conditions and makes a significant contribution to the chronic disease epidemic.

Extensive research suggests that the etiology of PCOS involves an interaction between environmental factors and gene variants, although it has been suggested that genetic factors contribute less than 10% to disease susceptibility [26–28]. A large number of genetic and genome-wide association studies (GWAS) have identified common gene loci associated with PCOS phenotypes in different ethnic populations [29–31]. These appear to be normal gene variants or polymorphisms, given the frequency and type of genes that have been identified. PCOS is therefore viewed as a polygenic trait that results from an interaction between susceptible genomic variants and the environment.

PCOS affects upward of 10% of reproductive-aged women, estimated at over 200 million women worldwide [32,33]. PCOS is thought to be increasing in incidence in both developing and developed nations as a result of lifestyle-related changes in diet quality, reduced physical activity, ubiquitous environmental endocrine-disrupting chemicals (EDC), altered light exposures, sleep disturbance, heightened levels of stress and other environmental factors [11,34–38]. These factors, and the high prevalence of PCOS, suggest that there could be an evolutionary basis for the syndrome [15,16,39]. Evolutionary medicine has changed the paradigm for understanding PCOS, acknowledging many of the contributing lifestyle and environmental factors that facilitate the observed metabolic and clinical features and that are also shared with related metabolic diseases [8]. These “mismatch disorders” are estimated to make a significant contribution to chronic disease in developed countries and a growing proportion of disability and death in developing nations [3]. According to the Global Burden of Disease Study, the human diet is now the leading risk factor for morbidity and mortality worldwide [3]. In keeping with these findings, diet is recognized as one of the major contributors to the growing prevalence of PCOS globally [7,40].

Dietary and environmental factors are hypothesized to have an impact on developmental programming of susceptible gene variants in women with PCOS [41–43]. Extensive experimental evidence suggests that prenatal androgen exposure may play a role in the pathogenesis of PCOS-like syndromes in animal models [19,44–46]. The discovery of naturally occurring PCOS phenotypes in non-human primates supports a survival advantage of a hyperandrogenic, insulin resistant phenotype with delayed fertility [47]. In humans, the origin of excess androgens may be from maternal, fetal or placental sources. In addition, emerging and concerning evidence suggests that EDC may contribute to altered fetal programming and play a role in the pathogenesis of PCOS [41,48].

In utero genomic programming of metabolic and endocrine pathways can increase the susceptibility of offspring to develop PCOS following exposure to specific nutritional and environmental conditions [45]. This view of the pathogenesis of PCOS is consistent with the Developmental Origins of Health and Disease (DOHaD) model proposed by Neel [49]. Postnatal exposure to lifestyle and environmental factors, such as poor-quality diet and EDC, may activate epigenetically programmed pathways that further promote the observed features of PCOS. Dietary and lifestyle interventions have demonstrated that many of the clinical, metabolic and endocrine features of PCOS can be reversed [7,50,51].

Lifestyle-induced changes in the gastrointestinal tract microbiome are another significant factor in the etiology of PCOS [52,53]. Dysbiosis of the gut microbiota has been hypothesized to play a role in increased gastrointestinal permeability, initiating chronic inflammation, insulin resistance (IR) and hyperandrogenism [40]. Numerous studies have reported reduced alpha diversity of the microbiome that has been associated with the metabolic, endocrine and clinical features observed in women with PCOS [54,55]. The resulting dysbiosis has been shown to be reversible after interventions aimed at improving diet quality or treatment with probiotics or synbiotics [50,51,56–58].

A unified evolutionary theory of the pathogenesis of PCOS proposes that ancient genetic polymorphisms that were aligned with the environment of that era, resulted in an adaptive survival advantage in offspring in ancestral populations [14–16,28]. When these same genetic variants are exposed to modern lifestyle and environmental influences, maladaptive physiological responses occur. The prior advantages of insulin resistance, hyperandrogenism, enhanced energy storage and reduced fertility in ancestral populations become pathological and result in the observed features of PCOS in contemporary women (Figure 1).

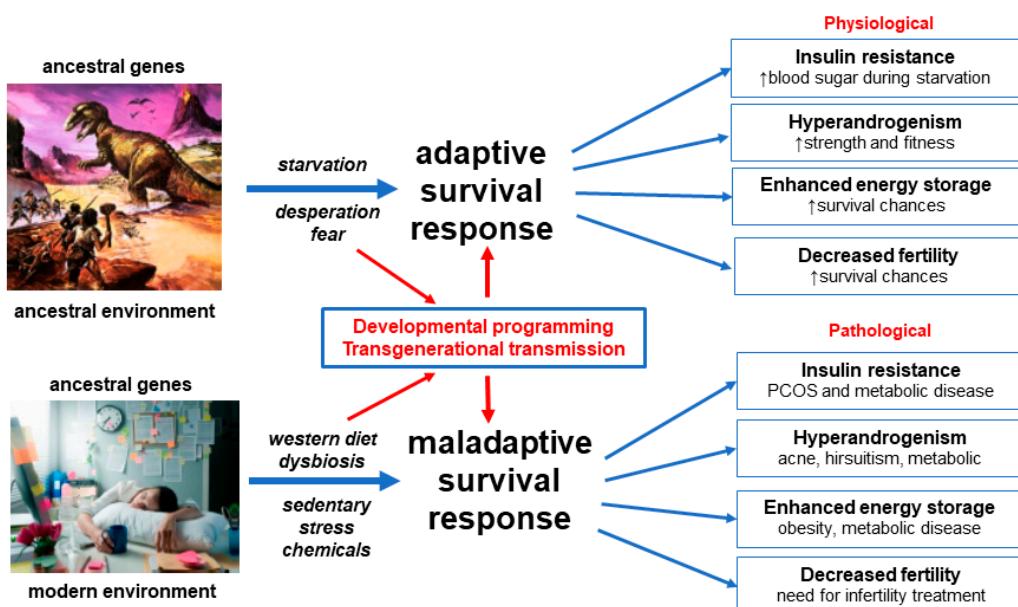


Figure 1. Evolutionary model of the pathogenesis of polycystic ovary syndrome. Adapted with permission from Ref. [12]. 2021 Journal of ACNEM.

2. Materials and Methods

The literature search focused on research publications related to the pathogenesis of PCOS using the keywords listed above and related mesh terms for data on the evolutionary aspects of PCOS, genetic studies, in utero developmental epigenetic programming, transgenerational inheritance, metabolic features including insulin resistance, obese and lean PCOS phenotypes, reproductive changes and subfertility, impact of the microbiome and dysbiosis, possible effects of endocrine-disrupting chemical exposure and the influence of lifestyle factors such as diet and physical activity. The databases searched included PubMed,

Scopus, Cochrane and Google Scholar. Relevant papers were selected, and citation searches were performed.

The present manuscript synthesizes the findings into a unified evolutionary model. The following text is presented as a narrative review of factors involved in the pathogenesis of PCOS and is discussed in ten main subject areas that provide the rationale for the development of a unified model. 1. Evolution 2. Genetics 3. Developmental Epigenetic Programming 4. Microbiome and Dysbiosis 5. Insulin resistance 6. Obesity and the lean paradox 7. Endocrine-Disrupting Chemical Exposure 8. Lifestyle contributors to the pathogenesis of PCOS 9. Circadian Rhythm Disruption and PCOS 10. Conceptual Framework and Summary of the Unified Evolutionary Model.

3. Pathogenesis of PCOS

3.1. Evolution

The description of PCOS phenotypes can be found in medical records from antiquity and the modern syndrome was described over 80 years ago [17,59]. Nevertheless, there is ongoing debate regarding the evolutionary origins of PCOS [15–17,39,60–64]. PCOS susceptibility alleles may have arisen in our phylogenetic ancestors, in the hunter-gatherer Paleolithic period of the Stone Age, after the Neolithic Agricultural Revolution or following the Industrial Revolution [16,17]. From an evolutionary perspective, nearly all genetic variants that influence disease risk have human-specific origins, but the systems they relate to have ancient roots in our evolutionary ancestors [8]. Regardless of the precise timing of the origin of PCOS in humans, the complex metabolic and reproductive gene variants identified in women with PCOS relate to ancient evolutionary-conserved metabolic and reproductive survival pathways [15,29]. Although evolutionary hypotheses about disease vulnerability are impossible to prove they have the potential to frame medical thinking and direct scientific research for the proximate causes of disease [15,60].

Multiple hypotheses have been proposed regarding the evolutionary origins of PCOS and related metabolic diseases [8,60,63]. These hypotheses are focused on the relative importance of metabolic survival adaptations versus improved reproductive success, or a combination of both. A detailed analysis of these hypotheses, and the complexities of the evolutionary considerations, have been reviewed elsewhere and is beyond the scope of the present review [8,60]. One common theme is that PCOS may be viewed as a “conditional phenotype” where a specific set of conditions has unmasked normally unexpressed or partly expressed genetic pathways, which then provide a survival advantage under certain environmental conditions [14,16].

All organisms have physiological adaptive responses to deal with changing environmental conditions (starvation, fasting, physical threat, stress and infection) and the varying demands of internal physiological states (pregnancy, lactation and adolescence) [14,65]. It has been proposed that the PCOS phenotype may have been invoked in specific environmental conditions in ancestral populations as a short, medium or even long-term adaptive survival mechanism [15–17]. The view of PCOS as a conditional phenotype proposes that these physiological responses become pathological in our modern environment due to factors such as food abundance, reduced physical activity, circadian disruption, stress and environmental chemical exposure. The transgenerational evolutionary theory of the pathogenesis of PCOS encompasses all of the above ideas to explain the observed pathophysiological and clinical features of PCOS [28].

It is generally accepted that almost all pre-industrial societies and animal populations experienced seasonal or unpredictable episodes of food shortage that applied evolutionary pressure to develop metabolic and reproductive adaptive survival responses [17,49]. It is also appreciated that metabolic and reproductive pathways are interconnected and involve reciprocal feedback control mechanisms [66–68]. During periods of starvation, anorexia or excessive weight gain, reproduction is down-regulated and ovulation becomes irregular or ceases [69,70]. Similarly, metabolic function is coordinated with the menstrual cycle to ensure optimal physiological conditions for fertilization, implantation, pregnancy,

parturition and lactation [71]. Recent research has elaborated on the details of how some of these complex regulatory mechanisms interact using specific hormonal, nutrient sensing and intracellular signaling networks [72–74].

Details of the mechanisms underlying the proposed adaptive survival advantages of IR, hyperandrogenism, enhanced energy storage and subfertility have been obtained from paleolithic records, animal models and human populations exposed to adverse environmental conditions such as war and famine-inflicted starvation [14,16,62,63]. Multiple lines of evidence support the maladaptive response of human populations to rapidly changing nutritional, physical, psychological and cultural environments, in the modern world [5,11,14,75]. These “adaptations” result in pathological responses to IR, hyperandrogenism, enhanced energy storage and ovulation (Figure 1).

Theories of evolutionary mismatch have also been advanced to explain all of the cluster of metabolic diseases associated with PCOS (type 2 diabetes, metabolic syndrome, NAFLD and cardiovascular disease) and follow the same set of basic principles and explanations [14,76]. This common body of evolutionary evidence is supported by the increasing incidence of metabolic-related disease, such as diabetes and obesity, in developed countries and in developing nations adopting a Western diet and lifestyle [11,77]. In addition, the demonstrated reversibility of PCOS and related metabolic and biochemical features following changes in diet, increased physical activity and other lifestyle interventions, adds further support to a transgenerational evolutionary model [50,51].

3.2. Genetics

The heritable nature of PCOS has been proposed since the 1960’s following a range of familial, twin and chromosomal studies [78–80]. Cytogenetic studies failed to identify karyotypic abnormalities and genetic studies did not show a monogenic inheritance pattern following examination of candidate genes [81,82]. In addition, two or more phenotypes can be present in the same family suggesting that some of the phenotypic differences could be accounted for by variable expression of the same shared genes [81,83].

The mapping of the human genome in 2003 [84] and the publication of the human haplotype map (more than one million single nucleotide polymorphisms of common genetic variants) in 2005 [85], lead to the realization that most DNA variation is shared by all humans and is inherited as blocks of linked genes (linkage disequilibrium) [86]. These advances enabled a revolution in case-control studies and the development of GWAS which map the entire human genome looking for susceptibility genes for complex traits such as obesity, type 2 diabetes and PCOS [81].

The first PCOS GWAS was published in 2010 and demonstrated 11 gene loci associated with PCOS [87]. Additional loci have subsequently been found in several different ethnic groups [86,88]. The first GWAS analysis of quantitative traits was published in 2015 and showed that a variant (rs11031006) was associated with luteinizing hormone levels [88]. The largest GWAS included a meta-analysis of 10,074 PCOS cases and 103,164 controls and identified 19 loci that confer risk for PCOS [29]. The genes associated with these loci involve gonadotrophin action, ovarian steroidogenesis, insulin resistance and type 2 diabetes susceptibility genes. The first GWAS using electronic health record-linked biobanks has introduced greater investigative power and identified 2 additional loci [89]. These variants were associated with polycystic ovaries and hyperandrogenism (rs17186366 near SOD2) and oligomenorrhoea and infertility (rs144248326 near WWTR1) [89]. In addition to identifying common gene variants for PCOS phenotypes, finding the same signals (THADA, YAP1 and c9orf3) in Chinese and European populations suggests that PCOS is an ancient trait that was present before humans migrated out of Africa [81].

More recently Mendelian randomization (MR) studies have been used to explore the potential causative association between gene variants identified in GWAS and PCOS [90,91]. Many of the gene variants identified in GWAS are located in non-coding regions of DNA [92]. The genes or functional DNA elements through which these variants exert their effects are often unknown. Mendelian randomization is a statistical methodology

used to jointly analyze GWAS and quantitative gene loci to test for association between gene expression and a trait, due to a shared or potentially causal variant at a specific locus [93]. A detailed analysis of MR methodology and the limitations of this statistical tool is beyond the scope of the present review. Although MR studies have the potential to infer causation it is recognized that they also have limitations in PCOS research [90]. Nevertheless, preliminary evidence suggests that several genes related to obesity, metabolic and reproductive function, may play a causal role in the pathogenesis of PCOS [90,91].

Decades of genetic research has therefore characterized PCOS as a polygenic trait that results from interactions between the environment and susceptible genomic traits [27,29,79,88]. The failure to identify a qualitative or monogenic inheritance pattern and the findings from GWAS, MR, familial and twin studies, suggests that the heritability of PCOS is likely to be due to the combination of multiple genes with small effect size, as has been found with obesity and type 2 diabetes [79,80,94–96]. Polygenic traits are the result of gene variants that represent one end of the bell-shaped normal distribution curve of continuous variation in a population [97]. From an evolutionary perspective, women with PCOS may represent the “metabolic elite” end of the normal distribution curve, being able to efficiently store energy in periods of food abundance and down-regulate fertility in times of food scarcity, or even in anticipation of reduced seasonal food availability as a predictive adaptive response [16,17,60].

The realization that PCOS is a quantitative trait (phenotype determined by multiple genes and environmental factors) has far-reaching implications for the diagnosis, treatment and prevention of symptoms and pathology associated with PCOS. The implications require a shift in thinking about PCOS as a “disease” to a variation of normal metabolic and reproductive function. This shift invites a change in vocabulary from talking about “disorder” and “risk” to talking about “expression” and “variability” [97]. This new understanding supports and reinforces an evolutionary model of the pathogenesis of PCOS. In keeping with this model, multiple lines of evidence suggest that inherited PCOS gene variants are developmentally programmed in a way that primes them for activation by nutritional and environmental factors in postnatal life [41,42,98].

3.3. Developmental Epigenetic Programming

The developmental programming of PCOS represents changes in gene expression that occur during critical periods of fetal development [99]. Following fertilization, most parental epigenetic programming is erased and dramatic epigenomic reprogramming occurs [100]. This results in transformation of the parental epigenome to the zygote epigenome and determines personalized gene function. Compelling evidence shows that a wide range of maternal, nutritional and environmental factors can effect fetal development during these critical periods of programming [44,98,99,101,102]. These include hormones, vitamins, diet-derived metabolites and environmental chemicals [48,98,103,104]. In addition, epigenetic reprogramming of germ-line cells can lead to transgenerational inheritance resulting in phenotypic variation or pathology in the absence of continued direct exposure [98].

Experimental studies in primates, sheep, rats and mice show that PCOS-like syndromes can be induced by a range of treatments including androgens, anti-Mullerian hormone and letrozole [19,44,46]. Nevertheless, there is significant debate regarding when an animal model qualifies as PCOS-like [105]. The model used and the method of induction of PCOS phenotypes therefore needs to be carefully scrutinized when generalizing findings from animal research to women with PCOS. Most of the animal and human research on the developmental origins of PCOS has focused on the role of prenatal androgen exposure. This has been extensively reviewed in numerous previous publications [41,46]. This research has resulted in a proposed “two hit” hypothesis for the development of PCOS phenotypes [43,45]. The “first hit” involves developmental programming of inherited susceptibility genes and the “second hit” arises due to lifestyle and environmental influences in childhood, adolescence and adulthood [41,106].

If PCOS is a quantitative trait involving normal gene variants, as suggested by the evolutionary considerations and findings from genetic research, then the “first hit” may result from normal developmental programming events as occurs with other gene variants [102]. According to this hypothesis, the polygenic susceptibility genes would be normally “activated” and “primed” to respond to future maternal and environmental conditions and exposures, as would be the case with many other normal genes [28]. In addition, the susceptibility alleles may be “activated” or “functionally enhanced” by a range of maternal and environmental factors, as is usually presumed to be the case in PCOS [5,14,102]. This developmental plasticity would provide a mechanism for a predictive adaptive response, based on inputs from the maternal environment that could be used to program metabolic and reproductive survival pathways, to better prepare the offspring for the future world in which they may be expected to live [107].

Parental lifestyle factors including diet, obesity, smoking and endocrine-disrupting chemicals, have all been shown to modulate disease risk later in life [104,108,109]. The original description of the fetal origin’s hypothesis proposed that poor maternal nutrition would increase fetal susceptibility to the effects of a Western-style diet later in life [49]. Subsequent studies have confirmed that maternal exposure to either nutrient excess or deficit, can have long-term consequences for the health of the progeny [104]. Evidence from human and animal studies suggests that maternal obesity programs the offspring for increased risk of developing obesity, hyperglycemia, diabetes, hypertension and metabolic syndrome [108].

The developmental origins of PCOS may have been due to different factors in ancestral and modern populations [17,60]. It has been hypothesized that environmental stress, infection, nutrient deprivation, fetal growth restriction and stress hormone responses may have resulted in maternally mediated modulation of gene expression in ancestral offspring [17,110]. Some of these factors have been investigated and confirmed in modern populations subject to starvation and extreme environmental conditions [111]. In contrast, altered fetal programming in modern societies may be secondary to maternal overnutrition, sedentary behavior, obesity, emotional stress, circadian rhythm disruption, poor gut health or environmental chemical exposure [35,101,112,113]. The preconception and pregnancy periods therefore provide a unique opportunity for lifestyle interventions that promote optimal future health for both the mother and the offspring (Figure 2).

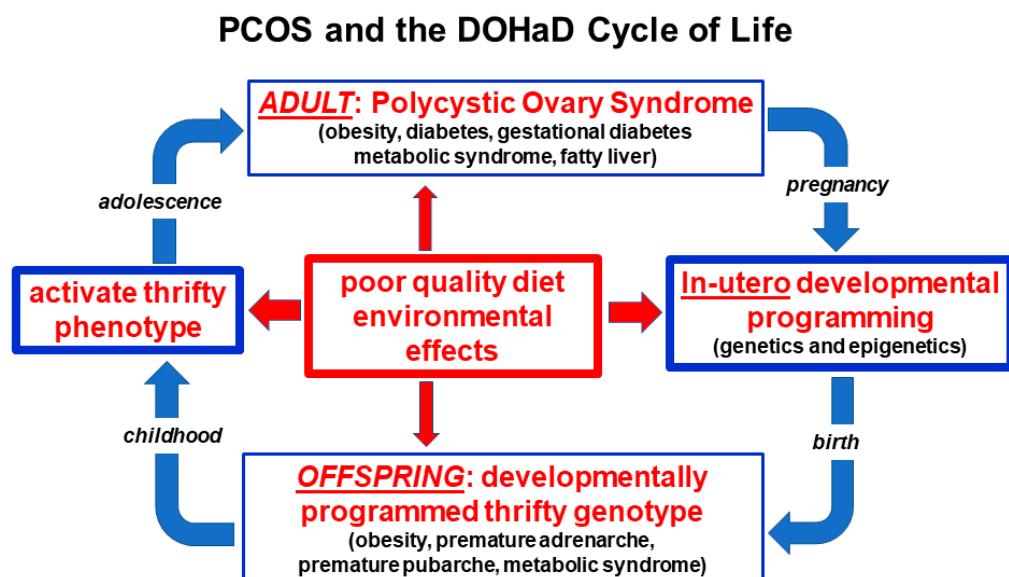


Figure 2. Nutritional and environmental influences throughout the life course and the perpetuation of the transgenerational inheritance of polycystic ovary syndrome. Reprinted from Ref. [28].

3.4. Microbiome and Dysbiosis

The gastrointestinal microbiome is now appreciated to play a central role in human health and disease [114,115]. The microbiome is known to co-regulate many physiological functions involving the immune, neuroendocrine and metabolic systems via complex reciprocal feedback mechanisms that operate between the microbial ecosystem and the host [116,117]. Evidence from studies in Western populations, hunter-gatherer societies and phylogenetic studies in other species, have attempted to place the human microbiome into an evolutionary context [118]. Although microbes clearly impact host physiology and have changed along branches of the evolutionary tree, there is ongoing debate regarding whether the microbiome can evolve according to the usual evolutionary forces [119,120]. Nevertheless, it has been argued that focusing on functional pathways and metabolic roles of microbial communities, rather than on specific microbes, provides a better model for understanding evolutionary fitness [118]. The co-evolution of the microbiome and human physiology may therefore be important in understanding the differences between ancient adaptive physiological survival mechanisms and modern lifestyle-related pathological responses, in women with PCOS (Figure 1).

Twin studies and GWAS show that host genetics can influence the microbiome composition, and microbes can exert effects on the host genome, although the environment has an important role [121,122]. Humans are constantly adapting to the gut microbiome to try to determine which microorganisms are beneficial or harmful. Immune genes involved in this process are the most rapidly evolving protein-encoding genes in the mammalian genome [123,124]. Diversification of microbes allows humans to access dietary niches and nutritional components they otherwise would not be able to access, which may be beneficial and ultimately lead to the integration of specific microbes into the ecosystem [125]. Although no living population today carries an ancestral microbiome, comparison studies of non-Western and Western populations show significant differences in the relative abundances of common phyla and a much greater species diversity in non-Western populations [126,127]. A review of non-human primate and human gut microbiome datasets, revealed a changing microbiome in response to host habitat, season and diet, although there appear to be common species-specific symbiotic communities [118].

Rapid human cultural changes have resulted in significant dietary modifications in urban-industrialized communities and shifted the microbiome at an unprecedented rate. The result has been the development of a mismatch between human metabolic genes and bacteria that enhance fat storage [128]. In our evolutionary past, when nutrients were scarce, it has been theorized that host selection led to the maintenance of microbes that enhance nutrient uptake or host energy storage. However, in the modern environment, where a high-fat, high-sugar, low-fiber diet has become common and easily accessible, integration of these microbes leads to maladaptive physiological responses [40]. For metabolically thrifty individuals with PCOS, harboring microbes that enhance energy storage escalates the evolutionary conflict, furthering the development of insulin resistance and therefore progression to obesity and type 2 diabetes [12,129]. Further compounding this maladaptive response is the loss of microbes that are required to access other dietary niches. One example is the loss of symbiotic species of *Treponema* in individuals living in urban-industrialized communities [130]. A change from the ancestral hunter-gatherer diet, where foods consumed changed seasonally and a wide variety of food components were eaten, to a diet that is similar across seasons and significantly less varied, is another likely contributor to reduced diversity of the microbiomes of individuals living in urbanized-industrialized communities [131].

The majority of women with PCOS are overweight or obese and evidence indicates that the microbiome of obese individuals is capable of extracting more energy from the host diet compared with the microbiome of lean individuals [132]. This is thought to be driven by an expansion in pro-inflammatory species of bacteria, such as *E. coli*, and a depletion of anti-inflammatory bacteria such as *Faecalibacterium prausnitzii* [133,134]. Chronic low-grade

'metabolic' inflammation, or meta-inflammation, is a result of an imbalanced gut microbiome that promotes the development of insulin resistance and type 2 diabetes [135–137].

The dysbiosis of gut microbiota theory of PCOS, proposed by Tremellen in 2012, accounts for the development of all of the components of PCOS (multiple ovarian follicles, anovulation or menstrual irregularity and hyperandrogenism) [40]. The theory proposes that a poor-quality diet and resulting imbalanced microbiome, induces intestinal permeability and endotoxemia, exacerbating hyperinsulinemia. Increased insulin levels promote higher androgen production by the ovaries and disrupts normal follicle development. Metabolic, endocrine and environmental factors associated with PCOS are not mutually exclusive, and therefore their relative contributions to dysbiosis in PCOS remains uncertain [138]. Consuming a balanced diet that is low in fat and high in fiber, can also restore balance to the ecosystem (termed eubiosis) [50]. A recent study showed that dietary intake of fiber and vitamin D was significantly decreased in both lean and obese women with PCOS, compared to healthy controls, and correlated with lower diversity of the gut microbiome [139]. Dysbiosis is reversible with improvement in diet quality augmented by the addition of probiotics or synbiotics [51,56–58].

Dysbiosis is a consistent finding when looking at the microbiome of women with PCOS [140–143]. Although most studies are small, dysbiosis has consistently been found to correlate with different physiological parameters, such as obesity, sex hormones and metabolic defects [140,141,143]. Similar to microbiomes associated with obesity, the microbiomes of individuals with PCOS have generally been found to have lower alpha diversity (lower numbers of bacterial taxa) than controls, and most studies describe an altered composition of taxa relative to controls [140,143]. However, the bacterial taxa observed to be either increased, depleted or absent in PCOS differs from study to study. This is likely due to both the immense inter-individual variation in microbiotas, as well the fact that PCOS is a quantitative trait with women with various degrees and levels of obesity and sex hormones.

In keeping with the developmental origins hypothesis previously discussed, maternal androgens may alter the composition and function of the microbiome, therefore facilitating the pathogenesis of PCOS [140]. One study showed that beta diversity, which is used to measure differences between groups, was negatively correlated with hyperandrogenism, suggesting that androgens play a significant role in dysbiosis [140]. The 'first hit' in utero may therefore combine with vertical transmission of a dysbiotic microbiome from a mother with PCOS, resulting in dysbiosis in the offspring. Preconception and pregnancy provide a unique opportunities for lifestyle and dietary interventions aimed at restoring eubiosis, to enable the transference of a balanced ecosystem to the offspring, via vertical transmission [118].

The accumulating scientific evidence strongly supports the significant role played by the microbiome in the pathogenesis and maintenance of PCOS, consistent with research in other related metabolic conditions. The role of dysbiosis is supported by over 30 proof-of-concept studies that have recently been reviewed [144]. Dysbiosis is therefore a significant factor in the pathogenesis of PCOS and an important component of a unified evolutionary model. Dysbiosis represents a maladaptive response of the microbiome to modern lifestyle influences and is a modifiable factor in the treatment of women with PCOS.

3.5. Insulin Resistance

There are several dilemmas when assessing the role of IR in women with PCOS. There is no consensus on the definition of IR [145,146], measurement is difficult [147,148], whole-body IR is usually measured although it is recognized that IR can be selective being either tissue-specific or pathway-specific within cells [149–151], normal values are categorical and determined by arbitrary cut-offs (4.45 mg/kg/min) [145], testing is not recommended in clinical practice [38], reported prevalence rates in obese and lean women vary widely [147,152], and the significance of IR as a pathognomonic component of PCOS is an area of debate [153–155].

Despite these limitations, it is hypothesized that IR is a significant proximate cause of PCOS and is intrinsic to the underlying pathophysiology [44,156]. In addition, it is recognized that IR plays a major role in the pathophysiology of all of the metabolic diseases, cardiovascular disease, some neurodegenerative diseases, and selected cancers [22,157]. Insulin resistance is therefore considered to be the main driver for many diseases and makes a significant contribution to the chronic disease epidemic [158]. Nevertheless, being able to vary the sensitivity and physiological action of insulin is thought to have conferred a significant adaptive survival role in many animals throughout evolutionary history [146,159]. It has been proposed that IR may have evolved as a switch in reproductive and metabolic strategies, since the development of IR can result in anovulation and reduced fertility, in addition to differential energy repartitioning to specific tissues [159].

Insulin receptors are located on the cell membranes of most tissues in the body [160]. Ligand binding to the alpha-subunit induces autophosphorylation of specific tyrosine residues on the cytoplasmic side of the membrane [160,161]. The activated insulin receptor initiates signal transduction via the phosphatidylinositol-3 kinase (PI-3K) metabolic pathway and the mitogen-activated protein kinase pathway (MAPK) which is involved in cell growth and proliferation [161]. Insulin is an anabolic hormone that facilitates glucose removal from the blood, enhances fat storage and inhibits lipolysis in adipose tissue, stimulates glycogen synthesis in muscle and liver and inhibits hepatic glucose output [161]. IR can be defined as a state where higher circulating insulin levels are necessary to achieve an integrated glucose-lowering response [146]. IR results from alterations to cellular membrane insulin-receptor function or intracellular signaling, enzyme, metabolic or gene function [146,160,161].

Insulin resistance can be caused by a wide variety of mechanisms that have the ability to disrupt any part of this metabolic signaling system [53,161]. These include autoantibodies, receptor agonists and antagonists, hormones, inflammatory cytokines, oxidative stress, nutrient sensors and metabolic intermediates [160–163]. Physiological regulation of insulin function can be viewed as an adaptive mechanism to regulate the metabolic pathway of insulin signaling (PI-3K), in response to changing environmental conditions [starvation, fear, stress] [164,165] or during normal alterations of internal states (pregnancy, lactation, adolescence) [65,146,152].

The physiological activation of IR allows the organism to switch from an anabolic energy storage state to a catabolic or energy mobilizing state. This allows free fatty acids to be mobilized from adipose tissue, which are then converted to glucose in the liver and released into the circulation [161]. As a result of this metabolic change, blood sugar levels are maintained for vital metabolic processes and brain function [14]. This adaptive protective mechanism can be pathway-specific during periods of growth, such as pregnancy, lactation and adolescence, so that only the metabolic signaling (PI-3K) is inhibited and not the mitogenic pathway (MAPK), which may even be up-regulated [30,65,160].

When the physiology of insulin function is considered to be a quantitative or continuous variable from an evolutionary perspective, it is likely that all women with PCOS, whether obese or lean, have reduced insulin sensitivity [152,155,166]. A systematic review and meta-analysis of euglycemic-hyperinsulinemic clamp studies found that women with PCOS have a 27% reduction in insulin sensitivity compared to body mass index (BMI) and age-matched controls [155]. In evolutionary terms, women with a PCOS metabolic phenotype would have increased survival chances during times of environmental or physiological demand for altered energy metabolism, but be more vulnerable to the pathological effects of IR when exposed to modern lifestyle factors [14,17,159]. In particular, a poor-quality, high-glycemic, high-fat, low-fiber diet has been shown to cause IR [40,167]. As discussed in the dysbiosis section, diet-related changes in the gastrointestinal microbiome have also been shown to cause IR in women with PCOS [53,55]. Numerous studies have shown that dietary modification [168–170], or treatment with probiotics or synbiotics, has the potential to restore normal insulin function [57,171].

Consumption of a high-glycemic-load diet results in rapid increases in blood sugar levels that cause compensatory hyperinsulinemia [167,172]. Excessive dietary intake of glucose and fructose are converted to fatty acids by de novo lipogenesis in the liver, transported to adipocytes via lipoproteins, released as fatty acids to adipocytes and stored in fat globules as triglycerides [161]. As a result of nutrient overload, diacylglycerol, the penultimate molecule in the synthesis of triglyceride, accumulates in the cytoplasm and binds with the threonine amino acid in the 1160 position of the insulin receptor. This inhibits autophosphorylation and down-regulates the metabolic PI-3K pathway and causes IR [161]. This process has the potential to be reversible following changes in diet quantity and quality, as has been shown to occur with calorie restriction, fasting, time-restricted eating, gastric bypass surgery, low saturated fat and low glycemic diets [168,170,173]. Diets high in animal protein or saturated fat can also cause IR independent of BMI [174,175]. These mechanisms provide the rationale for the principal recommendation of the International Guidelines that women with PCOS should be advised about dietary modification as the first line of management in all symptom presentations [38].

3.6. Obesity and the Lean PCOS Paradox

Insight can be obtained into the role of obesity in women with PCOS by examining the evolutionary history, genetic studies and pathological disorders of adipose tissue [151,176,177]. The ability to store energy is a basic function of life beginning with unicellular organisms [176]. In multicellular organisms, from yeast to humans, the largest source of stored energy is as triglycerides in lipid droplets in order to provide energy during periods when energy demands exceed caloric intake [176]. Understanding the biological functions of adipose tissue has progressed from energy storage and thermal insulation to that of a complex endocrine organ with immune and inflammatory effects and important reproductive and metabolic implications [176,178].

Adipose tissue is organized into brown adipose tissue (BAT) and white adipose tissue (WAT), both with different functions [178]. Although the evolutionary origins of BAT and WAT are the subject of ongoing debate [176], BAT is located in the supraclavicular and thoracic prevertebral areas and is primarily involved in cold thermogenesis and regulation of basal metabolic rate [179]. WAT is distributed in multiple anatomical areas such as visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) and functions as a fat storage depot and an endocrine organ [178,179]. An additional layer of SAT is thought to have evolved as insulation against cool night temperatures in the Pleistocene open Savannah [180]. The lower body distribution of SAT in women is hypothesized to have evolved to provide additional calorie storage for pregnancy and lactation and is unique to human females [14]. Lower body SAT has a metabolic program that makes it less readily available for every-day energy needs, but it can be mobilized during pregnancy and lactation [14]. In addition, excess accumulation of SAT is much less likely to cause IR and metabolic dysfunction and explains why IR is not observed in all obese individuals [151,181]. Visceral WAT is associated with IR in women with PCOS leading to both metabolic and reproductive problems [182].

Multiple lines of evidence from evolutionary history, genetic and twin studies, support a genetic basis for obesity and differences in obese and lean phenotypes in women with PCOS [183–186]. The majority of women with PCOS are overweight or obese, with reports ranging from 38–88% [152,186]. Studies comparing obese and lean women with PCOS have several methodological problems including small sample size, overlap of PCOS characteristics with normal pubertal changes, non-standardized diagnostic criteria, and limited generalizability to the entire population due to a focus on a specific ethnic group [166,182]. In addition, most of the studies examining body composition in PCOS have relied on anthropomorphic measurements (BMI, waist circumference, waist-to-hip ratio) which are considered inaccurate compared with the current gold-standard of magnetic resonance imaging [182]. Consequently, there is wide heterogeneity in reports examining the relation-

ship between body composition measures, including extent of VAT and metabolic changes such as IR [186].

In humans, there is large individual variation in the fat storage capability and expandability of different adipose tissue depots [151]. It has been hypothesized that once the genetically determined limit of expandability of SAT is reached, there is expansion of VAT and excess lipid accumulation in muscle, liver and other organs, resulting in IR, inflammation and metabolic dysregulation [151]. We hypothesize that lean women with PCOS have a genetically determined limited ability to store excess lipid in SAT, but develop increased lipid deposition in VAT and organs such as the liver, resulting in metabolic dysregulation and IR in a similar manner to what occurs in obese women with PCOS. The wide variation in the genetic limitation of SAT expansion is also supported by studies in individuals with lipodystrophy.

Lipodystrophies are a heterogeneous group of rare inherited and acquired disorders characterized by a selective loss of adipose tissue [177,187]. They are classified on the basis of the extent of fat loss as generalized, partial or localized [187]. Patients with congenital generalized lipodystrophy have a generalized deficiency of fat from birth, usually have severe IR and develop diabetes at puberty. As a consequence of genetically limited ability for SAT lipid storage, lipids can only be stored ectopically in non-adipocytes resulting in major health consequences including IR, fatty liver, diabetes and PCOS [188]. In contrast to generalized lipodystrophy, patients with familial partial lipodystrophy have normal fat distribution at birth but loose SAT in the limbs, buttocks and hips, at puberty. Fifty percent of women develop diabetes and 20–35% develop irregular periods and polycystic ovaries [177]. Despite the rare nature of these syndromes much has been learned about the underlying genetic variants involved [187].

Elucidation of clinical subtypes and the genetic background of patients with lipodystrophies may pave the way to new insights into the role of fat partitioning and obesity, and has implications for understanding the pathogenesis of insulin resistance, diabetes and PCOS [177]. Lean women with PCOS may have a genetic predisposition for limited SAT fat storage, coupled with underlying metabolic predispositions that result in deposition of excess lipid in VAT and liver and the observed metabolic features of IR, fatty liver and diabetes. If the extent of IR and ectopic fat deposition is excessive, the resulting hormonal changes may be sufficient to cause oligomenorrhea and subfertility as occurs with secondary familial partial lipodystrophy type 2 [188,189]. If this underlying mechanism is confirmed in future studies, the main difference between women with lean or obese PCOS may be the combined effects of metabolic programming and the genetically determined extent of SCT fat deposition. This would explain why lean women have all the same clinical, biochemical and endocrine features, although possibly less severe, than overweight and obese women with PCOS [186].

3.7. Endocrine-Disrupting Chemical Exposure

Anthropomorphic chemical exposure is ubiquitous in the environment and has possible effects on many aspects related to women's health and PCOS [36,190–192]. The identification of more than 1000 EDC in food, air, water, pesticides, plastics, personal care products, and other consumer goods, raises specific concerns for pregnant women and women with increased susceptibility to metabolic diseases such as PCOS [36,172,192–194]. Accumulating evidence suggests that EDC may be involved in the pathogenesis of PCOS given their known and potential hormonal and metabolic effects [36,190,195]. This includes many of the areas that have been considered in the unified evolutionary model, such as developmental epigenetic programming, microbiome composition and function, metabolic processes such as IR, and regulation of body weight.

Many observational studies have demonstrated the presence of EDC in maternal and fetal serum and urine, amniotic fluid, cord blood and breast milk [196–198]. Six classes of EDC have been shown to cross the placenta confirming that the fetus is exposed at all stages of development [109,196]. Although it is impossible to perform experimental studies

in humans, evidence from epidemiological, molecular toxicology and animal studies provide compelling evidence of adverse developmental effects and transgenerational toxicity [172,190,192,199]. The realization of the tragic effects of DES in the 1970's was first example of an in utero exposure causing serious transgenerational health effects [192].

Several estrogenic EDC have been associated with birth outcomes that are thought to be associated with the development of PCOS [190]. These include decreased birthweight (perfluoroalkyl substances [PFAS], perfluorooctanoic acid) and preterm birth (di-2-ethylhexyl phthalate) [190]. Prenatal exposure to androgenic EDC (triclosan, glyphosate, tributyltin, nicotine) is of increasing concern, given the suspected epigenetic role of in utero androgen exposure in the pathogenesis of PCOS [48,200,201].

As a result, implementation of the precautionary principle is a high priority in counselling women with PCOS [202]. International professional bodies (The Royal College of Obstetricians and Gynecologists, Endocrine Society, FIGO) have recommended that all pregnant women should be advised of the possible risks of EDC and that education programs be developed to inform health professionals [203–205]. An explanation of the pathogenesis of PCOS should include reference to environmental chemical exposure and open the way for more detailed discussion of specific personalized advice and lifestyle recommendations.

3.8. Lifestyle Contributors to the Pathogenesis of PCOS

Several lifestyle factors have been investigated for their role in the pathogenesis of PCOS. These include diet, exercise, stress, sleep disturbance, circadian disruption and exposure to environmental chemicals [28,41,206]. Recent advances in genomics, epigenetics, metabolomics, nutrigenomics, evolutionary biology, computer technology and artificial intelligence, are providing many insights into the mechanisms of how lifestyle factors impact the pathogenesis of PCOS [9,90,207,208]. Nutritional studies based on diet indices, diet composition and metabolomics have identified dietary components that contribute to a healthy eating pattern [51,207,209,210]. Healthy diet patterns, or wholefood diets, have been found to be effective in controlling and reversing many of the symptoms and metabolic alterations associated with PCOS [50].

As previously discussed, the modern Western diet and lifestyle is at odds with our evolutionary background. One dietary component that differs significantly in ancestral and modern populations is dietary fiber intake. Assessment of dietary fiber intake is also a good surrogate marker for a healthy wholefood diet. In general, our traditional hunter-gatherer ancestors consumed significantly more fiber than modern populations. Studies that have investigated the dietary patterns of remaining contemporary hunter-gatherer societies, have found their dietary fiber intake to be around 80–150 g per day [211]. This contrasts with the contemporary Western diet, where the average fiber intake is 18.2 g per day in children and 20.7 g per day in adults [212]. Adequate dietary fiber consumption is important as it has several benefits, such as improved insulin sensitivity, reduced blood glucose levels, decreased systemic inflammation, lower serum levels of androgens and LPS, all of which have been linked to the pathogenesis of PCOS [213–216].

Recent systematic reviews of observational studies and randomized controlled trials have found dietary fiber consumption to be inversely related to risk of obesity, type 2 diabetes, and cardiovascular disease [217,218]. A recent cohort study from Canada found that obese women with PCOS consumed significantly less dietary fiber than normal weight women without PCOS [219]. In addition, fiber intake of women with PCOS was negatively correlated with IR, fasting insulin, glucose tolerance and serum androgens [219]. Hence, the mismatch between the amount of fiber traditionally consumed and the fiber content of Western diets, may be an important dietary component contributing to the increased rates of PCOS seen in developed and developing nations.

3.9. Circadian Rhythm Disruption and PCOS

The circadian rhythm is a mechanism with which living organisms can synchronize their internal biological processes with the external light and dark pattern of the day [220].

Circadian rhythms have formed a central component of the evolutionary adaptation of all organisms to a variety of environmental conditions, from prokaryotes to complex multicellular organisms [221–223]. Most organisms experience daily changes in their environment, including light availability, temperature and food. Hundreds of thousands of years of evolution have synchronized the rhythmic daily programming of internal metabolic, endocrine and behavioral systems to the external environmental conditions [222]. Circadian clocks anticipate environmental changes and confer a predictive adaptive survival benefit to organisms.

The normal function of the circadian system is based on a hierarchical network of central and peripheral clocks [224]. The central, or master clock, is in the suprachiasmatic nucleus in the anterior hypothalamus. It is strategically placed to communicate with multiple physiological homeostatic control nuclei (body temperature, metabolic rate, appetite, sleep), pituitary hormonal systems (gonadal, thyroid, somatotrophic, adrenal), the autonomic nervous system (digestion, heart rate), and conscious cortical centers (behavior, motivation, reward, reproduction) [225]. Humans are programmed for specific day and night-time survival behaviors that are regulated by the availability of temperature, feeding and sunlight. Photons of light stimulate specialized photoreceptors in the retinal ganglion layer which transmit an electrical impulse to the cells of the master clock via the retinohypothalamic tract [226]. The central clock can then convey rhythmic information to peripheral clocks in other tissues and organs throughout the body [224]. Feeding and fasting cycles are the primary time cues for circadian clocks in peripheral tissues [227].

Circadian clocks exist in all cells, including the microbiome, and function as autonomous transcriptional-translational genetic feedback loops [228,229]. The changing length of daylight, determined by the rotation of the earth on its axis, requires that the autonomous clocks are reset, or entrained, on a daily basis [230]. The molecular mechanisms of circadian clocks are similar across all species and are regulated by genetic enhancer/repressor elements, epigenetic modulation by methylation and acetylation, post-translation modification of regulatory proteins, and a variety of hormonal and signaling molecules [220,229,231]. This complex interconnected regulatory framework, ensures that the same molecules that regulate metabolism and reproduction, also contribute to a bidirectional feedback system with the autonomous circadian circuits [224,231]. This results in synchronicity of internal physiology with environmental cues, to optimize both individual and species survival. Evolution has therefore provided a mechanism for humans to adapt and survive under the selective pressures of food scarcity, seasonal changes in sunlight and a range of temperature exposures.

The evolutionary adaptive survival benefit of synchronized circadian systems in ancient populations is in marked contrast to the multiple circadian disruptions that are associated with modern lifestyle. These include poor-quality diet [232], improper meal timing and altered feeding-fasting behavior [233,234], sub-optimal exercise timing [235], disrupted sleep-wake cycles [236], shift work [237], EDC [238], and stress [239,240]. Changes in all of these parameters are correlated with significant increases in obesity, diabetes, cardiovascular disease, and some cancers [222]. Not surprisingly, lifestyle-related disturbances of circadian rhythms have also been investigated for their role in the pathogenesis of PCOS [35,241,242]. The available evidence suggests that circadian disruption has detrimental effects on in utero development [243], altered metabolism and insulin resistance [241,244], body weight and obesity [245], and fertility [34]. All these influences are relevant to an evolutionary model of the pathogenesis of PCOS.

Recognition of the impact of lifestyle behaviors on circadian dysregulation and metabolic and reproductive function, opens the way for targeted intervention strategies to modulate and reverse these effects [246]. These include regular meal timing [222,247], time-restricted feeding [248,249], restoration of normal sleep cycles [250], optimal exercise timing [235], limitation of exposure to bright light at night [251], and improved diet quality [227]. Recognition of circadian dysfunction and the investigation of lifestyle interventions should be a priority in both clinical management and future research in PCOS.

3.10. Conceptual Framework and Summary of the Unified Evolutionary Model

The evolutionary model proposes that PCOS is a condition that arises from the inheritance of genomic variants derived from the maternal and paternal genome. In utero fetal metabolic, endocrine and environmental factors modulate developmental programming of susceptible genes and predispose the offspring to develop PCOS. Postnatal exposure to poor-quality diet, sedentary behavior, EDC, circadian disruption and other lifestyle factors activate epigenetically programmed pathways, resulting in the observed features.

Dietary factors cause gastrointestinal dysbiosis and systemic inflammation, insulin resistance and hyperandrogenism. Continued exposure to adverse lifestyle and environmental factors eventually leads to the development of associated metabolic conditions such as obesity, GDM, diabetes, NAFLD and metabolic syndrome (Figure 1).

Balanced evolutionary selection pressures result in transgenerational transmission of susceptible gene variants to PCOS offspring. Ongoing exposure to adverse nutritional and environmental factors activate developmentally programmed genes and ensure the perpetuation of the syndrome in subsequent generations. The DOHaD cycle can be interrupted at any point from pregnancy to birth, childhood, adolescence or adulthood by targeted intervention strategies (Figure 2).

In summary, we propose that PCOS is an environmental mismatch disorder that manifests after in utero developmental programming of a cluster of normal gene variants. Postnatal exposure to adverse lifestyle and environmental conditions results in the observed metabolic and endocrine features. PCOS therefore represents a maladaptive response of ancient genetic survival mechanisms to modern lifestyle practices.

Comprehensive International Guidelines have made 166 recommendations for the assessment and management of PCOS [38]. We believe the current unified evolutionary theory of the pathogenesis of PCOS provides a conceptual framework that may help practitioners and patients understand the development of PCOS symptoms and pathology in the context of our modern lifestyle and environment. It will hopefully contribute to improved communication, result in improved feelings of empowerment over the personal manifestations of PCOS, improve compliance, reduce morbidity, increase quality of life and inform future research (Figure 3).

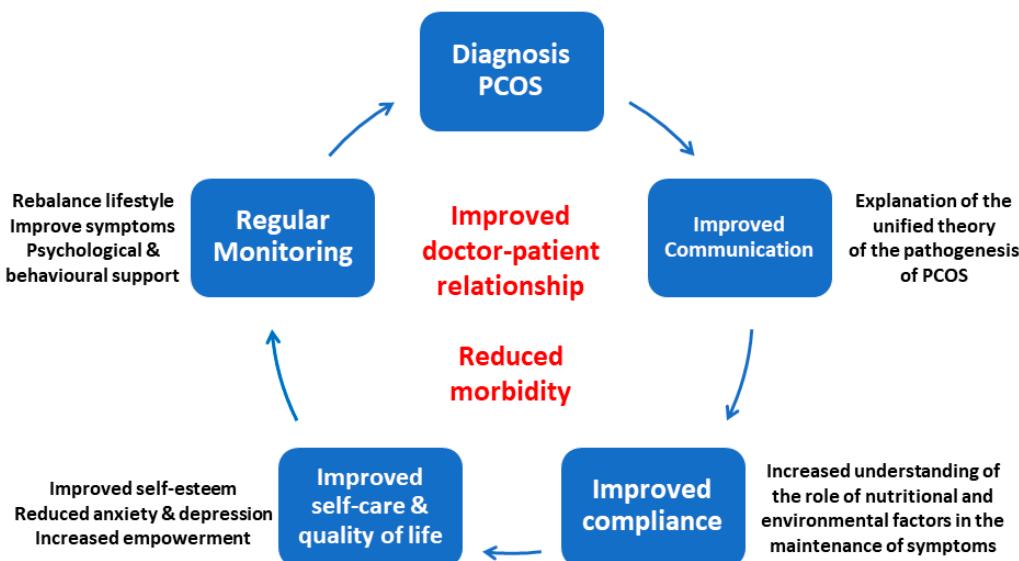


Figure 3. Impact of the unified theory on the management of polycystic ovary syndrome. Reprinted from Ref. [28].

4. Conclusions

Substantial evidence and discussion support an evolutionary basis for the pathogenesis of polycystic ovary syndrome, although many of the mechanistic details are yet to

be determined. Nevertheless, multiple lines of evidence from evolutionary theory, comparative biology, genetics, epigenetics, metabolism research, and cell biology, provide supportive evidence and hypothesis-generating data. The ability of animals to synchronize internal physiology, metabolism and reproductive function, with our changing external environment and habitat, are a necessary requirement for individual and species survival. The co-operative and sometimes competitive evolution of metabolism and reproduction provided adaptive survival mechanisms in ancestral environments that appear to be maladaptive in modern environments. An evolutionary model therefore provides a framework to enhance practitioner and patient understanding, improve compliance with lifestyle interventions, reduce morbidity, improve quality of life and will evolve and change over time.

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Polycystic Ovary Syndrome (PCOS): Bridging Gaps in Understanding, Diagnosis, and Management

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Abstract

People of reproductive age are frequently affected with Polycystic Ovary Syndrome (PCOS), a common endocrine disorder with a range of clinical, hormonal, and metabolic features. The goal of this review paper is to give a thorough summary of the clinical presentation, diagnostic criteria, aetiology, epidemiology, and treatment options for PCOS. Between 5% and 20% of women in reproductive age worldwide are estimated to have PCOS. This syndrome is widely known for being complicated, involving both environmental factors and genetic predisposition. Common clinical symptoms include irregular menstruation, hyperandrogenism, and an ultrasound that reveals polycystic ovarian morphology. Although there are other sets of diagnostic criteria, including the National Institutes of Health standards and the Rotterdam criteria, a precise diagnosis is still necessary. Those with PCOS are more likely to develop metabolic problems such as obesity, dyslipidemia, and insulin resistance. An elevated risk of type 2 diabetes, cardiovascular disease, and infertility are among the long-term health consequences. The primary objectives of therapeutic interventions, which are tailored to the patient's presentation and goals and involve both lifestyle modifications and pharmacological therapies, are improvements in hormonal imbalances, metabolic abnormalities, and reproductive outcomes. This study compiles the most recent findings and clinical observations to improve healthcare professionals' comprehension of PCOS.

Keywords: Polycystic Ovary Syndrome (PCOS), hyperandrogenism, insulin resistance, lifestyle modifications, hormonal imbalance, infertility, metabolic syndrome.

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INTRODUCTION

The complex endocrine condition known as polycystic ovarian syndrome (PCOS) has an impact on women's health all over the world. Since Stein and Leventhal first described it in 1935, a great deal of research has been done on its aetiology and clinical manifestations. PCOS symptoms include hyperandrogenism, irregular menstrual cycles, and polycystic ovaries on ultrasound imaging.

What do you mean by Polycystic ovary syndrome (PCOS)?

In patients with polycystic ovarian syndrome (PCOS), the ovaries produce an abnormally high amount of androgens, male sex hormones that are normally present in women in small amounts. A collection of microscopic cysts (fluid-filled sacs) that form in the ovaries is referred to as polycystic ovarian syndrome.

What factors lead to PCOS (polycystic ovarian syndrome)?

- It is unknown exactly what causes PCOS, however it often runs in families.
- The abnormal hormone levels in the body, including high insulin levels, are linked to it.
- An insulin-producing hormone controls blood sugar levels in the body.
- Many patients with PCOS produce larger amounts of insulin in an effort to overcome their body's resistance to it.
- The production and activation of hormones like testosterone increase as a result.

Pathophysiology:

The precise etiology of PCOS is still unknown, however a combination of genetic, environmental, and hormonal factors are considered to be involved in its development. Insulin resistance and hyperinsulinemia

are common findings in PCOS patients, and they can lead to compensatory hyperandrogenism and ovarian dysfunction. The relevance of inflammation and malfunctioning adipose tissue in the aetiology of PCOS has also been underscored by recent study.

Clinical Presentation: PCOS is characterized by a wide range of symptoms, which may differ from person to person.

1. Common clinical features include regular menstrual cycles or the absence of periods (oligo/anovulation).
2. Male-pattern baldness, acne, and hirsutism (excessive hair growth) are all associated with hyperandrogenism, which is defined by high levels of male hormones.
3. On ultrasonography, enlarged ovaries with multiple small follicles are diagnostic of polycystic ovaries.

Diagnosis

PCOS can be challenging to identify because of its variety of symptoms. Numerous criteria for diagnosis have been presented; the Rotterdam criteria is the most often used.

Two of the three qualities listed below have to be present, according to the Rotterdam criteria, for PCOS to be diagnosed:

1. Ultrasonography-detected polycystic ovaries,
2. Oligo/anovulation,
3. Clinical or biochemical signs of hyperandrogenism,

Excluding other disorders such as hyperprolactinemia and thyroid issues that mimic PCOS is crucial.

Management

PCOS is managed individually for each patient, taking into consideration their particular symptoms and concerns. To improve overall metabolic health and insulin sensitivity, lifestyle modifications like eating adjustments and frequent exercise are recommended. Pharmacological treatments for hyperandrogenism and irregular menstruation, including insulin sensitizers, anti-androgens, and oral contraceptives, can be effective.

Prospective Aspects:

Present research endeavors continue to explore novel therapeutic targets and decipher the complex pathophysiology of PCOS. With the use of phenotypic traits and genetic predisposition, personalised medicine improvements may result in more specific techniques of diagnosis and therapy. The long-term metabolic and

cardiovascular issues associated with PCOS are also being investigated and merit more research.

CONCLUSION

In conclusion, PCOS demands a comprehensive and multidisciplinary approach. Management strategies include lifestyle modifications, pharmacological interventions, and assisted reproductive technologies. Regular health monitoring is essential, considering the long-term implications for metabolic and cardiovascular health. Ongoing research on the genetic basis and emerging therapies offers hope for more personalized and effective treatments. This review underscores the need for continued collaboration between healthcare professionals, researchers, and individuals affected by PCOS to enhance our understanding and management of this prevalent endocrine disorder.

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REVIEW

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Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan

H Teede^{1,2}, A Deeks¹ and L Moran*¹

Abstract

Polycystic ovary syndrome (PCOS) is of clinical and public health importance as it is very common, affecting up to one in five women of reproductive age. It has significant and diverse clinical implications including reproductive (infertility, hyperandrogenism, hirsutism), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, adverse cardiovascular risk profiles) and psychological features (increased anxiety, depression and worsened quality of life). Polycystic ovary syndrome is a heterogeneous condition and, as such, clinical and research agendas are broad and involve many disciplines. The phenotype varies widely depending on life stage, genotype, ethnicity and environmental factors including lifestyle and bodyweight. Importantly, PCOS has unique interactions with the ever increasing obesity prevalence worldwide as obesity-induced insulin resistance significantly exacerbates all the features of PCOS. Furthermore, it has clinical implications across the lifespan and is relevant to related family members with an increased risk for metabolic conditions reported in first-degree relatives. Therapy should focus on both the short and long-term reproductive, metabolic and psychological features. Given the aetiological role of insulin resistance and the impact of obesity on both hyperinsulinaemia and hyperandrogenism, multidisciplinary lifestyle improvement aimed at normalising insulin resistance, improving androgen status and aiding weight management is recognised as a crucial initial treatment strategy. Modest weight loss of 5% to 10% of initial body weight has been demonstrated to improve many of the features of PCOS. Management should focus on support, education, addressing psychological factors and strongly emphasising healthy lifestyle with targeted medical therapy as required. Monitoring and management of long-term metabolic complications is also an important part of routine clinical care. Comprehensive evidence-based guidelines are needed to aid early diagnosis, appropriate investigation, regular screening and treatment of this common condition. Whilst reproductive features of PCOS are well recognised and are covered here, this review focuses primarily on the less appreciated cardiometabolic and psychological features of PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a frustrating experience for women, often complex for managing clinicians and is a scientific challenge for researchers. As research in PCOS is rapidly advancing, it is vital that research evidence is translated to knowledge and action among women, healthcare professionals and policy makers. PCOS is the most common endocrine abnormality in

reproductive-age women. The prevalence of PCOS is traditionally estimated at 4% to 8% from studies performed in Greece, Spain and the USA [1-4]. The prevalence of PCOS has increased with the use of different diagnostic criteria and has recently been shown to be 18% ($17.8 \pm 2.8\%$) in the first community-based prevalence study based on current Rotterdam diagnostic criteria [5]. Importantly, 70% of women in this recent study were undiagnosed [5]. While the upper limit of prevalence for this study was imputed using estimates of polycystic ovaries (PCO) for women who had not had an ultrasound, non-imputed prevalences were calculated as $11.9 \pm 2.4\%$

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[5]. PCOS has also been noted to affect 28% of unselected obese and 5% of lean women [5-8]. In 2006, based on US data and traditionally lower prevalence estimates the anticipated economic burden of PCOS in Australia was AU\$400 million (menstrual dysfunction 31%, infertility 12% and PCOS-associated diabetes 40% of total costs), representing a major health and economic burden [8]. With regards to fertility, the estimated cost per birth in overweight Australian women with PCOS is high [9]. Promisingly, lifestyle intervention comprising dietary, exercise and behavioural therapy improves fertility and reduces costs per birth significantly [9].

Aetiology: insulin resistance and hyperandrogenism

The exact pathophysiology of PCOS is complex and remains largely unclear. Although a detailed discussion is beyond the scope of this review, the underlying hormonal imbalance created by a combination of increased androgens and/or insulin underpin PCOS (Figure 1). Genetic and environmental contributors to hormonal disturbances combine with other factors, including obesity, ovarian dysfunction and hypothalamic pituitary abnormalities to contribute to the aetiology of PCOS [10,11]. However, greater understanding of pathophysiological contributors in PCOS have been hampered by a lack of ideal methods to assess either hyperandrogenism or insulin resistance. Hyperandrogenism is a well established contributor to PCOS aetiology, detected in around 60% to 80% of cases. Insulin resistance is a pathophysiological contributor in around 50% to 80% of women with PCOS [12], especially in those with more severe PCOS diagnosed on National Institutes of Health (NIH) criteria and in women who are overweight. Conversely, lean women

[13] and women with milder PCOS diagnosed on newer European Society for Human Reproduction (ESHRE)/American Society of Reproductive Medicine (ASRM) criteria [14] appear to have less severe hyperinsulinaemia and insulin resistance. Insulin resistance contributes to metabolic features but also to reproductive features [15] through augmenting androgen production and increasing free androgens by reducing sex hormone binding globulin (SHBG). In this setting of unclear aetiology and mechanisms of insulin resistance, further research is clearly needed.

Impact of obesity on polycystic ovary syndrome

Obesity and excess weight are major chronic diseases in Western world countries. Obesity increases hyperandrogenism, hirsutism, infertility and pregnancy complications both independently and by exacerbating PCOS [16,17]. In general populations, obesity and insulin resistance further increase type 2 diabetes (DM2) and cardiovascular disease (CVD). Likewise, in PCOS obesity worsens insulin resistance and exacerbates reproductive and metabolic features [16,17]. Furthermore, women with PCOS have increased risk factors for DM2 and CVD, increased impaired glucose tolerance (IGT), DM2 and potentially increased CVD [18]. As obesity rates rise, the public health significance of PCOS will increase [18]. Treatment of obesity through lifestyle intervention is a key treatment strategy in PCOS and improves insulin resistance, reproductive and metabolic features [19].

Diagnosis of PCOS

Until recently no universally accepted clinical definition existed for PCOS. Over the past three decades, research has highlighted that PCOS is a heterogeneous condition. Symptoms and signs related to PCOS have been evaluated and the initial NIH diagnostic criteria based on oligomenorrhoea/amenorrhoea and clinical or biochemical hyperandrogenism have been broadened in the 2003 Rotterdam or ESHRE/ASRM criteria to include PCO at ultrasound in the key diagnostic criteria [20]. A total of 25% of young women have PCO on ultrasound and the inclusion of PCO in diagnostic criteria has increased the prevalence of PCOS. Recent data indicates that the prevalence of PCOS may be doubled on use of the ESHRE/ASRM criteria with a prevalence of 12% (not imputing presence of polycystic ovaries) to 18% (imputing presence of polycystic ovaries) reported in a community sample [5]. In 2006 the Androgen Excess PCOS Society suggested further modification of the diagnostic criteria to exclude those without symptoms (PCO on ultrasound and oligomenorrhoea/amenorrhoea but no hyperandrogenism) (Table 1) [21]. It should be noted that PCOS is a diagnosis of exclusion and conditions including thyroid

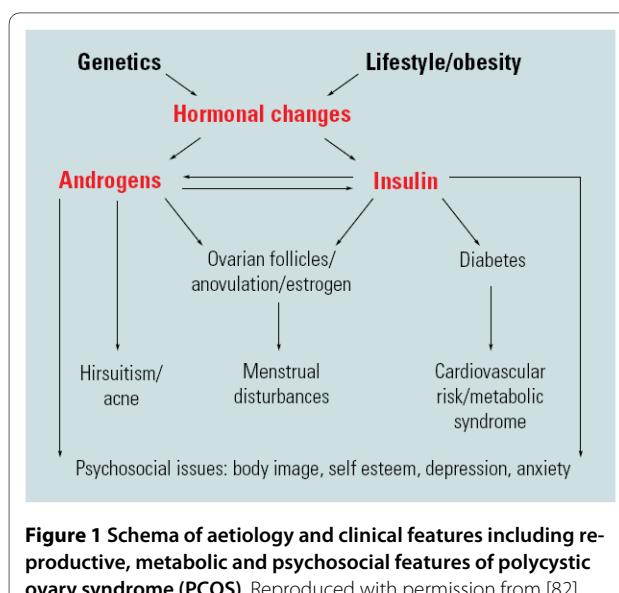


Figure 1 Schema of aetiology and clinical features including reproductive, metabolic and psychosocial features of polycystic ovary syndrome (PCOS). Reproduced with permission from [82].

Table 1: The different diagnostic criteria for polycystic ovary syndrome (PCOS)

National Institutes of Health criteria consensus statement [83]	European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine consensus statement [20]	Androgen Excess Society position statement [21]
Oligo-ovulation and clinical and/or biochemical signs of hyperandrogenism, and exclusion of other aetiologies*	Two out of three of: oligo-ovulation and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, or polycystic ovaries, and exclusion of other aetiologies*	Hyperandrogenism (hirsutism and/or hyperandrogenaemia), ovarian dysfunction (oligoanovulation and/or polycystic ovaries), and exclusion of other androgen excess related disorders*

Table adapted from [14], with permission of Oxford University Press, Oxford, UK.

*Congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome, 21-hydroxylase-deficient non-classic adrenal hyperplasia, androgenic/anabolic drug use or abuse, syndromes of severe insulin resistance, thyroid dysfunction, hyperprolactinaemia.

dysfunction and hyperprolactinaemia should be excluded biochemically, whilst more rare conditions should be excluded clinically (Cushing's syndrome, virilising tumours, and so on). However, cardiometabolic features and insulin resistance are not currently part of the PCOS diagnostic criteria. This is in part attributable to the lack of accurate methods to measure insulin resistance with measurement not currently recommended in clinical practice [22].

With the four key diagnostic features, (oligomenorrhoea/amenorrhoea, clinical or biochemical hyperandrogenism and PCO on ultrasound) there are many potential phenotypes (Table 1) [21]. This heterogeneity of the condition is further exacerbated by degree of obesity, insulin resistance, ethnicity and other factors [21]. Both the heterogeneity of PCOS and the lack of an understanding of its aetiology contribute to the evolving diagnostic criteria and ongoing controversy. Currently the ESHRE/ASRM or Rotterdam criteria are the agreed international diagnostic criteria for PCOS, although further research is needed.

Clinical features of PCOS

Women with PCOS may therefore present with a variety of serious clinical sequelae including psychological problems (reduced quality of life, poor self-esteem, depression, anxiety) [23,24], reproductive manifestations (hirsutism, infertility and pregnancy complications) [25], and metabolic implications (insulin resistance, metabolic syndrome, IGT, DM2 and potentially CVD) [14,26,27] (Figure 1 and Appendix 1). Given the heterogeneous nature of PCOS (Table 1) and the spectrum of clinical features, presentation can vary across the life cycle. PCOS is a chronic condition with psychological and reproductive manifestations usually beginning in adolescence then transitioning to include infertility and increasing metabolic complications over time. However, when combined with obesity, metabolic implications of PCOS such as IGT, DM2 and the metabolic syndrome can present in adolescence [28,29].

Reproductive features of PCOS

Ovarian dysfunction and infertility

Ovarian dysfunction usually manifests as oligomenorrhoea/amenorrhoea resulting from chronic oligo-ovulation/anovulation [30]. However, prolonged anovulation can lead to dysfunctional uterine bleeding which may mimic more regular menstrual cycles. The majority of PCOS patients have ovarian dysfunction, with 70% to 80% of women with PCOS presenting with oligomenorrhoea or amenorrhoea. Among those with oligomenorrhoea, 80% to 90% will be diagnosed with PCOS [30]. Among those with amenorrhoea, only 40% will be diagnosed with PCOS as hypothalamic dysfunction is a more common cause [31]. Oligomenorrhoea occurs usually in adolescence, with onset later in life often associated with weight gain. Menstrual irregularity is then often masked by the oral contraceptive pill (OCP), until cessation, when the underlying irregular cycles recur. Menorrhagia can occur with unopposed oestrogen and endometrial hyperplasia, further exacerbated by elevated oestrogen levels in obesity. Whilst inadequate research exists, it is generally recommended that greater than four cycles per year may protect the endometrium. Women with regular menstrual cycles can also now be diagnosed with PCOS based on newer diagnostic criteria (Table 1) [21].

PCOS is the most common cause of anovulatory infertility. It accounts for 90% to 95% of women attending infertility clinics with anovulation. However 60% of women with PCOS are fertile (defined as the ability to conceive within 12 months), although time to conceive is often increased [30]. In those with PCOS and infertility, 90% are overweight. Obesity independently exacerbates infertility, reduces efficacy of infertility treatment and induces a greater risk of miscarriage [30]. There is currently an active debate about the appropriate limit for body mass index for assisted reproduction therapies, given the reduced success rates and the demonstrated risks of pregnancy in overweight women [32]. Ideally, weight should be optimised prior to pregnancy. Age-

related infertility also exacerbates infertility and timely planning of families may warrant discussion.

Hyperandrogenism

The clinical and/or biochemical signs of androgen excess in PCOS result from increased synthesis and release of ovarian androgens. Elevated luteinising hormone and insulin synergistically increase androgen production. Insulin resistance leads to hyperinsulinaemia, reduces SHBG and raises free circulating testosterone and together, hyperandrogenism and hyperinsulinaemia impairs ovarian follicle development. Clinical hyperandrogenism primarily includes hirsutism, acne and male pattern alopecia [21]. Hirsutism is defined in females as male type terminal hair growth and distribution [33]. PCOS is a common cause of hirsutism occurring in approximately 60% of cases, however this varies with race and degree of obesity [21]. Hirsutism should be assessed with a standardised scoring system (Ferriman-Gallwey score). Acne affects one third of cases and is not particularly specific for PCOS [33]. Male pattern hair loss (androgenic alopecia) is less frequently seen in PCOS cases, as it generally requires a familial predisposition. Other features of hyperandrogenism include virilisation, which, especially if presenting with clitoromegaly and rapid onset, requires exclusion of other causes including adrenal or ovarian androgen-secreting tumours.

Biochemical hyperandrogenism is present in most patients with PCOS. Measurement of biochemical androgens in PCOS is limited by poor accuracy and reproducibility of assays, which are designed for significantly higher male androgen levels. Free androgen index measurements are generally recommended, derived in the lab from SHBG and total testosterone measurements [33]. Dehydroepiandrosterone sulfate (DHEAS) and androstenedione are not routinely recommended in PCOS [21].

Metabolic features of PCOS

Dyslipidaemia

Dyslipidaemia is common in PCOS compared to weight matched controls [34-37], with higher triglycerides and lower high density lipoprotein cholesterol [35]. The dyslipidaemia occurs independent of body mass index (BMI) [35,38], however there is a synergistic deleterious effect of obesity and insulin resistance in PCOS analogous to that seen in DM2. The causes of dyslipidaemia in PCOS are again multifactorial. Insulin resistance appears to have a pivotal role mediated in part by stimulation of lipolysis and altered expression of lipoprotein lipase and hepatic lipase [35].

Insulin resistance and abnormal glucose metabolism

Insulin resistance occurs in around 50% to 80% of women with PCOS [12], primarily in the more severe NIH diag-

nosed PCOS and in those who are overweight. Lean women [13] and milder Rotterdam diagnosed PCOS [14] appear to have less severe insulin resistance. A full discussion of the complex mechanisms involved in insulin resistance, hyperinsulinaemia, DM2 and CVD is beyond the scope of this review. Mechanisms involved in insulin resistance are likely to be complex with genetic and environmental contributors. Specific abnormalities of insulin metabolism identified in PCOS include reductions in secretion [39,40], reduced hepatic extraction [40], impaired suppression of hepatic gluconeogenesis [41] and abnormalities in insulin receptor signalling [42]. Interestingly, there is a paradoxical expression of insulin resistance in PCOS whereby insulin-stimulated androgen production persists while its role in glucose metabolism is impaired [42]. Therefore, insulin resistance in PCOS results in hyperinsulinaemia with its associated diverse and complex effects on regulating lipid metabolism, protein synthesis and modulation of androgen production. The cause of insulin resistance is likewise complex and multifactorial with genetic and environmental contributors [15]. Lean women with PCOS often but not always [13] have abnormalities of insulin secretion and action compared to weight-matched control subjects [41]. Where a woman with PCOS is overweight, she may also demonstrate extrinsic insulin resistance associated with adiposity, which is potentially mechanistically distinct from the insulin resistance present in lean women with PCOS. In women with insulin resistance and PCOS, only a subgroup develop coexistent pancreatic insufficiency with β cell failure and go on to DM2. In this setting, insulin output cannot overcome resistance and hyperglycaemia develops. Women with PCOS are at increased risk of developing IGT and DM2 with prevalence rates of 31.3% and 7.5%, respectively, compared to 14% for IGT and 0% for DM2 in age-matched and weight-matched non-PCOS control women [27].

Women with PCOS also develop abnormal glucose metabolism at a younger age and may demonstrate a more rapid conversion from IGT to DM2 [43]. The rate of conversion from IGT to DM2 in a general Australian population was estimated in the large cohort Australian Diabetes, Obesity and Lifestyle (AusDiab) study at 2.9% per year for young females [44]. Another Australian study has reported a substantially higher conversion rate (8.7% per year over 6.2 years) in women with PCOS [45], however this has not been uniformly reported [46]. Women with PCOS also have higher gestational diabetes (GDM) risk, with a recent meta-analysis reporting an odds ratio (OR) of 2.94 [25]. The risk of GDM occurs both independent of and is exacerbated by obesity [27,47]. Whilst there are few adequately powered studies assessing natural history of IGT, DM2 and CVD in PCOS and there is a need for further research, the International Diabetes Federa-

tion has identified PCOS as a significant non-modifiable risk factor associated with DM2 [48].

It is increasingly clear that IGT is also a clinically relevant state where early identification and intervention improve long-term outcomes [49]. IGT has been found to increase the risk of CVD, mortality and progression to DM2 in general populations [44]. Recent population-based data noted a mortality rate of 5.5% over 5 years for those with IGT versus 1.9% with normal glucose tolerance [44]. Furthermore, lifestyle intervention, metformin and glitazones can prevent IGT progression to DM2 [49], strengthening the argument for early detection of IGT, including in high-risk PCOS women.

There are currently no generic guidelines for IGT screening, only for DM2 based on fasting glucose or more recently on HbA1c as a first line. However, impaired fasting glucose is a poor predictor of IGT in women in general [50] and in PCOS [27,43]. Hence the ESHRE/ASRM-sponsored PCOS Consensus Workshop Group recommend an oral glucose tolerance test in all overweight women with PCOS [51]. Furthermore, emerging data shows increased risk of metabolic complications in first-degree family members of women with PCOS [52-56]. Screening for metabolic conditions may be also warranted in relatives of women with PCOS, although this requires further research.

Cardiovascular disease risk

Alongside insulin resistance, metabolic syndrome, IGT and DM2, women with PCOS also have increased novel cardiovascular risk factors (inflammation, oxidative stress and impaired fibrinolysis) [14]. Also, increased early clinical and subclinical markers of atherosclerosis seen in PCOS (endothelial dysfunction, impaired pulse wave velocity, increased carotid intima media wall thickness, presence of carotid plaque and increased coronary artery calcification) [34,57] are further exacerbated by obesity [27,58,59]. Given that large longitudinal cohort studies have reported up to 65% of CVD deaths occur in subjects with impaired glucose metabolism [60] and that IGT and DM2 are increased in PCOS, it would be expected that women with PCOS would have increased CVD risk. There is currently a lack of long-term studies in PCOS to appropriately address CVD risk. Some studies support an increased risk of CVD in PCOS [18], but these findings are not universal [61] and further research is needed. A recent study in postmenopausal women with premenopausal features of PCOS noted higher prevalence of angiographic coronary artery disease and that PCOS was associated with worsened cardiovascular event-free survival [18].

Psychological features of PCOS

Most research has focused on the biological and physiological aspects of the syndrome. The challenges to femi-

nine identity and body image due to obesity, acne and excess hair, as well infertility and long-term health-related concerns compromise quality of life and adversely impact on mood and psychological well-being [23,62]. Limited studies to date have reported that women who have PCOS are more prone to depression, anxiety, low self-esteem, negative body image, and psychosexual dysfunction [63,64]. The other critical aspect of psychosocial impact in PCOS is the negative impact of mood disturbance, poor self-esteem and reduced psychological well-being on motivation and on ability to implement and sustain successful lifestyle changes that are critical in this condition [19]. These issues all need to be explored and addressed as part of PCOS assessment and management.

Investigations and assessment in PCOS

There is no single diagnostic test for PCOS. Key investigations include prolactin and thyroid stimulating hormone to exclude other disorders and testosterone, SHBG and free androgen index to assess androgen status [33]. Other investigations include a pelvic ultrasound for ovarian morphology and endometrial thickness. An oral glucose tolerance test (rather than fasting glucose) and lipid profiles are appropriate in all women at diagnosis and 1 to 2 yearly after this, where women are overweight or have an increased risk of DM2 (for example, family history of DM2 in first-degree relatives, increased age or high-risk ethnic group). As noted, insulin levels should not be measured in clinical practice because of assay variability and inaccuracy. Metabolic syndrome and abnormal glucose metabolism best reflect insulin resistance in this population.

Treatment of PCOS

Targeted approach to therapy

Treatment options need to be tailored to the clinical presentation. Education on short-term and long-term sequelae of PCOS from a reliable independent source is important in allaying anxiety and minimising the impact of illness in chronic disease (Table 2). As a prelude to treatment psychological features need to be acknowledged, discussed and counselling considered [65], to enable lifestyle change which is unlikely to be successful without first addressing education and psychosocial issues (Figure 2 and Appendix 2).

Weight loss, exercise and lifestyle interventions

Lifestyle change is first line treatment in an evidence-based approach in the management of the majority of PCOS women who are overweight [19]. Furthermore, prevention of excess weight gain should be emphasised in all women with PCOS of both normal or increased body weight. As little as 5% to 10% weight loss has significant clinical benefits improving psychological outcomes [66], reproductive features (menstrual cyclicity, ovulation and

Table 2: Evidence-based government funded resources to inform consumers and/or health professionals in polycystic ovary syndrome (PCOS)

Resource	Description
http://www.managingpcos.org.au	Evidence-based independent consumer and health professional information
http://www.jeanhailes.org.au	Evidence-based independent consumer and health professional information
PCOS patient fact sheets	Freely available: link from website above

fertility) [9,67] and metabolic features (insulin resistance and risk factors for CVD and DM2). Evidence shows that lifestyle change with small achievable goals results in clinical benefits even when women remain in the overweight or obese range, [9,68,69]. Standard dietary management of obesity and related comorbidities [70] is a nutritionally adequate, low fat (approximately 30% of energy, saturated fat approximately 10%), moderate protein (approximately 15%) and high carbohydrate intake (approximately 55%), with increased fibre-rich wholegrain breads, cereals, fruits and vegetables and moderate regular exercise. A moderate energy reduction diet (500 to 1,000 kcal/day reduction) reduces body weight by 7% to 10% over a period of 6 to 12 months. Simple and practical tips that can be covered in minutes in medical consultation include targeting fruit juice, soft drinks, portion sizes and high-fat foods. Incorporating simple moderate physical

activity including structured exercise (at least 30 min/day) and incidental exercise increases weight loss and improves clinical outcomes in PCOS, compared to diet alone [71]. Exercise alone also improves clinical outcomes. As in the general population, goals for exercise must focus on overall health benefits not weight loss *per se*.

Fad diets are not encouraged as short-term weight loss, if achieved, is rarely sustainable [72]. The advantages of specific dietary approaches over that of caloric restriction alone are still unclear and more research is needed. Proposed specific dietary approaches in PCOS include high protein, low carbohydrate and low glycaemic index/glycaemic load diets. A number of small studies assessing specific dietary approaches in PCOS show similar results for diets moderately increased in dietary protein or carbohydrate [73-75] with one study reporting greater weight loss where a high protein supplement was added to a standard energy reduced diet [76]. Two small studies have assessed very low carbohydrate diets in PCOS, and one study reported on an audit of reduced glycaemic load diets in clinical practice. While reductions in weight, BMI, waist circumference, fasting insulin or testosterone were reported, these studies lacked a control group [77-79]. The current evidence suggests that a range of dietary strategies, as long as they are safe, nutritionally adequate and sustainable in the long term, will similarly improve weight, and reproductive and metabolic features in PCOS [19].

Pharmacological therapy in PCOS

There is currently no ideal medical PCOS therapy that fully reverses underlying hormonal disturbances and treats all clinical features. The OCP does improve hyperandrogenism and insulin sensitizers (primarily Metformin) reduce insulin resistance in PCOS [80]. Generally, medical therapy is targeted to symptoms and should not be used as an alternative to lifestyle therapy in PCOS (Figure 2). Simple medical therapy is summarised in Appendix 2. The OCP has long been used in PCOS to induce regular cycles, protect the endometrium and treat hyperandrogenism. Mechanisms of action include a significant first pass hepatic effect, increasing production of hepatic proteins including sex hormone binding globulin. This reduces free circulating androgen levels, even with low dose OCPs. This important mechanism of antiandrogenic action does not occur with progestin alone or non-oral oestrogen containing contraceptive preparations. The OCP also reduces ovarian androgen production. There has been concerning data that the OCP can increase insulin resistance and worsen glucose tolerance. Studies are inadequate and data conflicting with more research needed, however consideration should be given to cardiometabolic effects of medical therapy and low

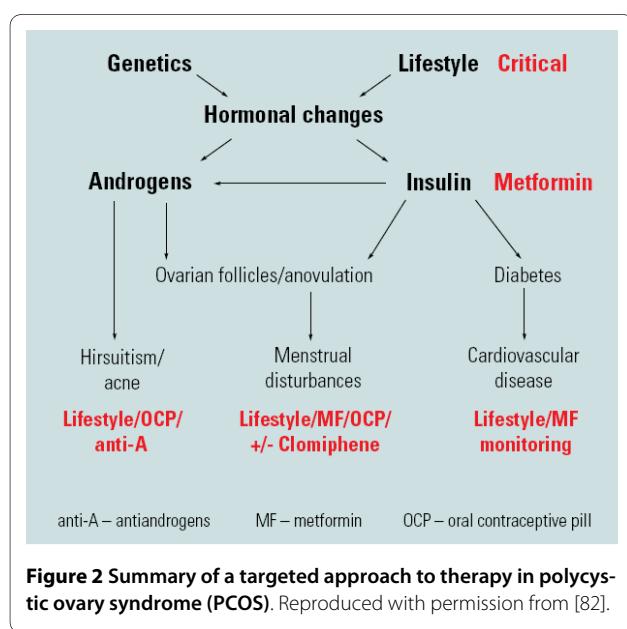


Figure 2 Summary of a targeted approach to therapy in polycystic ovary syndrome (PCOS). Reproduced with permission from [82].

dose OCP preparations may be a preferable alternative, with similar efficacy and reduced cardiometabolic effects [80].

Metformin has had an increasing role in PCOS management [22,81], improving clinical features (ovulation, cycle regulation, and potentially hirsutism) with positive cardiometabolic effects [22,81]. It does not appear to induce weight loss, although based on studies in DM2 it may assist in preventing future weight gain. Based on International Diabetes Federation recommendations [48,80], metformin has a role in prevention of diabetes where lifestyle therapy is inadequate. Given the increased insulin resistance and high risk of DM2, this includes PCOS especially if other risk factors including excess weight, family history of DM2, metabolic syndrome or prediabetes exist [22]. In infertility, the role of metformin remains controversial. It does reduce hyperstimulation in those on other fertility therapies, however more research here is important. When using metformin it is better tolerated if started at 500 mg of slow release daily and increased over weeks to months to reach 2 g daily. Lactic acidosis is a rare side effect in those with other significant illnesses including renal impairment [22]. It is important to note that neither metformin nor the OCP are approved by most regulatory authorities specifically for PCOS. The OCP is indicated for contraception and metformin for the treatment of diabetes. However, both treatments are recommended by international and national endocrine societies and are evidence based [20]. A detailed discussion of infertility therapy is beyond the scope of this review, however clomiphene is generally used as initial medical therapy.

Conclusions

PCOS is a common complex condition in women associated with psychological, reproductive and metabolic features. It is a chronic disease with manifestations across the lifespan and represents a major health and economic burden. Both hyperandrogenism and insulin resistance contribute to pathophysiology of PCOS. Insulin resistance occurs in the majority of women with PCOS, especially those who are overweight, and these women have a high risk of metabolic syndrome, prediabetes and DM2. Management should focus on support, education, addressing psychological factors and strongly emphasising healthy lifestyle with targeted medical therapy as required. Treatment for the large majority is lifestyle focused and an aggressive lifestyle-based multidisciplinary approach is optimal in most cases to manage the features of PCOS and prevent long-term complications. Small achievable goals of 5% loss of body weight result in significant clinical improvement even if women remain clinically in the unhealthy overweight or obese range. Addressing hyperandrogenism is clinically important and

monitoring for and managing longer-term metabolic complications, including dyslipidaemia, IGT, DM2, and cardiovascular risk factors, is crucial. Consideration should be given to screening high-risk family members for metabolic abnormalities also. Overall, further research is needed in this complex condition. In the interim, comprehensive evidence-based guidelines are needed to guide consumers and clinicians in optimal PCOS management.

Appendix 1

Reproductive, metabolic and psychosocial features of polycystic ovary syndrome (PCOS)

Clinical features of PCOS

(1) Reproductive features: hyperandrogenism, hirsutism, ovulatory and menstrual dysfunction, infertility, complications in pregnancy, miscarriage, pregnancy-induced diabetes (gestational diabetes), pregnancy-induced hypertensive disorders and neonatal complications and increased endometrial hyperplasia.

(2) Metabolic features: insulin resistance, metabolic syndrome, dyslipidaemia, high rates of premature impaired glucose tolerance, type 2 diabetes and increased cardiovascular risk factors.

(3) Psychological features: anxiety, depression, poor self-esteem, reduced quality of life, negative body image.

Appendix 2

Summary of treatment options in polycystic ovary syndrome (PCOS)

Oligomenorrhoea/amenorrhoea

- Lifestyle change (5% to 10% weight loss and structured exercise).
- Oral contraceptive pill (OCP; low oestrogen doses, for example 20 µg may be preferable).
- Cyclic progestins (for example, 10 mg medroxyprogesterone acetate for 14 days every 2 to 3 months).
- Metformin (improves ovulation and menstrual cyclicity).

Hirsutism treatment recommendations

- Cosmetic therapy.
- Laser treatment.
- Flornithine cream can be added and may induce a more rapid response.

Pharmacological therapy

- Medical therapy if patient concerned about hirsutism and cosmetic therapy ineffective, inaccessible or unaffordable.
- Primary therapy is the OCP (monitor glucose tolerance in those at risk of diabetes).
- Antiandrogen monotherapy should not be used without adequate contraception.
- Trial therapies for ≥ 6 months before changing dose or medication.

- Combination therapy: if ≥ 6 months of OCP is ineffective, add antiandrogen to OCP (daily spironolactone 50 mg twice a day or cyproterone acetate 25 mg/day for days 1 to 10 of the active OCP tablets).

Infertility

- Obesity independently exacerbates infertility and reduces effectiveness of interventions. Maternal and foetal pregnancy risks are greater and long-term metabolic outcomes in the child are related to maternal weight at conception. Consistent with international guidelines, women who are overweight prior to conception should be advised on folate, smoking cessation, weight loss and optimal exercise, prior to additional interventions.
- Given age-related infertility, advise women to optimise family planning.
- Infertility therapies may include clomiphene, gonadotrophins and *in vitro* fertilisation.

Metabolic syndrome, prediabetes, diabetes and cardiovascular disease risk

Obesity independently causes metabolic complications; lifestyle/exercise is critical:

- Lifestyle change with a 5% weight loss reduces diabetes risk by approximately 50% to 60% in high-risk groups [49].
- Metformin* reduces the risk of diabetes by approximately 50% in high-risk groups [49].

*Metformin and the OCP are not currently approved for use to manage PCOS by many regulatory bodies. The OCP is primarily indicated for contraception and metformin for diabetes. However, their use is recommended by international and national specialist societies and is evidence based [22].

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HT, AD and LM all made substantial contributions to conception and design of the paper, were involved in drafting the manuscript and revising it critically for important intellectual content and have given final approval of the version to be published.

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Polycystic ovary syndrome: reviewing diagnosis and management of metabolic disturbances

Síndrome dos ovários policísticos: revisando o diagnóstico e o manejo dos distúrbios metabólicos

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common condition in women at reproductive age associated with reproductive and metabolic dysfunction. Proposed diagnosed criteria for PCOS include two out of three features: androgen excess, menstrual irregularity, and polycystic ovary appearance on ultrasound (PCO), after other causes of hyperandrogenism and dysovulation are excluded. Based on these diagnostic criteria, the most common phenotypes are the "classic PCOS" – hyperandrogenism and oligomenorrhea, with or without PCO; the "ovulatory phenotype" – hyperandrogenism and PCO in ovulatory women; and the "non-hyperandrogenic phenotype", in which there is oligomenorrhea and PCO, without overt hyperandrogenism. The presence of obesity may exacerbate the metabolic and reproductive disorders associated with the syndrome. In addition, PCOS women present higher risk for type 2 diabetes and higher prevalence of cardiovascular risk factors that seems to be associated with the classic phenotype. The main interventions to minimize cardiovascular and metabolic risks in PCOS are lifestyle changes, pharmacological therapy, and bariatric surgery. Treatment with metformin has been shown to improve insulin sensitivity, lowering blood glucose and androgen levels. These effects are more potent when combined with lifestyle interventions. In conclusion, besides reproductive abnormalities, PCOS has been associated to metabolic comorbidities, most of them linked to obesity. Confounders, such as the lack of standard diagnostic criteria, heterogeneity of the clinical presentation, and presence of obesity, make management of PCOS difficult. Therefore, the approach to metabolic abnormalities should be tailored to the risks and treatment goals of each individual woman. Arq Bras Endocrinol Metab. 2014;58(2):182-7

Keywords

PCOS; obesity; insulin resistance; metformin

RESUMO

A síndrome dos ovários policísticos (PCOS) é um distúrbio frequente em mulheres em idade reprodutiva, associado com disfunção reprodutiva e metabólica. Os critérios diagnósticos atuais para PCOS incluem pelo menos dois dos três seguintes: hiperandrogenismo, irregularidade menstrual e aparência policística dos ovários à ultrassonografia (PCO), após exclusão de outras causas de hiperandrogenismo e anovulação. Com base nesses critérios diagnósticos, os fenótipos mais comuns são "PCOS clássico" – hiperandrogenismo e oligomenorreia, com ou sem PCO; o "fenótipo ovulatório" – hiperandrogenismo e PCO em mulheres ovulatórias; e o "fenótipo não hiperandrogênico" – no qual ocorrem oligomenorreia e PCO sem hiperandrogenismo evidente. A presença de obesidade pode exacerbar os distúrbios metabólicos e reprodutivos associados com a síndrome. Além disso, mulheres com PCOS apresentam maior risco para diabetes tipo 2 e maior prevalência de fatores de risco cardiovascular, que parecem estar associados com o fenótipo clássico. As principais intervenções para minimizar riscos metabólicos e cardiológicos em PCOS são mudanças de estilo de vida, tratamento farmacológico e cirurgia bariátrica. O tratamento com metformina melhora a sensibilidade à insulina, reduz a glicemia e os níveis de androgénios. Esses efeitos são mais evidentes quando a metformina é associada às mudanças de estilo de vida. Em conclusão, além das anormalidades reprodutivas, a PCOS tem sido associada com comorbidades metabólicas ligadas à obesidade. Fatores confundidores, como a falta de critérios diagnósticos padronizados, heterogeneidade da apresentação clínica e presença de obesidade, tornam difícil o manejo clínico de PCOS. Assim, a abordagem das anormalidades metabólicas deve ser individualizada para os riscos e objetivos terapêuticos de cada mulher. Arq Bras Endocrinol Metab. 2014;58(2):182-7

Descritores

PCOS; obesidade; resistência insulínica; metformina

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disease affecting women of reproductive age. The prevalence of PCOS varies according to the diagnostic criteria used, with estimates ranging from 9% in women of reproductive age, according to NIH criteria, up to 18%, with the Rotterdam criteria (1-3).

PCOS is a multifactorial disease, and the individual susceptibility is probably determined by multiple genetic and environmental risk factors. It is primarily characterized by ovulatory dysfunction and hyperandrogenism (1,2), but the clinical presentation is heterogeneous and patients may present some of various signs and symptoms (Table 1). This heterogeneity seems to be modulated by multiple factors, such as prenatal androgen exposure, nutritional status in the uterus, genetic factors, as well as ethnicity, insulin resistance of puberty and/or exaggerated adrenarche and changes in body weight (4-6). Environmental factors, such as obesity, appear to exacerbate the underlying genetic predisposition. Concerning ethnicity, the presence of hirsutism is less frequent in Asian patients (around 10%), compared to Caucasian ones (70%) (1,6).

Hirsutism is defined as a score of 8 or more on the modified Ferriman-Gallwey index (7). Oligo/amenorrheic cycles are defined as 8 or less cycles per year and biochemical androgen determinations should be performed in the follicular phase in patients with preserved menstrual cycles.

Table 1. Clinical presentation of PCOS

Hirsutism, acne, alopecia
Irregular menstrual cycles, oligomenorrhea, amenorrhea
Ovulatory dysfunction and infertility
Increased risk for T2 diabetes, dyslipidemia, hypertension

DIAGNOSTIC CRITERIA

Proposed diagnosed criteria for PCOS include the NIH Consensus (8), defined, in 1990, as the presence of clinical and/or biochemical hyperandrogenism and oligomenorrhea/anovulation (Table 2). Later, in 2003, the Rotterdam Consensus (9) introduced the polycystic ovary appearance (PCO) on ultrasound as a new criterion to be added to the two previous criteria of the NIH, and the diagnosis requires two out of these three criteria. In turn, the Androgen Excess and PCOS Society (10) considered that androgen excess is a central event in the pathogenesis and development of PCOS,

and established that this criterion should be present and accompanied by one of the others: oligomenorrhea and/or PCO (Table 2). In all cases, exclusion of other androgen excess disorders, such as non-classical congenital adrenal hyperplasia (NC-CAH), Cushing's syndrome, androgen-secreting tumors, hyperprolactinemia, thyroid diseases, drug-induced androgen excess should be excluded, as well as other causes of oligomenorrhea or anovulation.

Table 2. Diagnostic criteria for PCOS

NIH Consensus 1990 (all required)	Rotterdam Consensus 2003 (two out of three required)	AEPCOS definition 2006 (androgen excess and one other criterion)
Clinical and/or biochemical hyperandrogenism	Clinical and/or biochemical hyperandrogenism	Clinical and/or biochemical hyperandrogenism
Oligo/amenorrhea, anovulation	Oligo/amenorrhea, anovulation	Oligo/amenorrhea, anovulation
	Polycystic ovaries appearance on ultrasound	Polycystic ovaries appearance on ultrasound

Exclusion of other androgen excess disorders: NC-CAH, Cushing's syndrome, androgen secreting tumors, hyperprolactinemia, thyroid diseases, drug-induced androgen excess. Other causes for anovulation should also been excluded.

In consequence, new phenotypes have arisen in addition to the classic phenotype, in which patients present hyperandrogenism and oligomenorrhea with or without PCO on ultrasound. These new phenotypes are the "ovulatory phenotype", which means hyperandrogenism and PCO in an ovulatory woman, and the "non-hyperandrogenic phenotype", in which there is oligomenorrhea and PCO, without overt hyperandrogenism.

PCO has been defined as the presence of 12 or more follicles of 2-9 mm or ovarian volume greater than 10 cm³ (9). However, with the new equipment, it is possible to visualize and count small follicles of less than 2 mm nowadays (11). Therefore, the consequence of the improved ovarian imaging is the revaluation of the current follicle number threshold, and the probable increase in the number of follicles to more than 19-26 follicles per ovary and per age classes to better define PCOS (11,12). Anti-Müllerian Hormone (AMH) levels are correlated with follicle counts and its measurement has been useful for screening and prognosis of reproductive issues. The determination of an AMH cutoff value is still lacking, but may become an additional tool to define PCO and PCOS phenotypes in the near future (11-13).

In turn, morphological ovarian changes are not exclusive of PCOS, and the presence of PCO in non-hirsute women with normal cycles is not negligible, varying from 2.5 to 33% in different studies (10,14). In addition, while the inclusion of a non-hyperandrogenic phenotype of the diagnosis of PCOS is still controversial, some authors consider the presence of PCO as being itself a sign of hyperandrogenism.

Recently, an Expert Panel from a NIH Evidence-Based Methodology Workshop on PCOS reinforced the use of the wider Rotterdam Criteria to diagnose the Syndrome. Therefore, the prevalence of PCOS is now greater than before when using the NIH criteria (15). Classic PCOS is the most common phenotype, with a prevalence of around 70%, with the ovulatory and the non-androgenic phenotypes sharing the other 30% of prevalence (1,3,13).

Clinical characterization also changes throughout the lifespan, especially during the post-menarche years and in the menopause transition.

DEFINITION AND PREVALENCE OF PCOS IN ADOLESCENT GIRLS

PCOS is a persistent challenge to the clinician, as the phenotype of the syndrome can vary widely. This is still more evident during the post-pubertal period, as signs and symptoms of PCOS overlap with normal puberty. There is a relatively high rate of menstrual irregularity and anovulatory cycles in this period, as well as some difficulties in interpreting clinical and biochemical evidence of hyperandrogenism: acne is a very common complaint during adolescence, alopecia is a rare phenomenon in girls, and hirsutism is sometimes borderline and aggravates slowly.

Uncertainty also regards the significance of polycystic ovarian morphology on ultrasound: microcysts are often seen even before menarche. In a previous study with normal girls from 1 to 13 years old, we have shown the presence of paucicystic ovaries on ultrasound (up to five follicles measuring less than 10 ml) in 7% of girls before puberty and in 18% of girls with telarche. The prevalence of multicystic ovaries (more than six follicles measuring less than 10 mL) was found in 9% of girls 12 and 13 years with initial puberty (16). In contrast, ovary volume greater than 10 mL seems to be a better marker of PCOS in adolescent girls presenting hyperandrogenism and oligo/amenorrhea for at least 2 years post-menarche (17,18).

Because of these uncertainties, and the fact that the majority of ultrasound examinations in adolescent girls is abdominal and not transvaginal, the diagnosis of PCOS in adolescents needs all three Rotterdam criteria, and not only two (13). Therefore, for the diagnosis of PCOS in adolescent girls, one should consider: 1) oligo/amenorrhea at least 2 years post-menarche or primary amenorrhea at age 16 years; 2) PCO morphology including increased ovarian volume ($> 10 \text{ cm}^3$); 3) biochemical hyperandrogenemia, and not only clinical hyperandrogenism. However, even if the diagnosis cannot be confirmed and needs to be postponed, individual manifestations (hirsutism, irregular menses) should be treated.

PCOS IN MENOPAUSAL TRANSITION AND POST-MENOPAUSE: ARE THERE SPECIFIC FEATURES?

In menopausal transition, there may be an amelioration of clinical features. In fact, there is a trend towards more regular cycles and improvement on hirsutism with aging (19). This is in part due to the well-known decrease in androgen secretion from the third to the fifth decade of life that occurs in normal women (20), and has been also reported in PCOS (13,19,21). In addition, ovarian volume decreases along with pre-menopause and menopause transition, as previously reported (22). Thus, alterations in ovarian volume and morphology may be less evident in PCOS during menopausal transition, and PCO criteria are not useful after menopause.

In fact, no specific clinical presentation during menopause has been established, and the diagnosis of PCOS is, in general, confirmed before this period, based on the history of oligomenorrhea and hyperandrogenism. Additionally, clinical or biochemical hyperandrogenism appearing in previously normal peri- or post-menopausal women should be carefully investigated in order to screen them for androgen-secreting tumors.

OBESITY, INSULIN RESISTANCE AND METABOLIC COMORBIDITIES

Obesity is a prevalent characteristic of PCOS (9,23), ranging from 12.5% (24) to 100% (25), with a pooled estimated prevalence of 49% (26), as shown by a recent meta-analysis (27). The presence of obesity may exacerbate the metabolic and reproductive disorders

associated with the syndrome (28), including insulin resistance, dyslipidemia, and metabolic syndrome (23,29-31). A meta-analysis (32) has shown that women with PCOS have higher levels of triglycerides (TG), LDL-cholesterol and total cholesterol (TC), and lower HDL-cholesterol levels compared with control women, regardless of body mass index (BMI). In addition, PCOS women present higher risk for type 2 diabetes (13,14). PCOS is also associated with a clustering of cardiovascular risk factors (10,13,29,33,34). However, there is no definitive evidence for increased cardiovascular events, nor data showing that PCOS alone leads to increased cardiovascular risk independent of associated risk factors. In fact, more rigorous cohort studies of long-term cardiovascular outcomes and clinical trials of risk factor modification are required for women with PCOS.

In addition, evidence suggests clinical phenotypes are related with different metabolic risks (Table 3). In this sense, insulin resistance seems to be a specific feature of the classic phenotype and, to a lesser extent, of the ovulatory phenotype (29,35,36). Non-hyperandrogenic phenotype behave as a separate group that is metabolically similar to non-PCOS women (15,32).

Table 3. Clinical features of different phenotypes

Classic PCOS	Ovulatory PCOS	PCOS without hyperandrogenism
Hyperandrogenism and anovulation with or without PCO	Hyperandrogenism and PCO	Anovulation and PCO
More severe menstrual disturbances and hyperandrogenism	Lesser degrees of hyperandrogenism	Minor menstrual irregularity
Higher prevalence of total and abdominal obesity and metabolic syndrome	Lower prevalence of metabolic syndrome and milder forms of dyslipidemia	Metabolic profile often similar to normal women
Higher prevalence of T2DM and cardiovascular risk factors		

MANAGEMENT OF METABOLIC DISTURBANCES

Insulin resistance (and compensatory hyperinsulinemia) is an important factor in maintaining hyperandrogenemia by acting directly on theca cells inducing excess androgen production. Insulin also acts as a co-gonadotropin, increasing the effect of LH on ovarian androgen secretion. In consequence, both insulin and androgens act on the liver inhibiting SHBG secretion,

leading to increased free and bioactive androgen circulating levels and making clinical hyperandrogenism worse. In addition, insulin resistance plays a central role on the pathophysiology of metabolic syndrome and on the cardiovascular risk in PCOS women.

However, insulin resistance is a common, but not universal feature of PCOS, and treatment should be directed to the consequences rather than to insulin resistance *per se* (37). These consequences are metabolic syndrome; clinical features shown to improve with insulin-sensitizing drugs, such as acanthosis nigricans; total and abdominal adiposity, as well as impaired fasting glucose (IFG, fasting glucose equal or higher than 100 mg/dL); impaired glucose tolerance (IGT, 2 h post-glucose equal or higher than 140 mg/dL); and type 2 diabetes (T2DM) (37,38).

The main interventions to minimize cardiovascular and metabolic risks in PCOS are lifestyle changes, pharmacological therapy, and bariatric surgery (Table 4). Lifestyle modification is the first form of therapy combining behavioral (reduction of psychosocial stressors), dietary, and exercise management. Frequently, however, it will be necessary to add an insulin-sensitizing drug (ISD) to the treatment. Metformin and thiazolidinediones (pioglitazone) are the main available ISD. However, due to the eventual weight gain and cancer risks of thiazolidinediones, the prescription of these drugs has been limited to diabetic patients and will not be discussed here.

Table 4. Treatment of metabolic comorbidities in PCOS

Non pharmacological interventions
Physical activity
Diet and lifestyle changes
Insulin sensitizing drugs
Metformin
Specific treatment for diabetes, hypertension, dyslipidemia and obesity
Bariatric surgery

Metformin, a biguanide, has been widely used for PCOS patients, and evidence indicates it is beneficial for women with PCOS with metabolic syndrome and/or obesity, as well as for affected women who have impaired glucose tolerance, since the efficacy of metformin for diabetes prevention has been demonstrated in individuals with pre-diabetes (38). Its main action is in the liver, with suppression of gluconeogenesis and hepatic glucose output, but it also enhances peripheral insulin action, and reduces glucose absorption from the

digestive tract, with no significant direct effect on pancreatic insulin production (39). Metformin also directly inhibits thecal androgen production (40).

In women with PCOS, treatment with metformin has been shown to ameliorate the cardiometabolic profile by improving insulin sensitivity, lowering blood glucose and androgen levels and possibly by its effects on body weight (41-44). These effects of metformin are more potent when it is combined with lifestyle intervention (41). Diets with low caloric intake are part of the treatment and those with low glycemic index appear to be better adjusted for PCOS patients (26,43).

It is important to underscore, however, that the first-line treatment for hirsutism, menstrual irregularities and infertility are anti-androgens, contraceptive steroids, and clomiphene citrate, respectively. While metformin is more effective than oral contraceptives in reducing fasting insulin and not increasing triglycerides, it is less effective in improving menstrual pattern, hirsutism or decreasing testosterone (45). Importantly, there is no evidence of benefits in the absence of insulin resistance.

Metformin is also a reasonable treatment option for those women to whom oral contraceptives may not be recommended, such as PCOS patients presenting moderate to severe high blood pressure, high triglycerides levels, class II or III obesity and/or metabolic syndrome. In this case, and especially if antiandrogen drugs are added to the treatment, other options for contraception should be recommended, including progestogen-only pills (mini-pill) or IUDs.

The usual dose of metformin for PCOS is 1,500 to 2,500 mg per day. A main limitation can be side effects, which are predominantly gastroenterological, consisting of abdominal discomfort, nausea, and diarrhea. These symptoms are usually dose-dependent and can be minimized by gradually increasing the dose of metformin over a period of 1-2 months. Initial doses should be 250-500 mg/day, taken just before the main meal. In the case gastrointestinal side effects recidivate, the current dose may be reduced for a period of 7-10 days, followed by a resumption of the dosage increase. Hepatic and renal function should be monitored before and during treatment.

Specific additional treatment for high blood pressure, dyslipidemia or obesity may be needed for individual PCOS women. Additionally, bariatric surgery may be another option for severe obesity or obesity with metabolic comorbidities (13,46).

In conclusion, besides reproductive abnormalities, PCOS has been associated to metabolic comorbidities, most of them, but not all, linked to obesity. Confounders, such as the lack of standard diagnostic criteria, the heterogeneity of the clinical presentation, and the presence of obesity, make the management of PCOS difficult. Therefore, the approach to metabolic abnormalities should be tailored to the risks and treatment goals of each individual woman.

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Diagnosis and Challenges of Polycystic Ovary Syndrome in Adolescence

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Abstract

Although the diagnostic criteria for polycystic ovary syndrome (PCOS) have become less stringent over the years, determination of the minimum diagnostic features in adolescents is still an area of controversy. Of particular concern is that many of the features considered to be diagnostic for PCOS may evolve over time and change during the first few years after menarche. Nonetheless, attempts to define young women who may be at risk for development of PCOS is pertinent since associated morbidity such as obesity, insulin resistance, and dyslipidemia may benefit from early intervention. The relative utility of diagnostic tools such as persistence of anovulatory cycles, hyperandrogenemia, hyperandrogenism (hirsutism, acne, or alopecia), or ovarian findings on ultrasound is not established in adolescents. Some suggest that even using the strictest criteria, the diagnosis of PCOS may not be valid in adolescents younger than 18 years. In addition, evidence does not necessarily support that lack of treatment of PCOS in younger adolescents will result in untoward outcomes since features consistent with PCOS often resolve with time. The presented data will help determine if it is possible to establish firm criteria which may be used to reliably diagnose PCOS in adolescents.

Keywords

- polycystic ovary syndrome
- polycystic ovarian morphology
- type 2 diabetes mellitus

Polycystic ovary syndrome (PCOS) is a common endocrinopathy that by strictest definition affects 5 to 10% of women of reproductive age.¹ It is characterized by menstrual irregularity, hyperandrogenism, and polycystic ovarian morphology (PCOM) and is also associated with insulin resistance, obesity, and components of the metabolic syndrome (MetS).^{2,3} PCOS often presents during adolescence, but the diagnosis in this age group is complicated by the overlap between the features of PCOS and physiologic findings observed during the normal progression of puberty.⁴ Further, the diagnosis is difficult to make with certainty given the absence of universally accepted diagnostic criteria for adolescents.

Three distinct sets of diagnostic criteria have been suggested for the diagnosis of PCOS in adults. The National Institutes of Health Consensus Statement¹ proposed that PCOS be defined as menstrual irregularity (chronic anovulation or oligomenorrhea) and evidence of clinical or biochemical hyperandrogenism with the exclusion of other

etiologies. The 2003 European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine Rotterdam criteria (ESHRE/ASRM)⁵ broadened the diagnosis of PCOS, requiring two of three features: anovulation or oligo-ovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries by ultrasound (US). Finally, the Androgen Excess and PCOS Society⁶ defined PCOS as hyperandrogenism with ovarian dysfunction or polycystic ovaries. Most recently, the NIH Evidence-Based Methodology Workshop on PCOS³ recommended use of the 2003 Rotterdam criteria with identification of specific phenotypes within the diagnosis.

As stated, at present there is not a total agreement regarding definitive criteria for the diagnosis of PCOS in adolescents. We reviewed 73 papers published since 2006 where adolescents with PCOS were described (**►Table 1**).^{7–79} Of interest, 22 studies used NIH, 42 used Rotterdam, and 8 used Androgen Excess Society (AES) or other criteria to

Table 1 Review of diagnosis of PCOS in adolescents (2006–2013)^{7–79}

• Number of studies: 69; case reports: 4
• Criteria used ^a
– NIH 22
– Rotterdam 42
– AES/other 8
– Not specified 7
• Nationality
– USA 30, Canada 1, Chile 2, France 1, Italy 4, Spain 2, Finland 1, Germany 2, England 1, Poland 1, Tunisia 1, India 7, Greece 2, Turkey 3, Iran 2, Saudi Arabia 1, China 5, Taiwan 1, Hong Kong 1, Korea 1, Australia 3, New Zealand 1
• Study size: 1–1,563 subjects
• Mean age of subjects
– 15.1–29.1 y: 64 studies
– < 25 y: 62 studies
• Time since menarche: 0.5–5 y (22/73 data available)

Abbreviations: AES, Androgen Excess Society; NIH, National Institute of Health, PCOS, polycystic ovary syndrome.

^aFive of the above mentioned articles used multiple criteria.

diagnose PCOS, some using more than 1. Seven of the studies reviewed did not specify any diagnostic criteria used. Of these studies, 31 were from North America, 21 were from Asia, 14 were from Europe, 1 was from Africa, and 3 were from Australia and New Zealand. Only 22 of the studies mentioned number of years postmenarche of the subjects.

Further, the variability of diagnoses in and of PCOS poses various challenges. Use of different criteria can result in a different prevalence of PCOS, even within the same cohort.^{43,44} Clearly, while early diagnosis in adolescents may allow for earlier treatment and prevention of PCOS-associated morbidity, premature diagnosis carries risks of psychological distress and unnecessary treatment.

Numerous studies have called into question the appropriateness of applying adult criteria to adolescents because the features of PCOS are often physiologic or transitory during normal puberty.^{80,81} Thus, several adolescent-specific criteria have been proposed. Sultan and Paris⁸² suggests requiring four out of five of the following: oligomenorrhea or amenorrhea at least 2 years postmenarche, clinical hyperandrogenism, biologic hyperandrogenism, insulin resistance, and polycystic ovary morphology, while Carmina et al⁸⁰ and the 2012 ESHRE/ASRM Consensus Workshop Group⁸³ propose defining PCOS in adolescents by the presence of all three of the 2003 ESHRE/ASRM criteria: hyperandrogenism, chronic anovulation, and polycystic ovaries.

This review will discuss the components utilized by the many suggested criteria to allow one to establish the diagnosis of PCOS in adolescents as well as the ongoing challenge and controversy related to this goal.

Hyperandrogenism

Hyperandrogenism is a hallmark of PCOS; the NIH and AES criteria both require clinical and/or biochemical hyperandrogenism for the diagnosis of PCOS in adults, while the Rotterdam criteria recognize a phenotype of PCOS without androgen excess.^{1,5,6} This feature of PCOS is especially important given its reported association with metabolic dysfunction.^{21,29,35} However, the physiologic rise in androgens that occurs during puberty makes hyperandrogenism difficult to define in adolescents. Furthermore, there is not yet a consensus regarding the preferred assay or reference values for assessing hyperandrogenemia in this age group.⁸⁴

Clinical hyperandrogenism is defined by most adult PCOS diagnostic criteria as the presence of hirsutism, acne, or androgenic alopecia.^{1,5} Hirsutism, as measured by the modified Ferriman-Gallwey (mFG) score, is recognized as the most reliable marker of clinical hyperandrogenism in women with PCOS.⁸³ In Caucasian and African American women, an mFG score of ≥ 8 is often used to define hirsutism in the diagnosis of PCOS,⁷⁰ and this cutoff has been used by numerous studies of PCOS in adolescents.⁴⁴ However, because of less cumulative time of exposure to androgens, this cutoff may require modification for use in adolescents.⁸⁵ In addition, expression of hirsutism in and of itself appears to have ethnic variability.^{86,87}

Roe et al⁷⁰ recently reported that 65% of adolescents with PCOS presented with hirsutism, which is consistent with other studies that report a high prevalence.⁴⁰ The common finding of acne in healthy adolescents, which is as high as 69%,⁴⁴ precludes its utility as a specific marker of hyperandrogenism in PCOS. Hickey et al⁴⁴ found no relationship between acne score and free testosterone (T) level or PCOM. Finally, androgenic alopecia has not been studied widely in adolescents and does not appear to be important for the assessment of hyperandrogenism in this population.⁸⁸ Of the three markers of clinical hyperandrogenism, progressive hirsutism is considered the most useful in adolescents.^{80,88}

Biochemical hyperandrogenism, a more objective measure of excess androgens, can be assessed using a variety of assays to test for serum levels of total testosterone (TT), free T, androstenedione, and dehydroepiandrosterone sulfate. The adult PCOS criteria provide little consensus and guidance as to which assay to use, albeit use of highly specific assays is increasingly being recommended.⁸⁹

The 2007 Endocrine Society position statement about the utility, limitations, and pitfalls of measuring T⁸⁴ does not specifically discuss androgens in adolescents, but suggests the use of TT assays, as opposed to free T, when measuring androgens in children. The position statement also suggests the use of T assays that use extraction and chromatography techniques, instead of direct immunoassays, to maximize sensitivity and accuracy and also stresses the need for standardized assay-specific reference values. Because of diurnal and menstrual cycle variation of T, for consistency it is recommended to be measured between 08:00 and 10:00 hours during the follicular phase.⁸⁴

More recently, liquid chromatography-tandem mass spectrometry (LC-MS/MS) has been studied as a technique for measuring total T in adults^{90,91} and adolescents.^{92,93} Two groups^{92,93} recently developed reference ranges for total T in adolescents using LC-MS/MS and determined this method to be sufficiently sensitive and precise to be used in adolescents. Both groups measured T between 8:00 and 10:00 AM, and one made separate cutoffs based on menstrual cycle phase. However, a comparison of radioimmunoassay and LC-MS/MS measurement of TT in women did not find a significant difference between the results of the two methods although "there is significant variability between LC/MS assays and poor precision with all assays at low T levels."⁸⁹

Thus, while hirsutism appears to be an important clinical marker of hyperandrogenism in adolescents, and a common presenting sign of PCOS, some have argued that biochemical hyperandrogenism is a more reliable and consistent marker of hyperandrogenism in the diagnosis of PCOS in adolescents.^{4,5} Both should be evaluated in the workup of an adolescent with suspected PCOS.

Menstrual Irregularity

Menstrual irregularity is an important feature of PCOS in adults and common in the presentation of PCOS in adolescents.⁷⁰ Chronic oligo-ovulation or anovulation are included in all adult diagnostic criteria for PCOS. However, menstrual irregularity and anovulation are common among healthy adolescents, making their use in the diagnosis of PCOS in this group difficult.

In a study of 200 healthy girls, Apter and Vikho⁹⁴ found that at least 55% of menstrual cycles were anovulatory during the first 2 years postmenarche. The percentage of ovulatory cycles increased with age, reaching 80% at 4 to 5.5 years of gynecological age. While menstrual irregularity is common, its persistence after 2 years after menarche is associated with PCOS. Nair et al⁵¹ studied a cohort of 136 adolescent girls with confirmed menstrual irregularity; at 2 year follow-up, 51.5% continued to have menstrual irregularity and 36% were diagnosed with PCOS using the Rotterdam criteria. In their cohort, Roe et al⁷⁰ found that 98% of adolescents diagnosed with PCOS by the AE-PCOS criteria presented with menstrual irregularity—68.3% with oligomenorrhea, 27.7% with secondary amenorrhea, and 4% with primary amenorrhea.

There is evidence that greater menstrual irregularity is associated with a more severe PCOS phenotype and higher androgen levels.⁵ Rachmiel et al³⁰ reported that adolescents with primary amenorrhea and PCOS have increased features of MetS and higher androstenedione compared with those with oligomenorrhea. A study of a Finnish cohort found that adolescent girls with menstrual irregularity had increased T, decreased sex hormone binding globulin, and an increased free androgen index.⁵⁴ van Hooff et al found that about half of 14 to 16 year olds with oligomenorrhea remained oligomenorrheic at 18 years; body mass index (BMI) and menstrual history, but not androgen and luteinizing hormone concentrations, were predictive of persistent amenorrhea.⁹⁵

Although it is often difficult to distinguish physiologic adolescent anovulation from PCOS-related menstrual irregularity,⁹⁶ some have offered suggestions for how menstrual irregularity should be defined in adolescents and when it should be evaluated. Merino et al⁸⁸ suggested that adolescent ovulatory dysfunction should be considered with the absence of menstrual periods for longer than 90 days, or persistent cycles longer than 45 days. Rosenfield suggested evaluation for menstrual irregularity when adolescents exhibit abnormal menstruation for at least 1 year or if it is associated with other signs and symptoms.⁹⁶

The high prevalence of anovulatory cycles and menstrual irregularity in adolescence has led some to recommend that oligoamenorrhea should persist for at least 2 years and that only then can PCOS be diagnosed in adolescents who are at least 2 years postmenarche.^{5,40,80} Advocates of this proposal state that because of the high frequency of menstrual irregularity in healthy adolescent girls, the diagnosis of PCOS in adolescents should not be made on the basis of menstrual irregularity alone.^{80,97}

It is interesting to speculate that although dysfunctional intermittent uterine bleeding in adolescents can be confused with normal cycling with long interval cycles, in fact, it may be that these adolescents are actually those who already have evidence of chronic anovulation. In addition, some authors suggest that measurement of progesterone is the most specific way to assess ovulation⁹⁸; however this is usually impractical in a clinical setting.

Ovarian Morphology

PCOM is included in both the AES-PCOS and Rotterdam diagnostic criteria for PCOS, which define PCOM as 12 or more follicles of 2 to 9 mm or ovarian volume > 10 cm³ in at least one ovary.⁵ Recently Dewailly et al actually suggested that the former threshold of greater than 12 follicles per ovary may even be too low and a count of 19 follicles would be needed for more accurate diagnosis.⁹⁹ In adults, transvaginal US is the standard imaging method used to evaluate ovarian morphology, however because it is inappropriate for use in virginal adolescents, transabdominal US (TA-US) is instead often used in younger patients. Polycystic ovaries are a common finding in healthy adolescents, making the use of PCOM as a diagnostic criterion for PCOS in adolescents difficult.⁸¹

Mortensen et al⁹ reported that 54% of healthy eumenorrheic girls between 1.3 and 3.8 years postmenarche had polycystic ovaries on TA-US, with a significant correlation between ovarian size and gynecological age. This correlation between increasing age and decreasing ovarian volume has also been found in adults.¹⁰⁰ Several other studies of healthy adolescents found the incidence of PCO to be 33 to 35% by TA-US.^{43,44,101} While up to half of healthy adolescents meet PCO criteria, a third of adolescents with PCOS do not.⁹⁶

Furthermore, the limitations of TA-US present a challenge in using PCOM in the diagnostic criteria for adolescents. This method is less discriminating than transvaginal US and especially difficult to use in obese patients, who make up

about half of the PCOS population.⁹⁷ Transrectal US and magnetic resonance imaging (MRI) have been used in a few studies, but these methods may be less practical in a clinical setting.^{97,102}

Several authors have argued for the need for adolescent-specific thresholds for mean ovarian volume (MOV) for use in the diagnosis of PCOS. New thresholds have been suggested by groups using different imaging modalities. Villa et al⁵³ found that a MOV threshold of 5.6 mL was 89% sensitive and 80% specific for diagnosing PCOS using TA-US, while Chen et al¹⁰³ reported that a cutoff of 6.74 mL maximized specificity and sensitivity in Chinese adolescents using transvaginal US. Another study found an average MOV of 15.1 in adolescents with PCOS compared with 5.9 in healthy controls using MRI. In a comparison of TA-US and MRI in 11 obese adolescents with PCOS, Yoo et al found that MOV was not significantly different between the two methods, but that the number of patients who met Rotterdam criteria for PCO was different between the US and MRI groups.¹⁰⁴

The limitations of using US for the detection of PCO have led to interest in anti-Müllerian hormone (AMH) as a surrogate marker. AMH is a glycoprotein secreted by granulosa cells of growing follicles and has been found to correlate with the number of small antral follicles.⁸⁸ However, reports about the utility of AMH as a marker for PCO in adolescents have been mixed. Hart et al³⁶ found that while serum AMH is significantly higher in adolescent girls with PCO, AMH level had insufficient specificity and sensitivity for detecting PCO. Villarroel et al,¹⁰¹ who studied adolescents with regular menstrual cycles, and Li et al,³⁹ who studied Chinese adolescents with PCOS, developed similar cutoffs for AMH to predict PCO with sensitivities of 64 and 61% and specificities of 89.8 and 70%, respectively. Eilertsen et al¹⁰⁵ reported that serum AMH has good accuracy for diagnosing PCOS in adults when it replaces PCOM as a criterion for PCOS diagnosis. Although more work remains to assess the use of AMH as a surrogate marker for PCO, it may prove useful as a component to aid in the diagnosis of PCOS.

Obesity, Insulin Resistance, and Metabolic Syndrome

PCOS is associated with metabolic abnormalities including insulin resistance, obesity, type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease, dyslipidemia, and the MetS.^{2,4,106} There is evidence that these metabolic impairments begin as early as adolescence in women with PCOS. Although metabolic features are not included in the diagnostic criteria for PCOS, they are important to consider in adolescents given their implications on long-term health. At present, the molecular mechanisms responsible for the interactions between hyperandrogenism, obesity, and insulin resistance in PCOS are not fully understood.

Obesity is common in both adults and adolescents with PCOS. It is unclear whether PCOS predisposes women to obesity or whether obesity exacerbates PCOS.¹⁰⁷ Several studies show the prevalence of obesity in PCOS to be above 60%;¹⁰⁸ Glueck et al found that 73% of adolescents with PCOS had a BMI above the 95th percentile.¹⁰⁹

While a large portion of adolescents with PCOS are obese, obesity likely does not fully explain the other metabolic features associated with PCOS. Impaired glucose tolerance (IGT), which is associated with insulin resistance and is a strong predictor for T2DM, cardiovascular disease, and premature mortality,¹¹⁰ is found at an increased rate in adolescents with PCOS. Several studies of adolescents with PCOS have reported the incidence of IGT to be 10 to 30%.^{34,37,79,111} Flannery et al⁷⁹ found that IGT occurred across the spectrum of BMI and Huang et al³⁷ found that when matched for obesity, PCOS is associated with increased risk for insulin resistance, hyperinsulinemia, and prediabetes. However, Hart et al⁴³ found that PCOS was not associated with insulin resistance after controlling for BMI, and Glueck et al found that when matched for age, PCOS subjects did not have significantly different insulin or lipid levels than healthy controls.¹⁰⁹ While IGT is the most common form of abnormal glucose metabolism found in adolescents with PCOS, impaired fasting glucose and T2DM have also been reported in this group.^{1,56,79}

MetS, a group of risk factors that increase the risk for cardiovascular disease and diabetes, is also associated with PCOS. Up to 40% of adults with PCOS have MetS.³⁴ In adolescents, multiple sets of criteria are used to define MetS and the prevalence of MetS varies among different cohorts. Most studies, however, report an increased incidence of MetS in PCOS compared with control subjects.^{21,41,52,70} Coviello et al²¹ found that 35% of girls with PCOS had MetS compared with 5% of controls and that this difference could not be accounted for by obesity alone. The reported prevalence in other studies ranges from 10 to 60%.^{41,52,70} Gleuck et al¹⁰⁹ found that a diagnosis of PCOS at age 14 was a significant independent determinant for MetS at age 24. However, in a cohort that included only obese and overweight participants, Rossi et al³⁴ reported that the prevalence of MetS did not differ significantly between PCOS and controls when matched for obesity, regardless of the definition of MetS used. Similarly, Huang et al³⁷ found that PCOS was not associated with an increased risk for MetS when matched for obesity in a Chinese adolescent cohort.

It has been proposed that the hyperandrogenism associated with PCOS contributes to the metabolic abnormalities discussed above. Fruzzetti et al³⁵ reported that hyperandrogenemia was an important risk factor for lipid alterations in adolescents with PCOS. Another study²¹ found higher levels of free T in adolescents with MetS and reported that levels of the hormone were positively correlated with BMI percentile, waist circumference, and fasting insulin. Elevated systolic and diastolic blood pressures have also been shown to be related to androgen levels in girls with PCOS.^{21,29} In a large prospective study of schoolgirls, Glueck et al¹⁰⁹ reported that low sex hormone-binding globulin was the only significant predictor of MetS and that women with MetS at 24 years of age were more likely to have had a top decile free T at age 14. However, Forrester-Dumont et al⁵⁰ found that metabolic profile was not affected by the degree of hyperandrogenism in girls with PCOS, instead, low HDL best explained the high prevalence of MetS. While most studies agree that obesity and MetS occur

more frequently in adolescents with PCOS compared with the general population, the role of hyperandrogenism in this association remains controversial.

This review will not focus on therapy, however many clinical investigators still suggest that weight loss and lifestyle changes should be the first line of therapy. Metformin and oral contraceptive pills are also considered as secondary treatments that can improve the symptoms of PCOS. However, medical treatment of a condition not fully diagnosed can result in premature use of pharmacologic agents. The issue of treatment of PCOS in the adolescent further underlines the need for consensus and further research about the diagnosis of PCOS in this group. The many points of overlap between physiologic puberty and the features of PCOS may continue to suggest that a more conservative approach to the diagnosis of PCOS in adolescents compared with adults is prudent.

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ORIGINAL RESEARCH

Polycystic Ovary Syndrome in adolescents: a qualitative study

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Background: Adolescents with Polycystic Ovary Syndrome (PCOS) use different coping strategies to confront the challenges of this disorder. Various studies extracted coping strategies amongst adult women with PCOS, but regarding the mental difference between adults and adolescents, specific study was conducted to gain a deep understanding of how adolescents cope to the many health issues they experience.

Methods: Fifteen adolescents aged 13–19 years with PCOS participated in comprehensive individual interviews with goal-oriented, semi-structured questions. Sampling was purposive and continued until data saturation was reached. Data were analyzed using the thematic analysis technique. The validity of the data was verified through measures including credibility, transferability, dependability, confirmability and authenticity.

Results: The analysis of the data helped extract the main theme of the research as “dealing with PCOS”. The main theme consisted of three themes and 12 sub-theme: (1) Escaping the problem (sub-themes: Adopting a forgetting mindset, and concealment and minimization of the disorder); (2) Depressive mood (sub-themes: Poor self-perception and low self-esteem, isolation, sleep disturbances, passive aggressive behavior, emotional turmoil, feelings of humiliation, and adolescents’ perceptions); and (3) Coping with the disease (sub-themes: Recovery of health, positive thinking, hope for recovery).

Conclusion: In this study, the adolescents with PCOS showed a coping response to their disorder in the form of problem-solving, developing a depressive mood or adjusting to the disorder. Recognizing the mental health needs of these adolescents and improving their quality of life require the identification of ways through which they deal with PCOS.

Keywords: polycystic ovary syndrome, adolescents, qualitative research

Introduction

Polycystic Ovary Syndrome (PCOS) is a multifactorial disorder caused by interactions between genetic, environmental and intrauterine factors.¹ Various studies have reported the prevalence of this syndrome in adolescence as 9% to 15%.^{2–4} Based on the available evidence, metabolic, inflammatory, oxidative, emotional and psychological stress is an important part of PCOS.⁵ While the incidence of any disease or disorder can lead to anxiety and worry,⁶ studies have shown that women with PCOS experience emotional distress, depression and anxiety more frequently than others, and when confronted with the disorder, some become more anxious and stressful.^{7–10} PCOS therefore affects the daily life of many people.¹¹ It disturbs the joys of adolescence, because the stigma associated with hyperandrogenism is more intensely felt in this age group and is likely to damage the psychosocial development of adolescent girls.¹²

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Patients with this disorder have to go through different stages of coping wherein they will likely have to respond to internal stress (physiological and psychological stressors) and external stress (environmental and social factors related to the syndrome) using coping responses.¹³ The acceptance of any disorder is a complicated process that depends on factors such as the manifestation of the disorder, the availability and quality of treatment, individual demands (eg, mental demands, emotional demands, stress, coping strategies, etc.), support of the family members and other relatives and socioeconomic status.¹⁴ Adolescence is a time of physical, cognitive and emotional changes as well as a period of great change in various aspects of life.¹⁵ Adolescents usually deal with their problems through a variety of methods, including problem-solving methods that focus on changing the status quo, problem-solving, approaching others (seeking spiritual and social support from friends), using strategies to ignore their problems and running away from them, and self-blaming and non-coping behaviors.¹⁶ Managing chronic conditions such as chronic pain, diabetes and cancer in adolescents leads to a variety of coping responses and some are associated with successful adaptation.¹⁷

The aim of qualitative research is to understand the experiences and circumstances of individuals and explain concepts from their perspective, and experiences often vary from one person to the other.¹⁸ The review of literature suggests the diversity of the coping strategies used by adult women with PCOS,^{19,20} while studies on adolescents with this syndrome are rather limited. Given the crucial role of coping strategies in adolescents with this chronic disease, the present study was conducted to gain a comprehensive understanding of the strategies used by adolescents with PCOS to cope with the challenges of this disorder.

Methods

Fifteen adolescents with PCOS able to share their rich experiences of coping with the disorder participated in this qualitative study. All the interviews were in Persian. The entire research team members and participants were fluent in Persian. The research team was composed of a qualitative methodologist as the principal researcher, a gynecologist and a PhD student of reproductive health. Purposive sampling continued until data saturation was achieved. The inclusion criteria for the study consisted of being an adolescent with PCOS as diagnosed by a gynecologist (based on the National Institute of Child Health

and Human Development (NICHD) or the National Institutes of Health (NIH) criteria), having hyperandrogenism, oligo-ovulation/anovulation, age between 13 and 19 years, and willingness of the patient and their parents for participation in the study and sharing experiences. In this study parent or legal guardian provided written informed consent for any participant under the age of 18 years.

Before beginning data collection, the research project was approved by the ethics committee of Shahid Beheshti University of Medical Sciences in Tehran, Iran. The ethical principles observed for the research included obtaining informed consent, preserving the confidentiality of the data and giving the participants the right to leave the study whenever they desired.

Individual in-depth interviews were held with semi-structured questions ("What are your experiences with this disorder at this stage of life?" and "How has this disorder affected your mental state?"). The minimum and maximum duration of the interviews was 30 and 55 mins. The interviews were held in a relaxed and private environment in the health centers of Shahid Beheshti University of Medical Sciences in Tehran, Iran. All the interviews were recorded with prior permission from the participants. Thematic analysis was used in this study. Thematic analysis is a flexible and foundational method for qualitative analysis.²¹ In the beginning, to immerse in the data, the research team transcribed the recorded audio interviews and the members read transcripts thoroughly. In order to generate the initial codes, the research team members extracted the semantic units. Then, the codes were collated into potential themes. The themes were reviewed for generating a thematic map. Finally, the themes were defined and given names and the final report was prepared.

Trustworthiness

Credibility, transferability, dependability, confirmability and authenticity measures were used to verify the data. The methods used in this study to verify the accuracy of the data included the selection of contributors with a variety of experiences, persistent observation, member checking, use of a coding framework, prolonged engagement with data, team consensus on themes, thick descriptions of context, purposive maximum variation sampling (selection of adolescents with different characteristic such as age, family economic status, education, etc.) and discussing some of the findings with a number of the participants.

Results

Thematic analysis categorized coping strategy into one main-theme as “Dealing with PCOS” and 3 themes and 12 sub-themes. Themes and sub-themes are as follow:

Escaping the problem (sub-themes: Adopting a forgetting mindset, and concealment and minimization of the disorder).

Depressive mood (sub-themes: Poor self-perception and low self-esteem, isolation, sleep disturbances, passive aggressive behavior, emotional turmoil, feelings of humiliation, adolescents’ perceptions)

Coping with the disease (sub-themes: Recovery of health, positive thinking, hope for recovery), as shown in Figure 1.

The characteristics of selected participants are mentioned in Table 1.

Escaping the problem

The “escaping the problem” theme was formed in this study by combining two sub-themes, namely “forgetting” and “concealment and minimization of the disorder”. The adolescents tried to escape their challenges by not disclosing their disorder to others so as to reduce the burden of psychological issues, and they used the method of forgetting to rid themselves of intrusive thoughts. The experiences of some of the participants in the study showed that

they used the method of “forgetting” to escape their problems and tried to understand which thoughts resulted in their stress and then chose different ways to distract themselves from these thoughts. In the words of the participants:

“Sometimes, when I think of the disorder, I push the thoughts away. I’ve become inattentive” (Participant 1, 19 years old).

Because I was immersed in my university entrance exam, my mind was preoccupied. This issue (PCOS) has not been important to me at all. I’m always busy studying. I do not have the time to think about it. (Participant 8, 18 years old).

I’ve become indifferent now. It’s no more important to me how it has gotten on my nerves. I don’t think about it anymore because I can’t do anything about it. I went to the doctor, I took medicines, but it didn’t get better. (Participant 6, 19 years old).

The experiences of some of the participants also showed that they somehow tried to escape the problem by “concealing and minimizing the syndrome”. In the words of the participants:

“I’m not upset because they say it is very common and could happen to anyone, and it’s not a rare disorder. Anyone I see, I tell them I have PCOS and I’m taking medicines. It’s normal” (Participant 1, 19 years old).

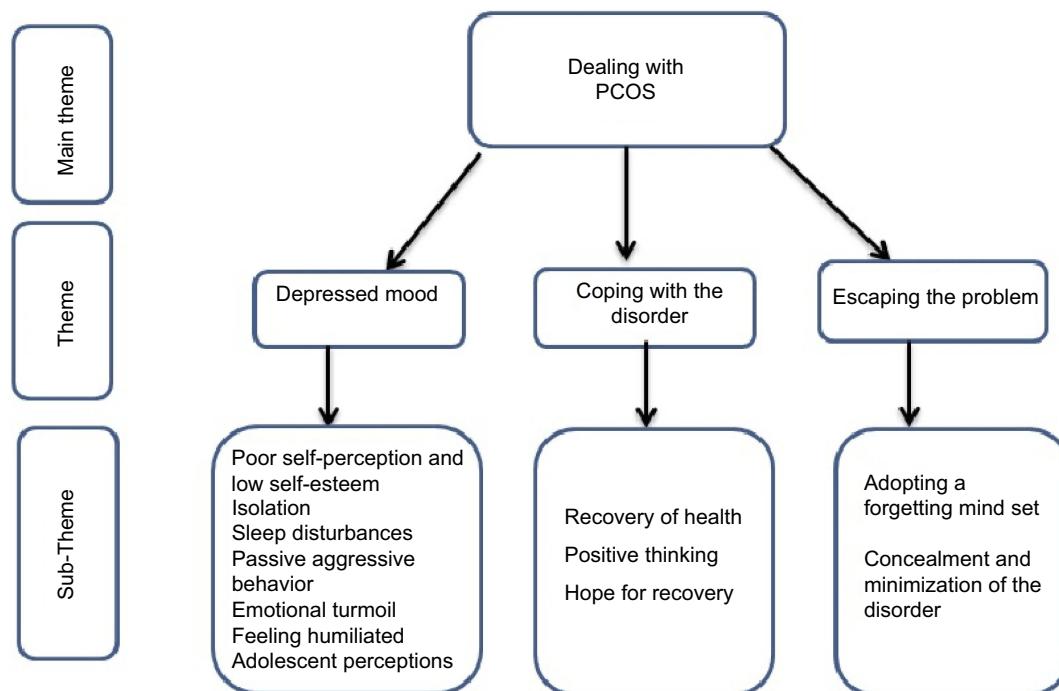


Figure 1 Theme and sub-themes.

Table I Characteristics of study samples (n=15)

Variable		Number
Age group	13–15	2
	15–17	3
	17–19	10
Marital status	Single	13
	Married	2
Years living with PCOS	<1 year	8
	>1 year	7
Main symptom	Obese or overweight	8
	Acne	11
	Hair loss	11
	Hirsutism	13
	Irregular menstruation	12

"I try not to take my pills in front of people because they ask why I'm taking pills. I don't tell anyone about my disorder" (Participant 9, 18 years old).

Depressive mood

The "depressive mood" theme was developed with seven sub-themes, including "poor self-perception and self-esteem", "isolation", "sleep disturbances", "passive aggressive behavior", "emotional turmoil", "feeling humiliated" and "adolescents' perceptions". Some of the adolescents experienced "laziness" and "sadness" after their diagnosis with PCOS and also concerns about failing to recover, constant worries about the disorder and psychological distress, which eventually ended in their "losing the joys of adolescence" and they began to lose focus. These experiences led to unpleasant feelings, and struggles with the disorder for many years caused "emotional disturbances" for some of the adolescents. According to participants' experiences, some of them tried to cope with their problems through "aggressiveness" and "making excuses." Often, they became isolated because of "limiting their relationships with their friends and close relatives" and "preferring to be alone than to be with others". The experiences of the participants also showed that, because of "internal feelings of distress when in gatherings where people were inquisitive" and "being in turmoil due to feeling different from peers", some of them felt humiliated and had a low self-esteem and sometimes also experienced symptoms of physical change caused by their psychological changes. The experiences of most participants showed that the visibility of their symptoms to their peers and others made them feel vulnerable, and as a result, they

preferred not to be in touch with anyone in order to avoid showing their vulnerability. In the words of the participants:

"When I'm in front of the mirror, I feel bad, cause I have a lot of hair and acne" (Participant 15, 19 years old).

"I do not have much confidence when with others, cause I think they are better than me. It's the same for my family, my friends ..." (Participant 3, 16 years old).

Loneliness and "isolation" were one of the common strategies of the adolescents in this study to cope with their disorder. In the words of the participants:

I don't have much patience for myself; I don't have patience for others; I prefer to be left alone at home. What I mean is that I prefer everyone to go out visiting and enjoying themselves but leaving me home alone. (Participant 13, 19 years old).

"I try not to be in touch with my friends ... I've only told my best friend about my polycystic ovary syndrome" (Participant 15, 19 years old).

Stressful conditions were associated with "sleep disturbances" in some of the participants. In the words of the participants:

"I'm always sleepy. I feel so sleepy. I'm constantly falling asleep. It's awful. It has been two or three years that I've become like this. I mean, since the morning, when I wake up, I feel sleepy" (Participant 6, 19 years old).

"I think so much about it that I can't sleep. I go out [of my bedroom] to drink water. I can't sleep at all until 5 or 7 am" (Participant 12, 13 years old).

Some of the adolescents who participated in the study expressed their agitation and negative feelings about the onset of their syndrome and were unknowingly showing passive aggressive behavior. In the words of the participants:

"I'm always fighting with everyone. I've become stubborn. When I get worried about something, I go to my room and shut the door. I start to cry and then lock the door" (Participant 3, 16 years old).

"I'm so distressed that I keep fighting with my family. I say, 'It's all your fault, you've caused this problem for me!' (Participant 12, 13 years old).

Concerns about the syndrome and its presentations and reasons caused tension in most of the participants and they were faced with "emotional disturbances". In the words of these participants:

"I'm worried about seeking further treatment because they told me that no special treatment exists yet" (Participant 2, 15 years old).

"I really don't have the patience, unlike in the past. For example, I had so many interests to pursue that I really enjoyed going out, but not anymore" (Participant 10, 19 years old).

"I don't think so much about it. It makes me very upset. My entire life has become consumed with this problem. I've lost my appetite. I'm so upset" (Participant 12, 13 years old).

"My inner feelings are such that, like, when you want to do something for yourself, say, make an effort for the sake of your life, continuing it causes problems because of this disorder" (Participant 2, 15 years old).

"Right now, I feel that, the way my friends hang out and are happy in each other's company, I'm not like that" (Participant 6, 19 years old).

"Most of the time, my mind was preoccupied and I couldn't concentrate on a particular problem" (Participant 2, 15 years old).

"My particular concern is that if this continues, what's going to happen ... Will this illness be with me all my life and will I have to always cope with it and take medications?" (Participant 4, 19 years old).

"I think so much about it. When I look at myself in the mirror, I say, 'What kind of life is this?'" (Participant 2, 15 years old).

"My nerves are so weakened ..." (Participant 12, 13 years old).

I didn't use to go and visit others ... not that I said I didn't like to go and see people. For example, when I sat down, someone would ask me if I was on a diet and I would get angry and want to answer back, but I had to keep the boundaries of respect, so I wouldn't say anything. And then, I wouldn't go to visit people at all because of this. (Participant 13, 19 years old).

Some of the adolescents who participated in the study perceived themselves as below optimal because of the symptoms of their syndrome and imagined that they were not worthy and felt "humiliated". In the words of the participants:

Compared to my friends, I see myself very different. For example, they wear fashionable items that I have always liked to own, but I could never be like that, because of the excessive hair that I have to hide, my obesity and hair loss. (Participant 2, 15 years old).

The manifestation of mental stress as a result of the syndrome and mental turmoil in some of the participants led to "adolescents' perceptions". In the words of the participants:

"I'm usually tired. My activities have diminished, unlike the vitality I had before" (Participant 14, 17 years old).

"I don't like to move too much. I like to just always sit somewhere" (Participant 10, 19 years old).

Coping with the disorder

"Coping with the disorder" consisted of three sub-themes, namely "the recovery of health", "positive thinking" and "hope for recovery". Most of the adolescents who participated in this study tried to reduce the mental stress of having PCOS through academic accomplishments and took measures to promote their physical health. Although the adolescents felt responsible for their own health, they neglected it nonetheless, because they prioritized their studies and future career prospects.

Some of the adolescents attempted to create a positive image of their disorder and created a positive vibe for seeking treatment by adopting a "hope for recovery" approach. Some of them coped with the syndrome through a "positive internal dialogue". Some of the participants in this study were taking "health recovery" measures to cope with their syndrome. In the words of the participants:

"Right now, studying is my priority, and when I've completed my studies, I want to go to the doctor again" (Participant 1, 19 years old).

"I am far too busy with the university entrance examination and my studies to have any time for this disease at all" (Participant 8, 18 year-old).

"I used to regard my disorder as trivial. I didn't think it was necessary for me to take my pills. Later, I began taking it very seriously" (Participant 9, 18 years old).

Some of the participants were able to rid themselves of disturbing thoughts through "positive thinking" and coped with their disorder. In the words of these participants:

"I came to accept myself, 'Okay, you have this condition, you have this pimple!' I accepted it as it was and then wouldn't think about it" (Participant 4, 19 years old).

"It's a mild illness –not a very dangerous disorder" (Participant 4, 19 years old).

Some of the participants took steps to cope with the disorder through a "hope for recovery". In the words of this group of the participants:

"My medications are one too many, but I take them with the hope of getting better. Just like this. I take my

medications to get better soon" (Participant 6, 19 years old).

"When I take my medicines, since they regulate my period, I feel good" (Participant 8, 18 years old).

Discussion

The findings of this study include concepts such as escaping the problem, depressed mood and coping with the disorder. In conjunction with each other, these concepts led to the formulation of dealing with PCOS.

As the sociocultural context of any society can affect individuals' strategies for coping with critical situations, the sociocultural and religious contexts of the Iranian society can also affect the type of strategies adolescents adopt to cope with PCOS. Like in many Middle Eastern countries, cultural and educational issues also have a major role in adolescents' mental health in Iran.²²

Evidence suggests that dealing with a chronic disease, such as adolescent diabetes, requires a coping strategy that can help improve the health outcomes and quality of life of the patient.²³

Other chronic diseases such as adolescent cancer or serious infections that may cause future infertility have also become a serious concern for both adolescent patients and their parents as per their responses.^{24,25} The diagnosis of any fertility disorder in adolescents can disrupt the normal psychosocial development of the individual.²⁶ In general, the manifestation of symptoms such as obesity, acne, hirsutism and the disruption of the menstrual cycle lead to stress in these patients and they cope with this stress in different ways.

In the experiences of the participants, some of the adolescents with PCOS were trying to escape their problems by forgetting and often with the concealment and minimization of their disorder. The results of a study on women with PCOS showed that those who suffered more psychological problems used maladaptive coping strategies, such as avoidance strategies, and used less problem-focused coping strategies.²⁷ Avoidance coping is known as an effective short-term strategy, but in the long term, it prevents psychological adjustment and increases depression.^{28,29}

The results of other studies on social coping strategies have shown that adolescents use different coping techniques, such as avoidance coping, problem-solving and seeking social support.³⁰

It seems that most participants in the present study were turning to these strategies to escape being labeled

as "sick" and to be able to cope with the disorder in some way by denying its existence to themselves and others. It is a proven fact, however, that avoidance coping could cause a downward spiral in the long-term.

The experiences of the participants of this study showed that adaptation to illness could emerge as a depressive mood in some adolescents. The diagnosis of PCOS has psychological ramifications.³¹ Depression and moodiness in adolescents and the appearance of a depressive mood have been argued to be associated with symptoms such as disturbed sleep, lethargy, restlessness, changes in appetite and weight, decreased motivation and concentration, decreased self-esteem and isolation.³² In one qualitative study, the experiences of 12 people with PCOS aged 17 to 51 years revealed great mental anxiety in coping with this disorder.¹⁹ The onset of PCOS is associated with the instability of emotions, confusion and moodiness and leads to feelings of irritability, fear and despair in social relationships and a general sense of unhappiness.^{33,34}

The establishment of social relationships is vital during adolescence.³⁵ Adolescents with this disorder choose isolation to counteract the reactions of those around them. The acceptance of adolescents with PCOS by the community and those close to them helps improve their behavior, while increased criticism, especially in this vulnerable age group, reduces self-esteem and increases anxiety and depression and ultimately leads to abandoned social relationships.³⁶ In contrast, a negative body image destroys the individual's social competence and causes the abandoning of intimate relationships.^{37,38} Changes in one's physical appearance, concerns over changes in one's mental body image and the development of anxiety about the ramifications of the disorder seem to play a role in the manifestation of a depressive mood as a kind of coping response to the disease.

The experiences of the participants in this study also showed that those who responded with positive thoughts and had hope for their future well-being and recovery chose an adaptive coping response to the disorder. The various factors affecting the acceptance of the disorder also contribute to the PCOS patient's coping with the disorder.³⁹ The results of a study on women with PCOS showed that coping strategies were more excitement-oriented.⁴⁰ Another qualitative study on women with PCOS also showed that coping strategies include deliberation (religious beliefs, paradoxical thoughts), practical steps (positive steps such as seeking information and treatment as well as negative steps such as detachment and

concealment) and seeking support (family support and peer support) in these patients.⁴¹ Evidence suggests that the types of coping strategies chosen by women with PCOS affect their quality of life.²⁰ Some studies have even suggested that hope is a very powerful force that can play a key role in coping with adolescent illnesses.⁴² Hope is occasionally a solution to tension that increases the individual's ability to adapt.⁴³ Some of the participants of this study were able to cope with their mental turmoil through their hope to recover. Meanwhile, some attempted to take steps towards coping with their disorder through positive thoughts. Positive thoughts comprise a branch of cognitive therapy that can be defined as the usage of hopefulness, happiness and positive mental abilities.⁴⁴

A study by Benson et al (2010) conducted on 449 women with PCOS showed that some participants had a passive coping strategy in dealing with this syndrome (retreating and accepting one's fate regarding the disorder), which is an unharmonious strategy that leads to the emergence of anxiety and depression and in turn decreases the quality of life. In contrast, some participants who adopted active coping strategies (problem-solving and information-seeking) had lower levels of depression.⁴⁵ The participating adolescents of this study had a positive attitude and took health-recovery measures to cope with the disorder.

Active coping involves problem-solving and social support-seeking while passive coping involves social isolation.¹⁷ The results of one study on children and adolescents with a chronic illness showed that coping with such a disease may lead to effective coping with daily stressors of life.⁴⁶

Some of the participants used problem-solving through positive thoughts and measures to deal with the stressful conditions of life. They used a rational strategy to accept their disorder and their tensions thus decreased. In general, chronic PCOS requires self-efficacy and lifestyle modifications.⁴⁷ As for the psychological burden of PCOS, choosing a proper coping strategy plays a decisive role in the quality of life of adolescents with the disorder, as irrational strategies could cause harm and threaten different dimensions of life. The use of clinical counseling, mental health services, beauty counseling services and support services for patients and their families can contribute significantly to the improvement of the quality of life of adolescents with chronic PCOS.⁴⁸

Implementing psychological counseling programs (by psychologists and other allied health professionals) and

teaching adolescents adaptive coping strategies are recommended to prevent future mental health problems. Attention to mental health and related care measures is imperative for medical teams.

The study limitations include the non-generalizability of the results to all adolescents with this syndrome, although this limitation applies to all qualitative studies in nature. Furthermore, forgetting certain experiences or the unwillingness to actually express these experiences and feelings on the part of the adolescents could be considered another limitation of the study.

Conclusion

When confronted with the stressful symptoms of PCOS, the participants adolescents of this study showed coping responses such as escaping the problem, depressive mood or coping with the syndrome. Identifying the ways through which these adolescents cope with their syndrome is vital for recognizing the mental health needs of PCOS patients and improving their quality of life.

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Disclosure

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ORIGINAL RESEARCH

Polycystic Ovary Syndrome in adolescents: a qualitative study

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Background: Adolescents with Polycystic Ovary Syndrome (PCOS) use different coping strategies to confront the challenges of this disorder. Various studies extracted coping strategies amongst adult women with PCOS, but regarding the mental difference between adults and adolescents, specific study was conducted to gain a deep understanding of how adolescents cope to the many health issues they experience.

Methods: Fifteen adolescents aged 13–19 years with PCOS participated in comprehensive individual interviews with goal-oriented, semi-structured questions. Sampling was purposive and continued until data saturation was reached. Data were analyzed using the thematic analysis technique. The validity of the data was verified through measures including credibility, transferability, dependability, confirmability and authenticity.

Results: The analysis of the data helped extract the main theme of the research as “dealing with PCOS”. The main theme consisted of three themes and 12 sub-theme: (1) Escaping the problem (sub-themes: Adopting a forgetting mindset, and concealment and minimization of the disorder); (2) Depressive mood (sub-themes: Poor self-perception and low self-esteem, isolation, sleep disturbances, passive aggressive behavior, emotional turmoil, feelings of humiliation, and adolescents’ perceptions); and (3) Coping with the disease (sub-themes: Recovery of health, positive thinking, hope for recovery).

Conclusion: In this study, the adolescents with PCOS showed a coping response to their disorder in the form of problem-solving, developing a depressive mood or adjusting to the disorder. Recognizing the mental health needs of these adolescents and improving their quality of life require the identification of ways through which they deal with PCOS.

Keywords: polycystic ovary syndrome, adolescents, qualitative research

Introduction

Polycystic Ovary Syndrome (PCOS) is a multifactorial disorder caused by interactions between genetic, environmental and intrauterine factors.¹ Various studies have reported the prevalence of this syndrome in adolescence as 9% to 15%.^{2–4} Based on the available evidence, metabolic, inflammatory, oxidative, emotional and psychological stress is an important part of PCOS.⁵ While the incidence of any disease or disorder can lead to anxiety and worry,⁶ studies have shown that women with PCOS experience emotional distress, depression and anxiety more frequently than others, and when confronted with the disorder, some become more anxious and stressful.^{7–10} PCOS therefore affects the daily life of many people.¹¹ It disturbs the joys of adolescence, because the stigma associated with hyperandrogenism is more intensely felt in this age group and is likely to damage the psychosocial development of adolescent girls.¹²

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Patients with this disorder have to go through different stages of coping wherein they will likely have to respond to internal stress (physiological and psychological stressors) and external stress (environmental and social factors related to the syndrome) using coping responses.¹³ The acceptance of any disorder is a complicated process that depends on factors such as the manifestation of the disorder, the availability and quality of treatment, individual demands (eg, mental demands, emotional demands, stress, coping strategies, etc.), support of the family members and other relatives and socioeconomic status.¹⁴ Adolescence is a time of physical, cognitive and emotional changes as well as a period of great change in various aspects of life.¹⁵ Adolescents usually deal with their problems through a variety of methods, including problem-solving methods that focus on changing the status quo, problem-solving, approaching others (seeking spiritual and social support from friends), using strategies to ignore their problems and running away from them, and self-blaming and non-coping behaviors.¹⁶ Managing chronic conditions such as chronic pain, diabetes and cancer in adolescents leads to a variety of coping responses and some are associated with successful adaptation.¹⁷

The aim of qualitative research is to understand the experiences and circumstances of individuals and explain concepts from their perspective, and experiences often vary from one person to the other.¹⁸ The review of literature suggests the diversity of the coping strategies used by adult women with PCOS,^{19,20} while studies on adolescents with this syndrome are rather limited. Given the crucial role of coping strategies in adolescents with this chronic disease, the present study was conducted to gain a comprehensive understanding of the strategies used by adolescents with PCOS to cope with the challenges of this disorder.

Methods

Fifteen adolescents with PCOS able to share their rich experiences of coping with the disorder participated in this qualitative study. All the interviews were in Persian. The entire research team members and participants were fluent in Persian. The research team was composed of a qualitative methodologist as the principal researcher, a gynecologist and a PhD student of reproductive health. Purposive sampling continued until data saturation was achieved. The inclusion criteria for the study consisted of being an adolescent with PCOS as diagnosed by a gynecologist (based on the National Institute of Child Health

and Human Development (NICHD) or the National Institutes of Health (NIH) criteria), having hyperandrogenism, oligo-ovulation/anovulation, age between 13 and 19 years, and willingness of the patient and their parents for participation in the study and sharing experiences. In this study parent or legal guardian provided written informed consent for any participant under the age of 18 years.

Before beginning data collection, the research project was approved by the ethics committee of Shahid Beheshti University of Medical Sciences in Tehran, Iran. The ethical principles observed for the research included obtaining informed consent, preserving the confidentiality of the data and giving the participants the right to leave the study whenever they desired.

Individual in-depth interviews were held with semi-structured questions ("What are your experiences with this disorder at this stage of life?" and "How has this disorder affected your mental state?"). The minimum and maximum duration of the interviews was 30 and 55 mins. The interviews were held in a relaxed and private environment in the health centers of Shahid Beheshti University of Medical Sciences in Tehran, Iran. All the interviews were recorded with prior permission from the participants. Thematic analysis was used in this study. Thematic analysis is a flexible and foundational method for qualitative analysis.²¹ In the beginning, to immerse in the data, the research team transcribed the recorded audio interviews and the members read transcripts thoroughly. In order to generate the initial codes, the research team members extracted the semantic units. Then, the codes were collated into potential themes. The themes were reviewed for generating a thematic map. Finally, the themes were defined and given names and the final report was prepared.

Trustworthiness

Credibility, transferability, dependability, confirmability and authenticity measures were used to verify the data. The methods used in this study to verify the accuracy of the data included the selection of contributors with a variety of experiences, persistent observation, member checking, use of a coding framework, prolonged engagement with data, team consensus on themes, thick descriptions of context, purposive maximum variation sampling (selection of adolescents with different characteristic such as age, family economic status, education, etc.) and discussing some of the findings with a number of the participants.

Results

Thematic analysis categorized coping strategy into one main-theme as “Dealing with PCOS” and 3 themes and 12 sub-themes. Themes and sub-themes are as follow:

Escaping the problem (sub-themes: Adopting a forgetting mindset, and concealment and minimization of the disorder).

Depressive mood (sub-themes: Poor self-perception and low self-esteem, isolation, sleep disturbances, passive aggressive behavior, emotional turmoil, feelings of humiliation, adolescents’ perceptions)

Coping with the disease (sub-themes: Recovery of health, positive thinking, hope for recovery), as shown in Figure 1.

The characteristics of selected participants are mentioned in Table 1.

Escaping the problem

The “escaping the problem” theme was formed in this study by combining two sub-themes, namely “forgetting” and “concealment and minimization of the disorder”. The adolescents tried to escape their challenges by not disclosing their disorder to others so as to reduce the burden of psychological issues, and they used the method of forgetting to rid themselves of intrusive thoughts. The experiences of some of the participants in the study showed that

they used the method of “forgetting” to escape their problems and tried to understand which thoughts resulted in their stress and then chose different ways to distract themselves from these thoughts. In the words of the participants:

“Sometimes, when I think of the disorder, I push the thoughts away. I’ve become inattentive” (Participant 1, 19 years old).

Because I was immersed in my university entrance exam, my mind was preoccupied. This issue (PCOS) has not been important to me at all. I’m always busy studying. I do not have the time to think about it. (Participant 8, 18 years old).

I’ve become indifferent now. It’s no more important to me how it has gotten on my nerves. I don’t think about it anymore because I can’t do anything about it. I went to the doctor, I took medicines, but it didn’t get better. (Participant 6, 19 years old).

The experiences of some of the participants also showed that they somehow tried to escape the problem by “concealing and minimizing the syndrome”. In the words of the participants:

“I’m not upset because they say it is very common and could happen to anyone, and it’s not a rare disorder. Anyone I see, I tell them I have PCOS and I’m taking medicines. It’s normal” (Participant 1, 19 years old).

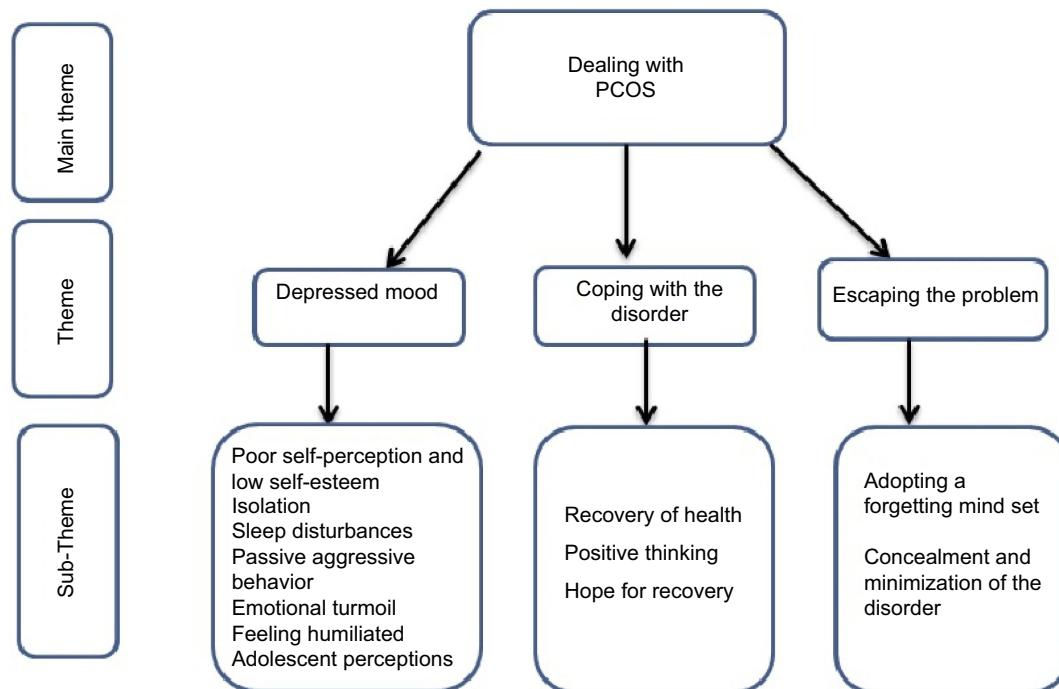


Figure 1 Theme and sub-themes.

Table I Characteristics of study samples (n=15)

Variable		Number
Age group	13–15	2
	15–17	3
	17–19	10
Marital status	Single	13
	Married	2
Years living with PCOS	<1 year	8
	>1 year	7
Main symptom	Obese or overweight	8
	Acne	11
	Hair loss	11
	Hirsutism	13
	Irregular menstruation	12

"I try not to take my pills in front of people because they ask why I'm taking pills. I don't tell anyone about my disorder" (Participant 9, 18 years old).

Depressive mood

The "depressive mood" theme was developed with seven sub-themes, including "poor self-perception and self-esteem", "isolation", "sleep disturbances", "passive aggressive behavior", "emotional turmoil", "feeling humiliated" and "adolescents' perceptions". Some of the adolescents experienced "laziness" and "sadness" after their diagnosis with PCOS and also concerns about failing to recover, constant worries about the disorder and psychological distress, which eventually ended in their "losing the joys of adolescence" and they began to lose focus. These experiences led to unpleasant feelings, and struggles with the disorder for many years caused "emotional disturbances" for some of the adolescents. According to participants' experiences, some of them tried to cope with their problems through "aggressiveness" and "making excuses." Often, they became isolated because of "limiting their relationships with their friends and close relatives" and "preferring to be alone than to be with others". The experiences of the participants also showed that, because of "internal feelings of distress when in gatherings where people were inquisitive" and "being in turmoil due to feeling different from peers", some of them felt humiliated and had a low self-esteem and sometimes also experienced symptoms of physical change caused by their psychological changes. The experiences of most participants showed that the visibility of their symptoms to their peers and others made them feel vulnerable, and as a result, they

preferred not to be in touch with anyone in order to avoid showing their vulnerability. In the words of the participants:

"When I'm in front of the mirror, I feel bad, cause I have a lot of hair and acne" (Participant 15, 19 years old).

"I do not have much confidence when with others, cause I think they are better than me. It's the same for my family, my friends ..." (Participant 3, 16 years old).

Loneliness and "isolation" were one of the common strategies of the adolescents in this study to cope with their disorder. In the words of the participants:

I don't have much patience for myself; I don't have patience for others; I prefer to be left alone at home. What I mean is that I prefer everyone to go out visiting and enjoying themselves but leaving me home alone. (Participant 13, 19 years old).

"I try not to be in touch with my friends ... I've only told my best friend about my polycystic ovary syndrome" (Participant 15, 19 years old).

Stressful conditions were associated with "sleep disturbances" in some of the participants. In the words of the participants:

"I'm always sleepy. I feel so sleepy. I'm constantly falling asleep. It's awful. It has been two or three years that I've become like this. I mean, since the morning, when I wake up, I feel sleepy" (Participant 6, 19 years old).

"I think so much about it that I can't sleep. I go out [of my bedroom] to drink water. I can't sleep at all until 5 or 7 am" (Participant 12, 13 years old).

Some of the adolescents who participated in the study expressed their agitation and negative feelings about the onset of their syndrome and were unknowingly showing passive aggressive behavior. In the words of the participants:

"I'm always fighting with everyone. I've become stubborn. When I get worried about something, I go to my room and shut the door. I start to cry and then lock the door" (Participant 3, 16 years old).

"I'm so distressed that I keep fighting with my family. I say, 'It's all your fault, you've caused this problem for me!' (Participant 12, 13 years old).

Concerns about the syndrome and its presentations and reasons caused tension in most of the participants and they were faced with "emotional disturbances". In the words of these participants:

"I'm worried about seeking further treatment because they told me that no special treatment exists yet" (Participant 2, 15 years old).

"I really don't have the patience, unlike in the past. For example, I had so many interests to pursue that I really enjoyed going out, but not anymore" (Participant 10, 19 years old).

"I don't think so much about it. It makes me very upset. My entire life has become consumed with this problem. I've lost my appetite. I'm so upset" (Participant 12, 13 years old).

"My inner feelings are such that, like, when you want to do something for yourself, say, make an effort for the sake of your life, continuing it causes problems because of this disorder" (Participant 2, 15 years old).

"Right now, I feel that, the way my friends hang out and are happy in each other's company, I'm not like that" (Participant 6, 19 years old).

"Most of the time, my mind was preoccupied and I couldn't concentrate on a particular problem" (Participant 2, 15 years old).

"My particular concern is that if this continues, what's going to happen ... Will this illness be with me all my life and will I have to always cope with it and take medications?" (Participant 4, 19 years old).

"I think so much about it. When I look at myself in the mirror, I say, 'What kind of life is this?'" (Participant 2, 15 years old).

"My nerves are so weakened ..." (Participant 12, 13 years old).

I didn't use to go and visit others ... not that I said I didn't like to go and see people. For example, when I sat down, someone would ask me if I was on a diet and I would get angry and want to answer back, but I had to keep the boundaries of respect, so I wouldn't say anything. And then, I wouldn't go to visit people at all because of this. (Participant 13, 19 years old).

Some of the adolescents who participated in the study perceived themselves as below optimal because of the symptoms of their syndrome and imagined that they were not worthy and felt "humiliated". In the words of the participants:

Compared to my friends, I see myself very different. For example, they wear fashionable items that I have always liked to own, but I could never be like that, because of the excessive hair that I have to hide, my obesity and hair loss. (Participant 2, 15 years old).

The manifestation of mental stress as a result of the syndrome and mental turmoil in some of the participants led to "adolescents' perceptions". In the words of the participants:

"I'm usually tired. My activities have diminished, unlike the vitality I had before" (Participant 14, 17 years old).

"I don't like to move too much. I like to just always sit somewhere" (Participant 10, 19 years old).

Coping with the disorder

"Coping with the disorder" consisted of three sub-themes, namely "the recovery of health", "positive thinking" and "hope for recovery". Most of the adolescents who participated in this study tried to reduce the mental stress of having PCOS through academic accomplishments and took measures to promote their physical health. Although the adolescents felt responsible for their own health, they neglected it nonetheless, because they prioritized their studies and future career prospects.

Some of the adolescents attempted to create a positive image of their disorder and created a positive vibe for seeking treatment by adopting a "hope for recovery" approach. Some of them coped with the syndrome through a "positive internal dialogue". Some of the participants in this study were taking "health recovery" measures to cope with their syndrome. In the words of the participants:

"Right now, studying is my priority, and when I've completed my studies, I want to go to the doctor again" (Participant 1, 19 years old).

"I am far too busy with the university entrance examination and my studies to have any time for this disease at all" (Participant 8, 18 year-old).

"I used to regard my disorder as trivial. I didn't think it was necessary for me to take my pills. Later, I began taking it very seriously" (Participant 9, 18 years old).

Some of the participants were able to rid themselves of disturbing thoughts through "positive thinking" and coped with their disorder. In the words of these participants:

"I came to accept myself, 'Okay, you have this condition, you have this pimple!' I accepted it as it was and then wouldn't think about it" (Participant 4, 19 years old).

"It's a mild illness –not a very dangerous disorder" (Participant 4, 19 years old).

Some of the participants took steps to cope with the disorder through a "hope for recovery". In the words of this group of the participants:

"My medications are one too many, but I take them with the hope of getting better. Just like this. I take my

medications to get better soon" (Participant 6, 19 years old).

"When I take my medicines, since they regulate my period, I feel good" (Participant 8, 18 years old).

Discussion

The findings of this study include concepts such as escaping the problem, depressed mood and coping with the disorder. In conjunction with each other, these concepts led to the formulation of dealing with PCOS.

As the sociocultural context of any society can affect individuals' strategies for coping with critical situations, the sociocultural and religious contexts of the Iranian society can also affect the type of strategies adolescents adopt to cope with PCOS. Like in many Middle Eastern countries, cultural and educational issues also have a major role in adolescents' mental health in Iran.²²

Evidence suggests that dealing with a chronic disease, such as adolescent diabetes, requires a coping strategy that can help improve the health outcomes and quality of life of the patient.²³

Other chronic diseases such as adolescent cancer or serious infections that may cause future infertility have also become a serious concern for both adolescent patients and their parents as per their responses.^{24,25} The diagnosis of any fertility disorder in adolescents can disrupt the normal psychosocial development of the individual.²⁶ In general, the manifestation of symptoms such as obesity, acne, hirsutism and the disruption of the menstrual cycle lead to stress in these patients and they cope with this stress in different ways.

In the experiences of the participants, some of the adolescents with PCOS were trying to escape their problems by forgetting and often with the concealment and minimization of their disorder. The results of a study on women with PCOS showed that those who suffered more psychological problems used maladaptive coping strategies, such as avoidance strategies, and used less problem-focused coping strategies.²⁷ Avoidance coping is known as an effective short-term strategy, but in the long term, it prevents psychological adjustment and increases depression.^{28,29}

The results of other studies on social coping strategies have shown that adolescents use different coping techniques, such as avoidance coping, problem-solving and seeking social support.³⁰

It seems that most participants in the present study were turning to these strategies to escape being labeled

as "sick" and to be able to cope with the disorder in some way by denying its existence to themselves and others. It is a proven fact, however, that avoidance coping could cause a downward spiral in the long-term.

The experiences of the participants of this study showed that adaptation to illness could emerge as a depressive mood in some adolescents. The diagnosis of PCOS has psychological ramifications.³¹ Depression and moodiness in adolescents and the appearance of a depressive mood have been argued to be associated with symptoms such as disturbed sleep, lethargy, restlessness, changes in appetite and weight, decreased motivation and concentration, decreased self-esteem and isolation.³² In one qualitative study, the experiences of 12 people with PCOS aged 17 to 51 years revealed great mental anxiety in coping with this disorder.¹⁹ The onset of PCOS is associated with the instability of emotions, confusion and moodiness and leads to feelings of irritability, fear and despair in social relationships and a general sense of unhappiness.^{33,34}

The establishment of social relationships is vital during adolescence.³⁵ Adolescents with this disorder choose isolation to counteract the reactions of those around them. The acceptance of adolescents with PCOS by the community and those close to them helps improve their behavior, while increased criticism, especially in this vulnerable age group, reduces self-esteem and increases anxiety and depression and ultimately leads to abandoned social relationships.³⁶ In contrast, a negative body image destroys the individual's social competence and causes the abandoning of intimate relationships.^{37,38} Changes in one's physical appearance, concerns over changes in one's mental body image and the development of anxiety about the ramifications of the disorder seem to play a role in the manifestation of a depressive mood as a kind of coping response to the disease.

The experiences of the participants in this study also showed that those who responded with positive thoughts and had hope for their future well-being and recovery chose an adaptive coping response to the disorder. The various factors affecting the acceptance of the disorder also contribute to the PCOS patient's coping with the disorder.³⁹ The results of a study on women with PCOS showed that coping strategies were more excitement-oriented.⁴⁰ Another qualitative study on women with PCOS also showed that coping strategies include deliberation (religious beliefs, paradoxical thoughts), practical steps (positive steps such as seeking information and treatment as well as negative steps such as detachment and

concealment) and seeking support (family support and peer support) in these patients.⁴¹ Evidence suggests that the types of coping strategies chosen by women with PCOS affect their quality of life.²⁰ Some studies have even suggested that hope is a very powerful force that can play a key role in coping with adolescent illnesses.⁴² Hope is occasionally a solution to tension that increases the individual's ability to adapt.⁴³ Some of the participants of this study were able to cope with their mental turmoil through their hope to recover. Meanwhile, some attempted to take steps towards coping with their disorder through positive thoughts. Positive thoughts comprise a branch of cognitive therapy that can be defined as the usage of hopefulness, happiness and positive mental abilities.⁴⁴

A study by Benson et al (2010) conducted on 449 women with PCOS showed that some participants had a passive coping strategy in dealing with this syndrome (retreating and accepting one's fate regarding the disorder), which is an unharmonious strategy that leads to the emergence of anxiety and depression and in turn decreases the quality of life. In contrast, some participants who adopted active coping strategies (problem-solving and information-seeking) had lower levels of depression.⁴⁵ The participating adolescents of this study had a positive attitude and took health-recovery measures to cope with the disorder.

Active coping involves problem-solving and social support-seeking while passive coping involves social isolation.¹⁷ The results of one study on children and adolescents with a chronic illness showed that coping with such a disease may lead to effective coping with daily stressors of life.⁴⁶

Some of the participants used problem-solving through positive thoughts and measures to deal with the stressful conditions of life. They used a rational strategy to accept their disorder and their tensions thus decreased. In general, chronic PCOS requires self-efficacy and lifestyle modifications.⁴⁷ As for the psychological burden of PCOS, choosing a proper coping strategy plays a decisive role in the quality of life of adolescents with the disorder, as irrational strategies could cause harm and threaten different dimensions of life. The use of clinical counseling, mental health services, beauty counseling services and support services for patients and their families can contribute significantly to the improvement of the quality of life of adolescents with chronic PCOS.⁴⁸

Implementing psychological counseling programs (by psychologists and other allied health professionals) and

teaching adolescents adaptive coping strategies are recommended to prevent future mental health problems. Attention to mental health and related care measures is imperative for medical teams.

The study limitations include the non-generalizability of the results to all adolescents with this syndrome, although this limitation applies to all qualitative studies in nature. Furthermore, forgetting certain experiences or the unwillingness to actually express these experiences and feelings on the part of the adolescents could be considered another limitation of the study.

Conclusion

When confronted with the stressful symptoms of PCOS, the participants adolescents of this study showed coping responses such as escaping the problem, depressive mood or coping with the syndrome. Identifying the ways through which these adolescents cope with their syndrome is vital for recognizing the mental health needs of PCOS patients and improving their quality of life.

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Polycystic ovary syndrome in globalizing India: An ecosocial perspective on an emerging lifestyle disease

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ABSTRACT

Polycystic ovary syndrome (PCOS) is an endocrine disorder linked to type II diabetes and the leading cause of female infertility worldwide. Despite being considered a "lifestyle" disease, PCOS has received scant attention in the social science literature. In India, media accounts citing prominent doctors have expressed concern that the syndrome affects a growing number of urban middle-class Indian women. The general public, doctors, and afflicted women all attribute the condition to stress, lifestyle changes, "Westernization," modernization, and disrupted circadian rhythms. These factors are associated with changes in diets, gender roles, and aspirations since 1991, when the introduction of neoliberal reforms opened up the country to processes of globalization. Women with PCOS have come to be seen as living embodiments of the biosocial stresses associated with modern urban middle-class living, and discourse about PCOS serves as commentary indexing anxieties about social and political-economic shifts in the country. In this paper, based on ethnographic fieldwork in Mumbai, India, with 141 participants from 2012 to 2014, we point to local understanding of PCOS as corresponding to an ecosocial perspective that highlights the structural vulnerabilities of urban middle-class women. Whereas most research on structural vulnerabilities and health has centered on economically and otherwise disadvantaged groups, we use PCOS as a case study to draw attention to the rise of lifestyle disorders linked to the impact of globalization and the pressures of "modern" identities and aspirations among middle-class populations.

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1. Introduction

Polycystic ovary syndrome (PCOS), an endocrine disorder with no known cure, is the leading cause of female infertility worldwide (Boomsma et al., 2008; Goldenberg and Glueck, 2008). The syndrome gets its name from multiple ovarian follicles—which look like cysts—often seen upon a gynecological sonography of women with the condition. In a normal menstrual cycle, an egg is released from a dominant follicle. In PCOS, several follicles develop, but none of them becomes dominant (Soulez et al., 1996). There is often a lack of ovulation, and the menstrual cycle may be delayed or absent, resulting in subfertility. The exact etiology of PCOS is unknown, but genetic history and lifestyle factors are known to play a part, and PCOS is considered a lifestyle disease in which genetic predispositions may in fact be activated by lifestyle factors (Balen et al., 2009; Ehrmann, 2005; Franks, 1995).

PCOS is associated with symptoms such as cystic acne, male-pattern hair loss, hirsutism, insulin resistance (precursor to diabetes; cells become less responsive to insulin), and darkened skin patches (acanthosis nigricans). Obesity is both a symptom and a contributory factor and is associated with the worsening of other symptoms. Weight loss is therefore often the first recommended line of management. Management also involves medication, such as hormonal contraceptives to regulate menstruation, ovulation inducers and fertility treatments, and insulin sensitizers. The syndrome is also associated with increased risks of diabetes and cardiovascular disease (Franks, 1995; Legro et al., 1999). Not all women with PCOS manifest all symptoms, and not all women with PCOS are overweight; the syndrome also manifests in a "lean" phenotype (Franks, 1995). An emerging contention is that PCOS results from insulin resistance (Franks, 1995), and some argue that PCOS has a male equivalent associated with early baldness, obesity, insulin resistance, and hormonal changes (Kurzrock and Cohen, 2007; Starka et al., 2005). Thus, although the name suggests that the ovaries are the primary organs affected, PCOS is a multisystem endocrine condition.

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2. PCOS in India

Media accounts have suggested that PCOS is on the rise in India and most prevalent among the urban middle and upper classes because of their lifestyles (e.g., [Garari, 2014](#); [Pal, 2013](#); [Times of India, 2012](#)). The prevalence of obesity, overweight, and insulin resistance, which are all associated with PCOS pathogenesis, appear to be higher among members of higher socioeconomic strata living in urban areas; medical researchers have attributed this to more sedentary lifestyles and access to more calorie-dense foods and laborsaving devices in urban and higher socioeconomic populations ([Chopra et al., 2013](#); [Kalra and Unnikrishnan, 2012](#); [Khandelwal and Reddy, 2013](#); [Wasir and Misra, 2004](#)). Although there have been no rigorous community-based epidemiological studies of PCOS published in India to date, a preliminary study among women aged 15–24 from the lower socioeconomic strata in Mumbai placed prevalence at near 22.5 percent (around one in four women) ([Joshi et al., 2014](#)). The authors of the study further observed that given trends in other metabolic disorders and nutritional and physical activity patterns, this prevalence might be even higher among the higher socioeconomic strata. This contrasts quite markedly with a prevalence of around 11 percent in Australia, 8 percent in the UK, and 4 percent in the US, using similar diagnostic criteria ([Wijeyaratne et al., 2013](#)). A prominent gynecologist conducting an epidemiological study of PCOS which compared prevalence across India was interviewed regarding whether the reported rise might be an artifact of improved diagnosis, increased clinician focus, or shifting health concerns in the population. Based on preliminary findings from a year of research, the gynecologist rejected these factors as the primary drivers and confirmed the trend of higher PCOS prevalence among urban middle-to upper middle-class women. Irregular menstrual cycles and subfertility have long been of considerable concern in India (e.g., [Leslie, 1996](#)), and a common reason for medical consultation from both allopathic and ayurvedic practitioners (vaidyas). These practitioners routinely ask patients about symptoms encompassed by PCOS, with allopaths inquiring about them for decades and vaidyas treating them as basic to their humoral science. The yet-to-be published research as well as the observations of several such practitioners interviewed (sample described below) indicated that PCOS was rapidly increasing among urban middle- and upper-class women and that with increasing prosperity, it was beginning to increase among women from the urban lower classes and those living in urbanizing semi-rural areas.

3. Economic liberalization and the emergence of “modern lifestyles”

Most features of the “modern” urban middle-class lifestyles associated with PCOS described by the media are relatively recent to India. Prior to 1991, the Indian economy was largely closed to the world. Economic policy emphasized business regulations, state-driven investment, and import restrictions. The result was a protected economy with limited consumer choice. In 1991, however, a balance-of-payments crisis forced the Indian government to hasten the opening up of the economy. This came to mark a watershed moment referred to as “economic liberalization” or “liberalization.” Since then, there has been a steady shift to a market-driven, globally integrated economy. India has been experiencing rapid economic growth, surfacing as one of the world’s ten largest economies. It has also seen the emergence of new middle classes, with many moving out from below the poverty line ([United Nations Development Programme, 2011](#)).

The resultant higher disposable incomes have contributed to a “nutrition transition” ([Popkin, 1993](#)), with increased consumption

of fats, oils, and sugars ([Griffiths and Bentley, 2001](#); [Nagesh, 2012](#)). Eating out, once rare and circumscribed by caste proscriptions (and for women by lack of access to certain public spaces), has become integral to India’s urban-centered public culture and a marker of middle-classness ([Conlon, 1995](#); [Fernandes, 2006](#)). Meanwhile, increased access to laborsaving devices and cars has reduced physical activity. As a result of the rise in these risk factors, the prevalence of diabetes and cardiovascular disease has escalated among India’s middle classes, especially in urban areas, and public health practitioners have identified these conditions as emerging epidemics ([Celermajer et al., 2012](#); [Khandelwal and Reddy, 2013](#); [Misra and Khurana, 2008](#); [Wasir and Misra, 2004](#)).

Another change following liberalization has been the new availability of previously inaccessible consumer products and services. The advent of satellite television also resulted in a host of new aspirational messages being aligned with this increased consumer choice, and such representations are based on a vision of the nation as tied to consumption, with an idealized portrayal of the urban middle classes ([Fernandes, 2000](#); [Mazzarella, 2003](#)). There has been an increasing acceptance of consumer culture ([Mazzarella, 2003](#); [Venkatesh, 1994](#)), consumption is now closely tied to notions of middle-classness ([Van Wessel, 2004](#)), and new spaces of consumption, such as coffee shops, shopping malls, and multiplexes, form the spaces where this new middle-classness is performed ([McGuire, 2011](#)).

Post-liberalization, the pace of life, especially for the middle classes, has also been affected by the restructuring of the labor market. Leela [Fernandes \(2000\)](#) describes how traditional middle-class public-sector employment in industries such as banking has been marginalized, and the middle classes are now associated with growth in the service sector and private sector white-collar employment. Middle-class ambition has moved away from old, stable government jobs toward jobs in multinationals with expanded chances for career and salary growth. The contemporary job market is characterized by higher job insecurity and emphasis on efficiency. The old, secure middle-class work environment of regular hours has shifted to a highly competitive, unstable environment requiring longer hours and continual improvements in productivity and skills. For women, in particular, the effects have been contradictory and pronounced:

On the one hand, the expansion of service sector and private sector employment has produced employment opportunities for middle class women in metropolitan centers. However, such opportunities often represent coping strategies as households attempt to negotiate increasing household costs and new lifestyle standards that correspond to public representations of the new middle class. This has produced familiar gendered pressures as middle class women must perform a dual shift of paid and unpaid household work. ([Fernandes, 2000:100–101](#))

Liberalization has, however, brought increased opportunities for urban middle-class women in terms of employment. Professional women, working in jobs requiring educational achievement, occupy an important social, economic, and symbolic position in contemporary India ([Radhakrishnan, 2009](#)). The public visibility of women and their freedom to pursue careers is considered another marker of new middle-class identity ([Ganguly—Scrase, 2003](#)). Being well educated and holding a professional position improves both, a woman’s career and marriage prospects ([Radhakrishnan, 2011](#); [Sharangpani, 2010](#)). This has, in turn, affected the age of marriage among the middle classes, as women pursue higher education and work before getting married.

Nevertheless, domestic tasks, child-rearing, and household management are still seen as the responsibility of women, and new

opportunities are circumscribed by the enactment of what has variously been called “respectable femininity” (Radhakrishnan, 2009), “respectable modernity” (Thapan, 2004), or “demure” modernity (Lukose, 2009), which tasks women with balancing their cosmopolitanism and modernity with their familial and community obligations (Donner, 2008). Their ability to successfully navigate these expectations can affect not just their own social standing and reputation but also that of their families (Dickey, 2002); what constitutes a “good balance” between tradition and modernity, however, varies across segments of the middle classes (Gilbertson, 2014). Women are required to exist between two cultural worlds and move seamlessly between them; they must take on the responsibility of being modern without foregoing the traditional. Therefore, increased opportunities for middle-class women place additional burdens upon them and expose them to new aspirations while circumscribing their ambitions.

A number of health problems have been linked, in both popular and medical discourse, to the middle classes and such changes following on the heels of economic liberalization, such as the stresses of consumer aspiration (Chua, 2014) and the “tensions” of balancing self-care with conforming to gender-specific roles (Weaver and Hadley, 2011). In this paper, we document how PCOS is interpreted in India as a condition that is both a reflection and a cost of modern middle-class living. Moreover, despite being one of the most reported endocrine disorders, PCOS has been largely ignored in the social scientific literature, although a rare sociological study in the UK (Kitzinger and Willmott, 2002) found that PCOS challenged women's perceptions of themselves as feminine. We aim to address this gap and adopt an ecosocial approach (Krieger, 1994, 2001), combining a focus on biological, social, ecological, and historical factors, to investigate PCOS as an embodied manifestation of the biosocial stresses of economic liberalization and to examine the structural vulnerabilities associated with PCOS as an emerging health issue in globalizing India.

4. Methods

The present study investigated perceptions of PCOS among community, patient, and practitioner populations in Mumbai—India's commercial and media capital. Fieldwork, conducted by the first author in Mumbai and guided by the second author during field visits, included observation, participant—observation, and interviews with 141 participants from 2012 to 2014. Informants hailed from what may be termed the aspirational middle class. Middle-classness in India is a difficult category to pin down, but scholars of contemporary South Asia treat it as a performative socioeconomic grouping rather than an economic bracket (e.g., Fernandes, 2006; Mazzarella, 2005; McGuire, 2011; Radhakrishnan, 2011). Following understandings gleaned from informants, we define aspirational middle-class status as comprising comfort with English, knowledge of global (mostly American) popular culture, engagement with new spaces and practices of consumption, and at least an undergraduate education and potential for white-collar (usually professional) employment.

Fifty-one participants functioned as a base of informants for in-depth interviews to understand the practices of Mumbai's urban aspirational class and changing patterns of living since economic liberalization. In-depth semi-structured interviews were conducted among a purposive sample of 30 lay informants who did not have PCOS (10 women over age 36, 10 women aged 21–35, 5 men over age 36, 5 men aged 21–35) to gain a sense of what they saw as emerging urban women's health issues and what they knew about PCOS specifically. Semi-structured interviews were also conducted with 30 medical/paramedical practitioners who help diagnose or manage PCOS (5 each of endocrinologists, gynecologists,

dermatologists, dieticians/nutritionists, homeopaths, and vaidyas). Through referrals by key informants who were medical practitioners, we selected practitioners exposed to patients from a range of socioeconomic strata, not just the middle or upper classes. Additionally, in-depth interviews, including illness narratives, were carried out among a core sample of 30 women diagnosed with PCOS (10 never married, 10 ever married without children, 10 ever married with children). Many of these women were visited on several occasions across time points or followed up by phone interviews and observed during their day-to-day interactions. We identified women diagnosed with PCOS aged 21 and above from the urban aspirational middle class using the first author's social circles and through referrals from within social networks. Recruiting this way enabled triangulation of data from interviews with data from observation and participant—observation. It also enabled observation of the degree to which PCOS is hidden or discussed in popular discourse and the body-related practices of core informants in naturalistic settings. Interviews were conducted in informants' homes, offices, coffee shops, or in case of medical practitioners, their clinics or consulting rooms. As informants were drawn from the aspirational middle class, which is comfortable with English, interviews were primarily conducted in that language. Nevertheless, interviews involved significant code switching between English, Hindi, and sometimes Marathi; only the English translations are presented here. The Institutional Review Board of the University of Arizona approved the research. In what follows, we first describe our findings with regard to perceptions of PCOS among lay informants, medical practitioners, and briefly, women with PCOS (a forthcoming publication will explore women's lived experiences of PCOS, including stigma and its effects on identities and relationships, in more detail). Then, we present and discuss data from our investigation as they relate to structural vulnerabilities of modern middle-class lifestyles before summarizing our arguments in the conclusion.

5. Lay perceptions of PCOS

PCOS does not correlate to indigenous categories of illness, but as women's hormonal, reproductive, and menstrual issues have always been significant in India, we approached PCOS as a subset of these. To account for a possible unfamiliarity with the term PCOS as a diagnostic category, we solicited informants' opinions on major emerging urban women's health issues before asking specifically whether they had heard of PCOS. In some cases, informants mentioned PCOS as a key health problem before the interviewer mentioned the condition. Overall, PCOS came across as a recognized condition (70%; see Table 1), especially among women and men aged below 35—informants heard of PCOS either through friends or relatives with the condition or through media reports. Some lay informants pointed to a rise in hormonal/menstrual disorders as a “new normal” for the middle classes resulting from a hectic modern lifestyle. In particular, informants blamed these disorders on the stress of women having to juggle the responsibilities of home and work. As one 57-year old female informant put it:

Working plus there is the home also. I feel that sometimes they cannot tackle both. There is stress of both these sides....Basically, life has become stressful. These days basically the lifestyle has become very stressed out. One thing I feel is that these days, women feel they can do everything. They can do—it is not that they are different from the males of the world, but they themselves have more expectations out of themselves. I feel in that stress really increases a lot.

Table 1

Themes in lay perceptions of women's hormonal/menstrual issues.

Theme	Women over 36	Women under 35	Men over 36	Men under 35	Total
Total	10	10	5	5	30
Heard of PCOS	8 (80%)	8 (80%)	1 (20%)	4 (80%)	21 (70%)
Hormonal/menstrual problems are increasing	6 (60%)	7 (70%)	3 (60%)	3 (60%)	19 (63%)
Increased stress	10 (100%)	5 (50%)	4 (80%)	3 (60%)	22 (73%)
Unhealthy diet	7 (70%)	4 (40%)	4 (80%)	1 (20%)	16 (53%)
Irregular meal timings	3 (30%)	1 (10%)	1 (20%)	—	5 (17%)
Lack of exercise	2 (20%)	4 (40%)	3 (60%)	1 (20%)	10 (33%)
Lack of sleep routine	2 (20%)	2 (20%)	—	—	4 (13%)
Pollution/food additives	5 (50%)	1 (10%)	2 (40%)	2 (40%)	10 (33%)
Over-reliance on biomedicines	3 (30%)	—	1 (20%)	—	4 (13%)

Forty-two year old Rahul also felt that women were “leading two lives—one with the husband and one with the rest of the family.” By this, he meant that women were required to fill both the role of the dutiful traditional mother and daughter-in-law and the modern wife: “After coming home [from work] and cooking, they [women] still have to get ready and go out to a party if the husband wants to, so he can show off his hot wife.”

The theme of the stresses of transition was also common. One male informant over 36 said that in India,

Society is in transition. You want to follow the norms in terms of lifestyles and all that, but culturally, there are still pressures on women....the percentage of working women in urban areas is much higher, but the women are still solely responsible for everything at home.

A 28-year old male lawyer stated:

There's financial, family stress, traveling stress...it has just increased over time. More women are working...Now we have smaller [nuclear] families, so you have to do everything for yourself—earlier, non-working members used to take care. There are more work pressures on women also.

In addition to mentioning the pressures on working women to shoulder responsibilities for the home and the workplace, informants mentioned intense competition for education and jobs and the pressures of consumerism. Prachi, an informant over 36, thought that urban individuals had more financial pressures and needs because of “keeping up with the Joneses” and being “constantly exposed to new things.” All this negative stress, she said, had somatic results, with “hormones playing havoc with your body.” Leela agreed: “There is a lot of peer pressure. Competition is a lot these days, for admissions [for higher education], jobs. There is also this competition that what their friends have, they want.”

Farhana, a woman under 36, echoed many informants' sentiments when she compared contemporary urban women's food choices with those of an earlier generation: “We end up eating junk food. Our grandmothers and mothers—bread they would not even consider as a food. It was always *roti*. Now, we only want bread for breakfast. There is no time to make *rotis*.” Yet others spoke of “no proper eating time” and that “food timings are not proper.” Thirty-three year old Preeti combined several observations in saying that PCOS “has a lot to do with stress and [a lack of] routine,” including “sleeping late at night, not having meals at regular times.” Overall, informants blamed stress; faulty diets (especially eating out); pollution, pesticides, and food additives; lack of exercise; and the lack of a routine (see Table 1). These observations are not without merit; there is evidence to link PCOS and insulin resistance to weight gain, lack of exercise, skipped/delayed meals, sleep deprivation/late nights, stress, and endocrine disruptors in the

environment (Bensona et al., 2009; Jacobowicz et al., 2013; Kandaraki et al., 2010; Moran et al., 2006; Spiegel et al., 2009).

6. Medical practitioners' perceptions

In our interviews with medical practitioners, they also spoke of a rise in PCOS cases, especially among the urban middle classes, associated increased prevalence with “modern lifestyles,” “changing lifestyles,” “urbanization,” and “Westernization,” and blamed unhealthy diets, sedentary habits, the busy pace of life, lack of regularity in meal and sleep timings, insufficient sleep, and even changing gender roles (see Table 2). Diet was the most commonly cited factor—practitioners blamed eating out, junk food, an unbalanced diet, and eating more because of material prosperity. Dietitian Asha Parekh quipped that people were going from “*homo sapiens* to *homo junkiens*,” with a move toward food that was “high fat, high carbs, fructose-based” as well as fast food. Along with diet issues, most informants also commented on a lack of physical activity. Gynecologist Dr. Keskar pointed out that these issues start young:

I think lifestyle changes are the main cause. The type of foods the people are eating, more of junk food, not a very balanced diet, lack of exercise, too much of sedentary work, like, I see a lot of young girls who are studying, so they are—between the school, tuitions [academic coaching classes]—they have no time for exercise whatsoever. And maybe nowadays we have more of a nuclear family and small families, so I think [there is an] overindulgence by parents in feeding [their children].

Vaidya Dr. Dixit added another element—that of distracted eating:

These days, people, even when eating, they sit in front of the TV and eat. Meaning what happens is that there is actually no attentiveness to the food. Food is there, no? That has to be chewed 32 times. That makes a difference. But then you are eating while watching TV or on one side you are working on your laptop and another side you are eating.

A lack of regularity in timings was also mentioned, especially by all the dietitians and ayurvedic practitioners that were interviewed. Dr. Sapre, a vaidya, observed, “Circadian cycle [the body clock] is disturbed; that is main, important in PCOS.” She added that by “late sleeping, not eating at regular times, working at times of rest,” individuals “waste dopamine,” causing endocrine issues. Similarly, endocrinologist Dr. Prasad talked of the fact that, “Nowadays teenagers have a lot of distractions. They are constantly getting engaged because of internet and social media like Facebook,” which contributed to disturbed circadian rhythms, affecting the regularity of hormonal and menstrual cycles. In a similar vein, four ayurvedic

Table 2

Themes in medical practitioners' views of PCOS.

Theme	Endocrinologists	Gynecologists	Dermatologists	Dietitians	Homeopaths	Vaidyas	Total
Rise in PCOS prevalence	3 (60%)	5 (100%)	4 (80%)	5 (100%)	5 (100%)	5 (100%)	27 (90%)
Unhealthy diet	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	30 (100%)
Lack of exercise	5 (100%)	5 (100%)	5 (100%)	4 (80%)	5 (100%)	5 (100%)	29 (97%)
Irregular sleep/meal times	2 (40%)	1 (20%)	2 (40%)	5 (100%)	3 (60%)	5 (100%)	18 (60%)
Increased stress	1 (20%)	3 (60%)	4 (80%)	5 (100%)	1 (20%)	5 (100%)	19 (63%)
Pollution/food additives	1 (20%)	—	3 (60%)	1 (20%)	—	1 (20%)	6 (20%)
Over-reliance on biomedicines	—	—	—	—	—	2 (40%)	2 (7%)
Tight clothes	—	—	—	—	—	2 (40%)	2 (7%)
Total	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	30 (100%)

practitioners commented that PCOS was much more common among women in call centers or information technology jobs because of their irregular timings and night shifts.

Medical practitioners also blamed stress for PCOS. Dermatologist Dr. Desai spoke about the various stresses experienced by women:

What happens is, when you're living in a city like Bombay [Mumbai], the day-to-day life is also quite stressful and specially for women. Cause they are managing home, and they are managing outside. And there is a lot of peer pressure, there is a lot of pressure regards to work, and in India, of course, work is totally done by the woman, nobody is going to share the work, the household work. And then they are earning also—I mean the financial aspect and the work outside is of course also there, so it's double work. That is a lot of stress. It's not only women. Even the girls I see, I think the stress in the teenage population is also quite high. That goes for both boys and girls, but girls then get PCOD [PCOS], whereas boys would probably only manifest only as acne and hair loss—male-pattern hair loss also I'm seeing very early.

Dr. Gopalan, a gynecologist, highlighted examination stress: "Lot of stress in the lifestyle. There is a lot of education stress, any stress of that kind."

Another aspect of stress to come up was that of the stress caused by women's aspirations, as they demanded more of themselves and then were under the pressure of their own expectations. Dermatologist Dr. Fernandes had an interesting take that involved a feedback loop between cultural practices, behaviors, and biological outcomes: "Women want to excel but they have very little time for everything—they have to do more than they can. Their aggression fuels testosterone, which then energizes these traits." Two homeopaths suggested that PCOS was the body's response to defective features of modernization that were resulting in the masculinization of female attitudes and behaviors; for example, Dr. Shah felt that PCOS resulted from women "following the male pattern [of behavior] that is too aggressive, too dominating." Another theme was of endocrine disruptors in the environment and pollution, pesticides, and food additives (particularly hormones in dairy). Two ayurvedic practitioners also mentioned tight clothes that constricted the uterine area and reliance on painkillers for menstrual pain, which interfered with the body's processes.

7. Patients' perceptions

Women with PCOS also viewed it as a condition that was part and parcel of modern urban middle-class living. They regularly mentioned the fact that they had heard, read, or been told by their doctors that around one in four urban Indian women had PCOS. As 32-year old Sucheta put it, "I did realize it's very common and

[nearly] everybody has it and it's okay to have it." Many informants took similar solace in PCOS being common, especially in their social milieu. The condition's association with modern living (rather than patient characteristics), its ubiquity, and the fact that it was considered medically manageable (through medical cosmetic and fertility treatments), meant that none of the informants considered or experienced PCOS to be a source of stigma, and they were very comfortable talking about the condition with others, including boyfriends, spouses, friends, and colleagues.

While informants associated poor eating habits and lack of exercise with their PCOS, most were unaware of the association between PCOS, a family history of diabetes, and increased risks of diabetes. Informants spoke at length of the difficulties in making the lifestyle changes required to manage their PCOS given their hectic schedules. The attitude of vivacious 23-year old Jaclyn was typical: "I feel stressed about it [a hectic lifestyle]. I need a work-life balance but that doesn't mean that I should compromise on my likes." She had not made any lifestyle changes—whether related to diet or physical activity—to manage the condition, relying instead on medication. It is beyond the scope of this paper to deal with the experiences and perceptions of women with PCOS in detail—these will be dealt with in a forthcoming publication—but fieldwork revealed that her strategy of accommodating rather than actively managing PCOS was not unusual. This usually entailed turning to medication or cosmetic technologies to manage symptoms or erratic attempts at basic dietary changes (such as reducing eating out) or increasing exercise (such as daily walks).

8. PCOS and structural vulnerabilities among the urban middle classes

Scholarship within medical and biocultural anthropology has long recognized that the body literally incorporates the social and material world it inhabits into its biology (e.g., Baer, 1996; Dressler et al., 2005; Farmer, 1999; Lock and Kaufert, 2001). The histories and socioeconomic contexts of individuals (and groups) are reflected in their bodies, and bodies cannot be understood in isolation from their contexts. By noting that urban middle-class women are the population most likely to be affected by PCOS, study participants were pointing to a health disparity and implicating urban environments and middle-class lifestyles in this disparity. The factors they associated with a rise in PCOS and women's health issues highlighted the role of rapid social and structural changes in India since liberalization, along with environmental concerns such as those regarding food additives and the overuse of pesticides. In many ways, their popular epidemiological (Brown, 1997) views are in concert with the ecocosial approach to epidemiology espoused by Nancy Krieger.

Nancy Krieger (1994, 2001) has criticized theories of the social production and political economy of health that highlight political-economic and sociocultural factors in illness distribution for

failing to focus on specific political and economic determinants in pathways to pathogenesis, rendering biology opaque. An ecosocial framework recognizes disease distribution as determined through multiple levels of influence, including biological, environmental, social, and historical factors. It combines analysis through biological pathways of the embodiment of social and environmental forces, attention to how social inequalities result in differentiated exposures, susceptibilities, and resistance to illness, and emphasis on the responsibility of the sociopolitical system on patterns of disease. We would argue that to truly understand PCOS in India, an ecosocial approach is necessary to situate the emergence of the condition as a significant health issue within the specific circumstances and biological pathways in which PCOS-affected bodies are enmeshed. To illustrate this point, we provide examples related to the impacts of examination pressures and modern expectations on urban middle-class women.

Research revealed that pernicious ecosocial feedback loops implicated in PCOS start early in the life course. In India, major school-finishing examinations are taken in the 10th and 12th grades. After these, students apply for admissions to educational institutes and fields of study—their exam results determine their ability to enter the educational streams of their choice. Additionally, admission to professional courses, such as medicine and engineering, depends upon performance in competitive entrance exams that occur directly after the 12th exams. Education is valued as both a marker of and pathway to success, particularly among the middle classes, and educational expectations of students are very high. Combined with the unforgiving examination system, this results in an intensely competitive educational environment. Furthermore, new expectations on girls to do well have made competition even fiercer, with boys and girls now competing for limited admissions.

As a result of this intense emphasis on academic performance, children lead increasingly sedentary lives as they enter grade six, if not sooner (see also Swaminathan et al., 2011). After-school academic coaching classes (“tuitions”) are common as early as the primary school level, and by secondary school, tuitions are the norm. Numerous tuitions, heavy homework loads, and extensive examination preparation leave little time for outdoor play or sports. A lack of available open spaces compounds the problem. The average age at menarche across parts of India has been reported to be in the 9–15 range (Bagga and Kulkarni, 2000; Dambhare et al., 2012; Khadilkar et al., 2006; Rokade and Mane, 2008). Thus, the formative years before and after menarche correspond to a time of drastically reduced movement. Informants also suggested that the time around menarche results in more gender-segregated play, with physical activity for girls dropping even more than it does for boys. Physical education classes cannot fill the gap, as few schools have the requisite space, and the time dedicated to physical education is at best two hours a week.

The time around menarche is also a period of decreased insulin sensitivity, which typically returns to pre-pubertal levels a couple of years after menarche (Goran and Gower, 2001). Weight gain (from insulin resistance and lack of physical activity) further decreases insulin sensitivity, leading to a negative spiral. PCOS, which is linked to reduced insulin sensitivity, even for lean women, is also implicated in this spiral. This makes menarche a particularly vulnerable time, but this is when examination-related stress is most intense. This is even more so for girls from the middle classes. Although studies show that students in India are often stressed or depressed in the years of crucial exams (Bhasin et al., 2010; Verma et al., 2002), middle-class students suffer more school-related stress than their upper- and lower-class counterparts (Deb et al., 2010). Furthermore, this stress is reinforced by a lack of physical activity and hectic schedules. Sleep cycles are disturbed, as students

study into the night and wake early, functioning on insufficient sleep—another factor contributing to insulin resistance and PCOS. Furthermore, students face high degrees of surveillance; parents supervise studying, and activities that can be sources of entertainment and leisure—such as socializing, television viewing, or play—are heavily curtailed. Typically, eating is the only sanctioned source of pleasure, and parents offer junk food and sugary treats to students to motivate or reward grueling examination preparation. Overall then, among the middle classes, adolescence—a key point in the developmental cycle—is precisely when the susceptible body is buffeted on all sides by multiple concurrent stressors.

For women of the aspirational middle class, stressors continue to accumulate across life stages, even after adolescence. The need to display empowered “modern” identities that correspond to the new emphasis on women’s education and employment results in competition for limited admissions into institutes of higher education into the early 20s, followed by struggles to build careers. Meanwhile, new work structures result in very little time (and energy) for exercise, skipped or late lunches (at 4 or 5pm), long hours, and late dinners (up to 11pm). Sedentary jobs that involve working late or taking work home at night and over weekends are the norm. At the same time, new communications technologies, such as email and mobile phones, allow individuals to be constantly accessible for work.

Furthermore, the lifestyle standards coming from representations of the new hegemonic middle class have led to greater desire for consumer goods and the financial pressures of such consumption. Living up to this consuming middle-class ideal has resulted in new ways of enacting “modern” identities at the site of the body. The emergence of social media has meant that the enactment of these identities is publicly chronicled for all to see. Eating out, staying up late, working hard, and playing harder were common among informants under the age of 35 (especially those without children), and these are all characteristic of new “modern” identities.

Informants spoke of their inability to make the lifestyle changes required to achieve peak wellness; eating on time, sleeping early, reducing stressful activities, and exercising religiously were deemed impractical to their circumstances. As one informant observed, “This is the age [the 20s and 30s] you can’t be slowed down, and thinking of health means you have to slow down.” It was not just a question of work or situational factors but also social pressures. To be concerned with eating or sleeping on time or not being seen consuming resulted in being teased, labeled, or left out. One informant with PCOS stated, “I’m always the first in the house party to leave, and I’m labeled by my friends for it.” Individuals were called terms such as “*behenji*” (Hindi word meaning sister with connotations of provinciality and lack of attractiveness), “*paavam*” (Tamil word with connotations of naivety and pity), “aunty” (meaning old and frumpy, which also points to a generational divide), or having “no life,” for not wanting to stay up late, party, drink, eat fast food, or eat out.

Even beyond the 20s, stressors continue to accumulate. Once married, women bear the burden of fulfilling multiple roles in their home and work lives, juggling workplace expectations with household responsibilities and familial obligations. Meanwhile, urban living exposes these women to an assortment of endocrine disruptors (present in pesticides, plastics, and other petrochemical residues) and constant sensory stimuli in the form of city noises, billboards, and bright lighting. Long urban commutes exacerbate the problem. Together, these elements synergize to create a perfect storm of health pressures implicated in PCOS. They also amplify the long-term risks of PCOS—such as the risk of diabetes—and the cumulative effect of exposure to these stressors can affect the illness trajectory of PCOS, worsening outcomes.

9. Conclusion

Urban middle-class living is placing unique burdens on Indian women that are associated with rising rates of PCOS in both popular and medical discourse. Rather than emphasizing genetic predispositions, popular and medical discourse on PCOS in India highlights changes in the lifestyles of the urban middle classes following economic liberalization, particularly disrupted meal and sleep routines and new stresses on women resulting from competition for education and jobs, consumerism, and juggling responsibilities of home and work. These perceptions also point to specific structural vulnerabilities linked to the pressures of aspiration and globalization on the urban middle classes, such as those associated with examination pressures and modern expectations of women. We have focused on these perceptions of PCOS and how these tie in to an ecosocial framework for understanding the condition as related to modern middle-class living.

While such an interpretation is supported by preliminary scientific data and observations from medical practitioners, more research is required into PCOS prevalence, the stressors of modern living that relate to it, and how these vary by class. It would also be interesting to examine the history of PCOS as a diagnostic category across India and to investigate patterns in perceptions of PCOS amongst different types of medical practitioners. Furthermore, an apparent rise in PCOS needs to be viewed in relation to other problems associated with the health transition in India. India is facing an epidemic of diabetes with a notable rise in prevalence that is related to increased urbanization, expansion of the middle classes, and the changing lifestyles accompanying these trends (Ramachandran, 2005).

We would argue that although urban middle-class women (especially women of the urban aspirational class) are in a position of relative privilege in India, they nevertheless face structural vulnerabilities resulting from the health pressures of globalization and economic liberalization. Indeed, these structural vulnerabilities and their associated health risks can even be thought to result from their position of privilege and the gains made from economic liberalization. To date, research on structural vulnerabilities, health disparities, and syndemics (e.g., Baer, 1996; Farmer, 1999; Holmes, 2011; Kim et al., 2000; Mendenhall, 2012; Mendenhall et al., 2012; Navarro, 2002; Quesada et al., 2011; Singer and Clair, 2003; Weaver and Mendenhall, 2014) has focused on populations that are socially or economically marginalized. In the age of the anthropocene, such a focus is dangerously limited. To truly address the human costs of the rise of PCOS and other metabolic disorders, medical anthropology needs to move beyond the underprivileged to investigate other structural vulnerabilities embroiled in the health pressures of globalization and the human manufacture of risks.

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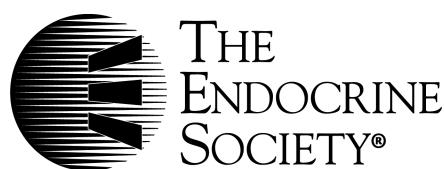
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POSITION STATEMENT: CRITERIA FOR DEFINING POLYCYSTIC OVARY SYNDROME AS A PREDOMINANTLY HYPERANDROGENIC SYNDROME: AN ANDROGEN EXCESS SOCIETY GUIDELINE

Ricardo Azziz, Enrico Carmina, Didier Dewailly, Evangelia Diamanti-Kandarakis, Hector F. Escobar-Morreale, Walter Futterweit, Onno E. Janssen, Richard S. Legro, Robert J. Norman, Ann E. Taylor and Selma F. Witchel

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1 **POSITION STATEMENT:**

2 **CRITERIA FOR DEFINING POLYCYSTIC OVARY SYNDROME AS A PREDOMINANTLY**
3 **HYPERANDROGENIC SYNDROME: AN ANDROGEN EXCESS SOCIETY GUIDELINE**

5 Task Force on the Phenotype of the Polycystic Ovary Syndrome

6 of The Androgen Excess Society

7
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32

33 **Key words:** Polycystic ovary syndrome, hirsutism, menstrual dysfunction, phenotype, criteria.

34

35 **Abbreviated title:** The AES criteria for defining PCOS

36

37 **Words:** 3633

38

39

ABSTRACT

40 **Objective:** The Androgen Excess Society (AES) charged a Task Force to review all available
41 data and recommend an evidence-based definition for Polycystic Ovary Syndrome (PCOS),
42 whether already in use or not, to guide clinical diagnosis and future research.

43 **Participants:** Expert investigators in the field.

44 **Evidence:** Based on a systematic review of the published peer-reviewed medical literature,
45 by querying MEDLINE databases, to identify studies evaluating the epidemiology or phenotypic
46 aspects of PCOS.

47 **Consensus Process:** The Task Force drafted the initial report, following a consensus
48 process via electronic communication, which was then reviewed and critiqued by the AES
49 Board of Directors. No section was finalized until all members were satisfied with the
50 contents, and minority opinions noted. Statements were not included that were not
51 supported by peer-reviewed evidence.

52 **Conclusions:** Based on the available data, it is the view of the AES Task Force on the
53 Phenotype of PCOS that there should be acceptance of the original 1990 National Institutes of
54 Health criteria with some modifications, taking into consideration the concerns expressed in the
55 proceedings of the 2003 Rotterdam conference. A principal conclusion that PCOS should be
56 firstly considered a disorder of androgen excess or hyperandrogenism, although a minority
57 considered the possibility that there may be forms of PCOS without overt evidence of
58 hyperandrogenism, but recognized that more data are required before validating this
59 supposition. Finally, the Task Force recognized, and fully expects, that the definition of this
60 syndrome will evolve over time to incorporate new research findings.

61 **Abstract:** 245 words

62

63 The disorder that eventually would be known as the polycystic ovary syndrome (PCOS) was
64 initially described by Stein and Leventhal in 1935 (1). There is little disagreement that PCOS
65 should be considered a syndrome, that is, a collection of signs and features, where no single
66 test is diagnostic. In essence, the whole (or global assessment) is greater than the sum of the
67 individual features. However, establishing a clear, contemporaneous, and evidence-based
68 definition for this syndrome has important clinical and investigational implications. Nonetheless,
69 the definition of PCOS has continued to generate significant controversy (2-4).

70 Clinically, diagnosing a woman as having PCOS implies an increased risk for infertility,
71 dysfunctional bleeding, endometrial carcinoma, obesity, type 2 diabetes mellitus (DM),
72 dyslipidemia, hypertension, and possibly cardiovascular disease (CVD) (5). Furthermore, it has
73 important familial implications, principally, but not exclusively, for her sisters and daughters (6-
74 8). Finally, a diagnosis of PCOS may mandate life-long treatments (e.g. the use of insulin
75 sensitizers) and may negatively affect her ability to access healthcare coverage, principally in
76 capitalistic markets. Consequently, the diagnosis of PCOS should not be assigned lightly, and
77 diagnostic criteria should be based on robust data.

78 A judicious definition of PCOS is also essential to guide current and future research. The
79 inclusion of patients whose definition, characterization, and selection criteria are unclear
80 continues to plague the PCOS scientific literature. This issue is becoming critical as the field
81 moves to the establishment of larger clinical trials, and to studies of the molecular biology and
82 genetic nature of the disorder. In addition, definitions not based on clear-cut evidence have the
83 potential effect of discouraging future and needed research into the nature of the disorder, its
84 breadth and its phenotype. Consequently, a contemporaneous definition based on what is
85 currently known will benefit future investigation in this area.

86 The Androgen Excess Society (AES) is an international organization dedicated to promoting
87 knowledge, and original clinical and basic research, in every aspect of androgen excess
88 disorders, such as the polycystic ovary syndrome, non-classic adrenal hyperplasia, idiopathic

89 hirsutism, and premature adrenarche. The Society was founded in 2000, and currently has over
90 200 members principally composed of investigators whose primary focus is the study of
91 androgen excess disorders and polycystic ovary syndrome. The Board of Directors of the
92 Society appointed the Task Force on the Phenotype of PCOS and charged it with reviewing all
93 current data concerning the phenotype of PCOS to answer the query: 'What different
94 component phenotypes (features) constitute PCOS, based on the available published and peer-
95 reviewed data, assuming that long-term morbidity is the anchor?' The following summarizes the
96 results of this Task Force's yearlong investigation.

97

98 **1) PROCESS**

99 The Board of Directors of the AES appointed a seven member Task Force of experts in
100 the field, intentionally including international investigators. Members of the Task Force and the
101 Board of Directors constituted the Writing Committee. No external funding was accepted for this
102 project. The evidence gathered was based on a systematic review of the published peer-
103 reviewed medical literature to identify studies evaluating the epidemiology or phenotypic
104 aspects of PCOS, by querying MEDLINE databases. The Medical Subject Headings (MeSH®)
105 heading used was 'polycystic ovary syndrome' [C04.182.612.765], with the following limitations:
106 Major topic AND adolescent (13-18 years) OR Adult (19-44 years) AND English AND
107 Publication Date from 1980 to 2005 AND Core Clinical Journals AND Female AND Humans). A
108 total of 527 articles were initially available for this review, although additional studies (cross-
109 references and those published in 2006) were also considered. Emphasis was placed on those
110 studies which included greater than 100 subjects, although in some areas no studies of this
111 size were available, and the paucity of data was noted. Studies in which epidemiologic (e.g.
112 prevalence) data could not be ascertained or calculated, or which reported on the same
113 parameter in mostly the same population as a larger study, were eliminated from consideration.
114 Unpublished data or personal communications were not included. Although only studies

115 where the criteria for PCOS were clearly stated were included, we did not define the
116 disorder *a priori*, and rather used each individual investigator's own definition. In essence,
117 we allowed PCOS to have a variety of definitions in order to more clearly define common
118 phenotypes or features irrespective of the definition used.

119 The Task Force drafted the initial report, following a consensus process via electronic
120 communication, which was then reviewed and critiqued by the AES Board of Directors. No
121 section was finalized until all members were satisfied with the contents, and minority opinions
122 noted. Statements were not included that were not supported by peer-reviewed evidence.
123

124 **2) CURRENT DEFINITIONS OF PCOS**

125 Currently, two definitions of PCOS are in widespread use. The first arose from the
126 proceedings of an expert conference sponsored in part by the National Institute of Child Health
127 and Human Disease (NICHD) of the U.S. National Institutes of Health (NIH) on April 16-18,
128 1990. During the meeting all participants were surveyed regarding their perception of what
129 features formed part of PCOS, and Drs. Zawadski and Dunaif summarized these findings in the
130 meeting proceedings (9). They concluded that the major criteria for PCOS "*should include (in*
131 *order of importance) : i) hyperandrogenism and/or hyperandrogenemia, ii) oligo-ovulation, [and*
132 *the] iii) exclusion of other known disorders*". This survey identified PCOS as an androgen
133 excess disorder of exclusion, with an ovarian etiology and/or consequences.

134 Another expert conference was convened in Rotterdam, The Netherlands, May 1-3, 2003
135 sponsored in part by the European Society for Human Reproduction and Embryology (ESHRE)
136 and the American Society for Reproductive Medicine (ASRM) (10, 11). The meeting
137 proceedings recommended that PCOS be defined when at least two of the following three
138 features were present: i) oligo and/or anovulation, ii) clinical and/or biochemical signs of
139 hyperandrogenism, and iii) polycystic ovaries. These criteria also recognize that other androgen
140 excess or related disorders should be excluded prior to assigning the diagnosis of PCOS.

141 Whether these definitions are consistent with currently available data, and whether they are
142 overly narrow or unjustifiable broad, were explored by the Task Force.

143

144 **3) THE ESSENTIALS OF DEFINING A SYNDROME**

145 The difficulties and intricacies of defining a syndrome is a challenge that many other
146 organizations have and continue to struggle with (12-21). A syndrome may be defined by: a)
147 historical usage in medical practice and/or literature, b) expert knowledge and consensus
148 processes, or c) evidence-based, via analysis of published data.

149 One evidence-based approach to establishing the limits of a syndrome is to determine
150 whether the various phenotypes defined by the criteria behave in a manner suggestive that they
151 are part of the same disorder. Firstly, all possible phenotypes generated by the definition of a
152 syndrome are catalogued and examined. Secondly, a feature not included in the definition (i.e.
153 the 'anchor') is chosen to serve as the common thread (e.g. inheritance pattern, morbidities, a
154 response to intervention). Essentially, for the phenotypes to be part of the same syndrome they
155 should have a common thread above and beyond the commonality of their definition (which in
156 itself may be arbitrary). For example, if the various phenotypes of PCOS have the same overall
157 morbidity (e.g. insulin resistance and hyperinsulinism) then we could consider these phenotypes
158 to reflect the same overall syndrome. The Task Force opted for this latter approach in
159 determining what phenotypes (and hence, what criteria) reflected PCOS based on current data.

160 Essentially, the Task Force considered that PCOS was defined by all those component
161 phenotypes which potentially signaled an increased risk for insulin resistance and the resulting
162 metabolic abnormalities. This is not to say that all individuals with a component phenotype had
163 to demonstrate metabolic abnormalities, but that the phenotype as a group should demonstrate
164 an increased prevalence of markers for metabolic dysfunction. A similar approach has been
165 taken when defining the limits of the metabolic syndrome (22).

166

167 **4) THE FEATURES OF PCOS**

168 The Task Force recognized four key features of PCOS: a) ovulatory and menstrual
169 dysfunction, b) hyperandrogenemia, c) clinical features of hyperandrogenism, and d) polycystic
170 ovaries. Clinically evident menstrual dysfunction, such as oligo-amenorrhea or abnormal uterine
171 bleeding, can be observed in a majority of patients with PCOS.

172

173 a) Ovulatory and menstrual dysfunction: In large series of patients diagnosed with
174 PCOS, approximately 75% have clinically evident menstrual dysfunction (23-37) (**Table 1**).
175 Current data also suggests that ~20% of women with PCOS will present with a history of
176 apparent eumenorrhea (i.e. subclinical oligo-anovulation) (23, 25-39) (**Table 1**). In clinical
177 practice, the presence of anovulation in clinically hyperandrogenic (i.e. hirsute) eumenorrheic
178 women may be determined by measuring a serum progesterone level sometime during days 20
179 through 24 of the cycle. If anovulation is present, it may be prudent to confirm this finding with a
180 repeat study.

181

182 b) Hyperandrogenemia: Elevated circulating androgen levels are observed in
183 approximately 60-80% of PCOS patients(**Table 2**) (35-37, 40-42). The vast majority of the
184 abnormal values are in the form of free testosterone (T), with the sole measurement of total T
185 adding a limited amount to the diagnosis (36).

186 The value of also measuring androstenedione is unclear, but it may increase the number of
187 subjects identified as hyperandrogenemic by ~10% (43). Approximately 25% of patients with
188 PCOS will demonstrate supranormal levels of the androgen metabolite DHEAS (44) which may
189 be the sole abnormality in circulating androgens in ~10% of these patients (36, 43).
190 Alternatively, measuring the level of DHEA, a weak androgen primarily of adrenal origin, has
191 limited diagnostic value.

192 The Task Force noted that the measurement of circulating androgen levels, including free T,
193 was to be used only as an adjuvant for the diagnosis of hyperandrogenic disorders, and never
194 as the sole criterion for diagnosis or in lieu of the clinical assessment. This recommendation
195 reflects the fact that between 20% and 40% of women with PCOS will have androgen levels
196 within the 'normal' range (36), and that assays for androgens, particularly total T, tend to be
197 highly variable and inaccurate (45-47)

198

199 c) Hirsutism, acne and androgenic alopecia: Clinical features of hyperandrogenism
200 frequently seen in PCOS include hirsutism, acne, and androgenic alopecia. Among women of
201 White, Black, Southern Asia (Pakistani, Bengali, Gujarati, or Dravidian Indian), Maori, or Pacific
202 Island descent, with PCOS defined by the NIH criteria, approximately 60% are found to be
203 hirsute (**Table 2**) (24-26, 29-32, 35-37, 40-42, 48-50). We note that the degree of facial and
204 body terminal hair growth in women represents a continuum, and that a value as low as three,
205 using the modified Ferriman-Gallwey (mFG) score, may be considered abnormal (51). However,
206 most investigators have used the 95th percentile of controls as the upper normal limit, which
207 corresponds to an mFG score of 6-8 in the White or Black populations studied (51, 52).

208 Acne affects 15-25% of PCOS patients (38, 39, 53) although it is unclear whether the
209 prevalence of acne is significantly increased in these patients over that observed in the general
210 population (54-58). Finally, androgenic alopecia is a recognized sign of PCOS (39, 40, 59-61),
211 although the prevalence of this abnormality in PCOS is unclear. In one study of 257 patients
212 undergoing treatment for hyperandrogenic symptoms, only 5% complained of hair loss (39).
213 Further studies are needed to better define the prevalence of acne and androgenic alopecia in
214 PCOS.

215

216 d) Polycystic ovaries: Current data suggests that polycystic ovaries detected by transvaginal
217 ultrasonography may be found in ~75% of women with a clinical diagnosis of PCOS (25, 26, 30-

218 32, 35, 37, 42, 49, 62-66) (**Table 3**). However, the Task Force also recognized that the false
219 positive rate is relatively high, as evidenced by the high rate of polycystic ovaries in the general
220 population (see above). The Task Force noted that the diagnosis of polycystic ovaries requires
221 strict criteria (65, 67), and should not be assigned based solely on a 'polycystic' or 'multicystic'
222 appearance of the ovary. The diagnosis of polycystic ovaries has been recently reviewed (68).
223 The most commonly used criteria today are those proposed by Dewailly and colleagues (65),
224 and reaffirmed in the Rotterdam 2003 consensus (10, 11), which indicate that polycystic ovaries
225 can be established when at least one ovary demonstrates an ovarian volume of greater than 10
226 cm³ (mL), or 12 or more follicles measuring 2-9 mm in diameter.

227 The Task Force noted that the diagnosis of polycystic ovaries should not be considered
228 more or less objective than that of hirsutism or hyperandrogenemia. Witness the changing
229 definition of 'polycystic ovaries' (67) and the 10% to 30% of women with PCOS who do not
230 demonstrate polycystic ovaries on ultrasound (68). In addition, there are also technical
231 limitations to this parameter, including the fact that at least 20% of women will refuse
232 transvaginal ultrasonography (69) and that most clinicians (even gynecologists) do not perform
233 their own ovarian ultrasonography, relying instead on the expertise of radiologists who may be
234 less familiar with the diagnosis.

235 Finally a number of other features of PCOS have been recognized, including gonadotropin
236 abnormalities, insulin resistance, and obesity. These features have not formed part of any of the
237 recognized definitions to date, and the Task Force found no evidence to suggest that this should
238 be otherwise.

239

240 6) PCOS: EXCLUSION OF OTHER ANDROGEN EXCESS AND RELATED DISORDERS

241 In addition to PCOS, there are a number of other disorders of androgen excess in
242 women, including the adrenal hyperplasias (CAHs), the syndromes of severe insulin resistance,
243 and androgen-secreting neoplasms (ASNs); that have the appearance of androgen excess (e.g.
244 idiopathic hirsutism); or that have not yet been well characterized (e.g. idiopathic
245 hyperandrogenism). There are also a number of other disorders that may result in ovulatory
246 dysfunction, including hyperprolactinemia and thyroid abnormalities. These disorders account
247 for approximately 5-10% of all patients with androgen excess (24, 26, 39-42, 60, 70-76) (**Table**
248 **4**), and should be excluded when establishing the diagnosis of PCOS.

249 Although not a true disorder of androgen excess, idiopathic hirsutism (IH) should be
250 excluded when assessing a hirsute patient for PCOS. Using the NIH 1990 criteria for PCOS, IH
251 can be strictly defined as hirsutism, in the presence of regular ovulation and in the absence of
252 hyperandrogenemia (77), such that approximately 5-7% of hirsute patients will have IH (27, 28,
253 77). It is possible that these patients may also need to demonstrate normal ovarian morphology
254 on ultrasound, which would reduce their prevalence even further.

255

256 7) A PHENOTYPIC APPROACH TO DEFINING PCOS: TASK FORCE RECOMMENDATIONS

257 The Task Force considered all data published and summarized above, emphasizing larger
258 epidemiologic and phenotypic studies, in arriving to its conclusions and recommendations
259 regarding the phenotype of PCOS. These include the following:

260

261 a) **That PCOS is a hyperandrogenic disorder:** The Task Force concluded that PCOS was
262 above all a disorder of androgen biosynthesis, utilization, and/or metabolism in women. As
263 such, with currently available evidence the diagnosis of PCOS cannot be established without
264 evidence of either clinical or biochemical hyperandrogenism. While the exact measures for
265 these may vary, the Task Force felt that the single most reliable indices of this feature included

266 hirsutism and free T levels. Nonetheless, the Task Force recognized that the methods for
267 measuring androgens in the circulation were frequently inaccurate and insensitive, and that
268 determination of hirsutism using visual scales was subjective, with significant inter-observer
269 variation (78), and whose cut-off level may be unclear (51). Finally, the Task Force also noted
270 that while many patients with PCOS may have evidence of acne or androgenic alopecia, these
271 features could not be used reliably as clinical signs of hyperandrogenism. The Task Force also
272 noted that support for this criteria is based on the risk for metabolic morbidity in the disorder, not
273 on whether hyperandrogenism per se is present or not.

274

275 **b) That the ovarian morphology should be considered when establishing the**
276 **diagnosis, as polycystic ovaries are found in the majority, although not all, women with**
277 **PCOS:** The Task Force recognized that ~75% of women with PCOS will demonstrate a
278 polycystic ovarian morphology on transvaginal ultrasonography, although they also recognized
279 that the false positive rate is high with up to one-quarter of unselected reproductive aged
280 women demonstrating this ovarian morphology. The Task Force also noted that the diagnosis of
281 polycystic ovaries required the use of clear and strict criteria. Consistent with recommendation
282 (6.a) above, the Task Force felt strongly that in those women with polycystic ovaries, but no
283 evidence of clinical or biochemical hyperandrogenism, the diagnosis of PCOS is less certain,
284 regardless of the presence of concomitant ovulatory dysfunction.

285

286 **c) That ovulatory dysfunction is a prominent, but not universal feature, of PCOS:** The
287 Task Force recognized that some patients with PCOS may demonstrate regular ovulation at the
288 time of their evaluation, the so-called “ovulatory PCOS” (79, 80). However, it was noted that
289 patients with “ovulatory PCOS” constituted a minority of the PCOS population, and had less
290 severe androgenic and metabolic features than anovulatory women with PCOS. It was also
291 recognized that there exists little data regarding the long-term maintenance of ovulation in

292 women with "ovulatory PCOS". Nonetheless, the Task Force recognized that there were
293 persuasive, albeit limited, data to suggest that hyperandrogenic ovulatory women with polycystic
294 ovaries had some degree of metabolic dysfunction, and were amenable to the inclusion of this
295 phenotype as a form of PCOS.

296

297 **d) That eumenorrhea in the presence of dermatologic features suggestive of**
298 **hyperandrogenism (e.g. hirsutism) could not reliably be used to establish the presence**
299 **of normal ovulation:** A history of regular predictable vaginal bleeding in a patient without
300 clinical signs of hyperandrogenism can be used as strong evidence of normal ovulation.
301 Alternatively, a history of 'regular' menstrual cycles in patients who demonstrate
302 hyperandrogenic features (e.g. hirsutism) could not be relied upon as evidence of normal
303 ovulation, since up to 40% of these women have oligo-anovulation when examined more
304 carefully. In these patients, confirmation of ovulatory function by more objective means is
305 required.

306

307 **e) That other well-defined disorders that could result in ovulatory dysfunction,**
308 **polycystic ovaries, or clinical or biochemical hyperandrogenism had to be excluded:**
309 Although the Task Force recognized that specific androgen excess or other endocrine disorders
310 needed to be excluded when establishing the diagnosis of PCOS, they also recognized the
311 validity of tailoring testing to reflect the prevalence of these disorders in the population being
312 studied.

313

314 **f) Recognition of associated abnormalities:** The Task Force noted that the presence of
315 obesity, insulin resistance and hyperinsulinism, and increased LH levels or an LH/FSH ratio,
316 while observed in a significant fraction of patients, should not be used as part of the definition of
317 PCOS.

318

319 **8) MINORITY REPORT:**

320 Notwithstanding the above recommendations, the Writing Committee acknowledged that
321 two of its members considered the possibility that there are forms of PCOS without overt
322 evidence of hyperandrogenism, and which may be associated with metabolic abnormalities and
323 morbidity. However, these investigators also recognized, as did the Committee as a whole, that
324 more data are required before validating this supposition. For example, a recent study noted
325 that women with oligo-anovulation and polycystic ovaries but without evidence of
326 hyperandrogenism (n=66) had basal insulin levels, the principal metabolic parameter assessed,
327 similar to controls and lower than patients with hyperandrogenemia and oligo-anovulation, with
328 (n=246) or without (n=27) polycystic ovaries, or those with hyperandrogenemia and polycystic
329 ovaries but without oligo-anovulation (n=67) (81).

330

331 **9) CONCLUSIONS**

332 Based on the above review of the available data, it is the view of the AES Task Force on the
333 Phenotype of PCOS that there should be acceptance of the original NIH/NICHD criteria of 1990
334 with some modifications, taking into consideration the opinion expressed in the proceedings of
335 the 2003 Rotterdam conference (**Figure 1**). Considering the four features of ovulatory
336 dysfunction, hirsutism, hyperandrogenemia, and polycystic ovaries, the Task Force identified
337 nine different phenotypes that could be considered as being PCOS with currently available
338 evidence (**Table 5**).

339 The Task Force noted that there was ample data to support an increased risk of metabolic
340 dysfunction in women with the following phenotypes: a) hirsutism and/or hyperandrogenemia,
341 and oligo-ovulation with and without polycystic ovaries (phenotypes A-F in **Table 5**) and b)
342 hyperandrogenemia and/or hirsutism, and normo-ovulation with polycystic ovaries (phenotype G
343 and H in **Table 5**) (7, 34, 36, 37, 82-94). Current evidence generally did not support an

344 increased metabolic dysfunction among women with polycystic ovaries only, with or without
345 oligo-ovulation (phenotype J in **Table 5**) (95, 96), although not all agreed (97). As expected, the
346 incidence of metabolic dysfunction in PCOS is also significantly increased by the concomitant
347 presence of obesity). However, the Task Force recognized that clinical features may not be
348 constant even in a single patient and can be modified by changes in body weight and lifestyle
349 choices, and age. In addition, the Task Force also recognized that there may be a number of
350 women who have features suggestive of PCOS, but who do not fulfill the criteria; clearly these
351 women and their symptoms should be treated accordingly, regardless of whether a diagnosis of
352 PCOS is established or not.

353 A principal conclusion of this report is that PCOS should be firstly considered a disorder of
354 androgen excess or hyperandrogenism. The absence of clinical or biochemical
355 hyperandrogenism in the untreated state, or in women under the age of 40 years, makes a
356 diagnosis of PCOS less certain, regardless of the presence of ovulatory or menstrual
357 dysfunction or the presence of polycystic ovaries. Overall, at the present time in the Task
358 Force's assessment, women with oligo-amenorrhea and polycystic-appearing ovaries on
359 ultrasonography but no evidence of hyperandrogenism do not have PCOS.

360 The Writing Committee also acknowledged that some of its members considered the
361 possibility that there are forms of PCOS without overt evidence of hyperandrogenism, but
362 recognized that more data are required before validating this supposition. Alternatively, the
363 diagnosis of PCOS in women who have evidence of hyperandrogenism and polycystic ovaries,
364 in the presence of ovulatory cycles, appears justified based on current data. Finally, while the
365 aim of this report was to yield criteria based on currently available data to guide research and
366 clinical diagnosis, and future investigations, the Task Force recognized that the definition of this
367 syndrome will evolve over time to incorporate new research findings.

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369

394

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Table 1. Prevalence of menstrual dysfunction in PCOS

Study	Reference	Total No. PCOS	No. of PCOS patients with oligo- amenorrhea	% of PCOS patients with oligo- amenorrhea	No. of PCOS patients with eumenorrhea	% of PCOS patients with eumenorrhea
Ferriman & Purdie, 1983	(24)	280	237	84.6%	43	15.4%
Conway et al, 1989	(40)	556	395	71.0%	139	25.0%
Kiddy et al, 1990	(48)	263	203	77.2%	60	22.8%
Ardaens et al, 1991	(62)	144	105	72.9%	39	27.1%
Rajkhowa et al, 1995	(49)	153	129	84.3%		
Balen et al, 1995	(41)	1741	1043	59.9%	517	29.7%
Falsetti & Eleftheriou, 1996	(25)	240	207	86.3%	24	10.0%
Khoury et al, 1996	(26)	112	112	100.0%	0	0.0%
Talbott et al, 1998	(29)	244	229	93.9%	15	6.1%
Carmina et al, 1998	(28)	332	290	87.3%	42	12.7%
Alborzi et al, 2001	(30)	371	371	100.0%	0	0.0%
Williamson et al, 2001	(31)	162	144	88.9%		
Haddad et al, 2002	(33)	146	120	82.2%	26	17.8%
Amer et al, 2002	(32)	161	149	92.5%	12	7.5%
Glueck et al, 2003	(34)	138	138	100.0%	0	0.0%
Orio et al, 2003	(35)	100	100	100.0%	0	0.0%
Chang et al, 2005	(36)	316	265	83.9%	51	16.1%
Hahn et al, 2005	(37)	200	200	100.0%	0	0.0%
Total		5659	4437	78.4% ^a	968	18.1%

^aDifference in percentage between patients with oligo-amenorrhea and eumenorrhea and anovulation is composed of patients with polymenorrhea or menometrorragia

Table 2. Prevalence of hyperandrogenemia and hirsutism in PCOS

Study	Reference	Total No. PCOS	No. with elevated Total T	% with elevated Total T	No. with elevated Free T	% with elevated Free T	No. with elevated DHEAS	% with elevated DHEAS	No. with Hirsutism^c	% with Hirsutism^c
Ferriman & Purdie, 1983	(24)	280							230	82.14%
Conway et al, 1989	(40)	556	110	22.3% ^a					320	57.55%
Kiddy et al, 1990	(48)	263							129	49.05%
Rajkhowa et al, 1995	(49)	153							123	80.39%
Balen et al, 1995	(41)	1741	503	28.9%					1153	66.23%
Norman et al, 1995	(50)	122							103	84.43%
Falsetti & Eleftheriou, 1996	(25)	240							92	38.33%
Khoury et al, 1996	(26)	112							20	17.86%
Talbott et al, 1998	(29)	244							105	43.03%
Alborzi et al, 2001	(30)	371							300	80.86%
Williamson et al, 2001	(31)	162							147	90.74%
Amer et al, 2002	(32)	161							53	32.92%
Orio et al, 2003	(35)	100	33	33.0%			27	27.0%	100	100.00%
Chang et al, 2005	(36)	316	122	38.6%	216	68.4%	71	22.5%	224	70.89%
Hahn et al, 2005	(37)	200	162	81.0%			76	38.0%	129	64.50%
Legro et al, 2006	(42)	626	373	60.8% ^b					505	80.67%
Total		5647	1303	36.8%	216	68.4%	174	28.2%	3228	57.16%

Subjects included are mostly of White and Black race

^a Based on 494 patients who underwent androgen measurements

^b Based on 613 subjects who underwent androgen measurements

^c Hirsutism defined variously as mFG scores of 5-9

Table 3. Prevalence of polycystic ovaries (PCO)^a by transvaginal ultrasonography in PCOS

Study	Reference	Total No. PCOS	No. PCOS with PCO	% PCOS with PCO
Rajkhowa et al, 1995	(49)	153	141	92.2%
Falsetti & Eleftheriou, 1996	(25)	240	180	75.0%
Khoury et al, 1996	(26)	112	77	68.8%
Van Santbrink et al, 1997	(63)	198	148	74.7% ^b
Laven et al, 2001	(64)	190	154	81.1%
Alborzi et al, 2001	(30)	371	211	56.9%
Williamson et al, 2001	(31)	162	161	99.4%
Amer et al, 2002	(32)	161	93	57.8%
Jonard et al, 2003	(65)	214	160	74.8%
Orio et al, 2003	(35)	100	33	33.0%
Hahn et al, 2005	(37)	200	166	83.0%
Legro et al, 2006	(42)	626	573	91.5%
Total		2727	2097	76.9%

^aExcluding multicystic or multifollicular ovaries^bPCOS defined as oligo-amenorrhea with either increased androgens and/or high LH

Table 4. Prevalence of thyroid dysfunction, hyperprolactinemia (Hi-Prl), androgen secreting neoplasms (ASNs), 21-hydroxylase deficient nonclassic adrenal hyperplasia (NCAH), and Cushing's Syndrome (CS) in patients with hyperandrogenism or polycystic ovary syndrome

Study	Reference	Total No. PCOS	No. with thyroid dysfunction	% with thyroid dysfunction	No. with Hi-Prl	% with Hi-Prl	No. NCAH	% NCAH	No. CS	% CS	No. ASN	% ASN
Ferriman and Purdie 1983	(24)	467	0	0.0%	4	0.9%	^a					
Conway et al, 1989	(40)	556			58	11.0%	10	1.8%	^e			
Luciano et al. 1984	(70)	150			25	16.7%						
O'Driscoll et al. 1994	(60)	350			1	0.3%	3	0.9%	0	0.0%	2	0.6%
Moran et al, 1994	(71)	250					5	2.0%	1	0.0%	2	0.00%
Balen et al. 1995	(41)	1871	0	0.0%	25	1.3%	19	1.0%			0	%
Khoury et al, 1996	(26)	112			17	15.2%						
Romaguera et al, 2000	(72)	100					1	1.0%				
Azziz et al, 2004	(39)	873	6	0.7%	3	0.3%	18	16.5%	0	0.0%	2	%
Escobar-Morreale et al, 2004	(73)	109			4	3.7%	^b					
Janssen et al, 2004	(74)	175	36	20.6%			^c					
Glintborg et al, 2004	(75)	340			6	1.8%	^d					
Carmina et al, 2006	(76)	950					41	4.3%			2	%
Legro et al, 2006	(42)	626	45	7.2%							0.1	0.21%
Total		5353	42	1.2%	143	4.3%	99	2.3%	2	4%	9	0.21%

^a 4 of 467 subjects had amenorrhea and galactorrhea suggestive of hyperprolactinemia^b Another 3.7% also demonstrated macroprolactinemia^c 11 of 168 controls (6.5%) also had thyroid dysfunction^d 7 of 8 hyperprolactinemic PCOS patients demonstrated normalization of prolactin levels during extended follow-up^e Denominator is entire androgen excess population (n= 711)

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Table 5. All possible phenotypes based on the presence or absence of oligo-anovulation, hyperandrogenemia, hirsutism, and polycystic ovary syndrome.

FEATURES	POTENTIAL PHENOTYPES															
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Hyperandrogenemia	+	+	+	+	-	-	+	-	+	-	+	-	-	-	+	-
Hirsutism	+	+	-	-	+	+	+	+	-	-	+	-	-	+	-	-
Oligo-anovulation	+	+	+	+	+	+	-	-	-	+	-	-	+	-	-	-
Polycystic ovaries	+	-	+	-	+	-	+	+	+	+	-	+	-	-	-	-
NIH 1990 criteria	✓	✓	✓	✓	✓	✓										
Rotterdam 2003 criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						
AES 2006 criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓							

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Figure 1

**ANDROGEN EXCESS SOCIETY: SUGGESTED CRITERIA FOR
THE DIAGNOSIS OF THE POLYCYSTIC OVARY SYNDROME**

- 1- Hirsutism and/or hyperandrogenemia
and**
- 2 - Oligo-anovulation and/or polycystic ovaries
and**
- 3 - Exclusion of other androgen excess or related disorders^a**

^aPossibly including 21-hydroxylase deficient non-classic adrenal hyperplasia, androgen-secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing's syndrome, the syndromes of severe insulin resistance, thyroid dysfunction, and hyperprolactinemia.

PREVALENCE AND PREDICTORS OF IMPAIRED GLUCOSE TOLERANCE AND DIABETES MELLITUS TYPE 2 IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Aim: To estimate the prevalence of impaired glucose tolerance (IGT) and diabetes mellitus type 2 (DMT2), as well as the predictors for glucose abnormalities in women with polycystic ovary syndrome (PCOS).

Material and methods: A cross-sectional study with 80 consecutive patients with newly diagnosed PCOS who underwent the standard 75g oral glucose tolerance test (OGTT) and the measurement of sex steroid hormone and lipid profile.

Results: According to the results from the OGTT, 63% had a normal test (NT), 23% had IGT, and 9% had DMT2. The NT group was younger with lower BMI than IGT and DMT2 groups (25.1 ± 7.3 , 31.5 ± 6.5 , 37.4 ± 4.0 years, and 29.1 ± 8.3 kg/m², 31.7 ± 4.6 kg/m², and 34.5 ± 5.6 kg/m², respectively). The testosterone levels were highest in the group with a normal test (2.7 ± 0.8 nmol/l) and lowest in the DMT2 group (1.9 ± 0.8 nmol/L), with statistical significance. The sex hormone binding globulin (SHBG) levels were low in all three groups, with statistically significant differences between NG and IGT, and the NT and DMT2 groups. The multivariate linear regression model identified age, BMI, SHBG and testosterone as major independent predictors for abnormal glucose metabolism.

Conclusion: It seems that the prevalence of IGT and DMT2 among PCOS women in our country is not as high as in Western countries. Age, BMI, and SHBG increase the risk for the development of IGT and DMT2. Thus, close monitoring of older, obese women with low SHBG is needed because of the higher risk for the development of IGT and DMT2 in such patients.

Keywords: polycystic ovary syndrome, OGTT, IGT, DMT2, testosterone

INTRODUCTION

PCOS is the most common endocrine disease affecting from 3% to 16% of women of reproductive age. PCOS is a metabolic-reproductive disorder with a very complex and not fully understood pathophysiology. Of note, accumulating evidence in literature indicates

that hyperinsulinemia is secondary to insulin resistance (IR) and plays an important role in the pathogenesis of the syndrome [1]. Tissues normally responsive to insulin for glucose uptake, such as the heart and skeletal muscle, protect themselves from nutrient-induced toxicity

by becoming insulin resistant [2]. Insulin resistance is the central mechanism linking together all parameters of the metabolic syndrome, such as: impaired glucose tolerance (IGT), type 2 diabetes mellitus (DMT2), hyperlipidemia and cardiovascular disease over-time [3–5]. Adolescent girls with PCOS have been shown to have early-onset insulin hypersecretion in association with insulin resistance [2], and approaches for reversal of severe hyperinsulinemia early in its course, prevented them from developing health problems later in life, such as diabetes, cardiovascular disease and infertility [6].

In spite of insulin resistance, some women with PCOS demonstrated beta cell dysfunction. Thus, both IR and beta cell dysfunction contribute to the development of DMT2 [7, 8]. Defects in insulin action and inadequate insulin response to glucose load have been found predominantly in obese [1, 7] and less in lean women with PCOS [9]. The risk for DMT2 in women with PCOS is estimated to be 5 to 10-fold higher than factors including age and weight, when compared with the normal control population.

In 1921 Archer and Thiers first reported a relationship between hyperandrogenism and insulin metabolism in their description of “diabetes des femmes a barbe” [10]. In 1980, Burghen and colleagues described a strong correlation between plasma insulin concentrations and testosterone and androstenedione in obese women with PCOS [11]. It became clear that PCOS also includes major metabolic morbidities. Hyperinsulinemia and peripheral insulin resistance are, however, the central feature of metabolic disorders, which is recognized to be typical of PCOS. Epidemiological studies and meta-analysis showed that the onset of IGT and DMT2 appears at an earlier age in patients with PCOS [12–14]. The risk for dysglycemia is the highest among PCOS patients with both anovulation and hyperandrogenism, amplified by obesity, or the classic NIH phenotype [15]. Recently, it has become clear that not only age but also obesity, family history of DMT2 and hyperandrogenemia may contribute to the increasing risk of diabetes in PCOS.

PCOS is a major risk factor for IGT and DMT2, with different prevalence among countries worldwide. Other factors may contribute to this heterogeneous prevalence, such as ethnicity, age, BMI, insulin resistance, dyslipidemia, and reproductive hormones. The aim of this study is to estimate the prevalence of IGT and

DMT2 among Macedonian women diagnosed with PCOS and to identify the parameters (age, BMI, testosterone, sex hormone binding globulin, lipids) as predictors for abnormal glucose tolerance.

MATERIALS AND METHODS

At the University Clinic of Endocrinology, Diabetes and Metabolic Disorders, Skopje, we conducted a cross-sectional study, including patients with PCOS. Applying the Rotterdam diagnostic criteria for PCOS [16], 80 women with PCOS were included and they were screened for glucose intolerance using the oral glucose tolerance test (OGTT) according to the ADA criteria [17].

PCOS was diagnosed when 2 out of the following 3 criteria were present: oligoanovulation and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound examination. Oligoanovulation was defined as the presence of oligomenorrhea (menstrual cycles of >35 days) or amenorrhea (lack of a menstrual period for 6 months or more). Clinical signs of hyperandrogenism were the presence of hirsutism, acne/seborrhea or alopecia. Biochemical hyperandrogenism was established based on elevated total or bioavailable testosterone levels, and DHEAs. Hirsutism was defined as an Ferriman-Gallwey score that was >8. Ovaries were classified as polycystic if 10 or more follicles measuring 2–8 mm in diameter were present in each ovary, and/or there was an increase in the ovarian volume >10ml. Transvaginal ovarian ultrasound scanning was performed between days 5 and 10 from the beginning of the last menstrual cycle using a 7.5-MHz vaginal probe transducer (General Electric LOGIQ 400MD, Milwaukee, WI, USA). Both ovaries were measured in the sagittal, transverse, and coronal planes.

All patients were in their reproductive period, free of chronic disease, including diabetes and hypertension. None of the women with PCOS had taken any oral contraceptive, other forms of hormonal contraception or fertility treatments.

All of the patients underwent 75-g OGTT, following the ADA criteria [17]. 75-g of hydrous glucose load was briefly administered after a 12 to 14 hour period of fasting and 2 hours post –

load samples for glucose were obtained from an antecubital vein. The samples were collected in tubes containing fluoride and kept at 4°C until centrifugation up to 2 hours later. Plasma measurements were performed with glucose oxidase methods.

The patients were divided into three groups according to the results from the OGTT: patients with a normal test (NT), impaired glucose tolerance (IGT) and patients with type 2 diabetes mellitus (DMT2). IGT and DMT2 were diagnosed according to the recommendations of the American Diabetes Association [17].

In all patients the following parameters were analyzed: patients' age, body mass index (BMI), days of the menstrual cycle, Ferriman-Gallwey score, waist/hip ratio, FSH, LH, estradiol (E2), total and free testosterone, DEHAs, 17-OHP, PRL, SHBG, fasting plasma glucose (FPG), 2 hour OGTT glucose values, and lipid parameters.

The BMI of women was calculated by dividing their weight by their squared height in meters (kg/m^2). The days of the menstrual cycle were self-reported by the patients. Hirsutism scoring scale of Ferriman and Gallwey was used. Waist/hip ratio was calculated. A morning blood sample was obtained after an overnight fast from all subjects for measuring hormones and lipoprotein parameters.

All hormones were measured in our laboratory using commercial kits. These included ELISA (DRG Diagnostics, DRG Instruments GmbH, Marburg, Germany) for FSH, LH, E2, 17-OHP, PRL, total and free testosterone. Chemiluminescence assays were used for DHEAs and SHBG. The blood samples for lipoproteins were analyzed using Cobas Integra 700, according to standard methods. Total cholesterol and triglycerides were determined by full enzymatic methods (TH-CHOD-POD-PAP and triglycerides-GPO; Cobas Integra 700, Hoffmann-La Roche, Basel, Switzerland). HDL-C was measured using the polyanion precipitation method, while LDL-C was calculated using the Friedewald formula.

The criteria for diagnosing type 2 DM and IGT were, as recommended by ADA [17], as follows: fasting plasma glucose, normal <5.6 mmol/l; IFG, 5.6-6.9 mmol/l; DMT2, 7.0 mmol/l. Two hour values: normal, 7.7 mmol/l; IGT, 7.8-11.0 mmol/l; DMT2, 11.1 mmol/l.

Normal laboratory values of other testing used were: total testosterone, normal, <2.1 nmol/l; SHBG, 52 - 150 nmol/l; cholesterol 3.4 -5.2 mmol/l; triglycerides, 0.45 – 1.7 mmol/l.

All patients gave informed consent to participate in the study after receiving explanations regarding the research protocols. The study was done according to the Helsinki Declaration.

Table 1. Comparison of the analyzed parameters between patients with normal OGTT, IGT and DMT2

	NT n=58 (1)	IGT n=16 (2)	DMT2 n=6 (3)	significance
Age (years)	25.1±7.3	31.5±6.5	37.4±4.0	1:2; 1:3 (p<0.05)
F-G scor	17.2±7.4	18.5±7.8	11.3±3.0	HC
Days of the menstrual cycle	75.7±52	76.1±50.9	54±22.2	HC
BMI (kg/m²)	29.1±8.3	31.7±4.6	34.5±5.6	HC
waist/hip ratio (cm)	0.76±0.06	0.78±0.08	0.77±0.02	HC
FSH (IU/L)	5.4±1.7	4.7±1.4	7.5±2.3	2:3 (p<0.05)
LH (IU/L)	9.8±4.9	8.6±6.5	11.2±4.4	HC
E2 (pmol/L)	55.4±39	63.4±52.5	50.1±15.0	HC
Testosteron (ng/dL)	2.7±0.8	2.4±0.9	1.9±0.8	1:3 (p<0.05)
F Testosteron	9.1±8.1	10.3±7.1	8.9±4.7	HC
DEHAs (μmol/L)	9.0±3.6	6.7±3.5	3.5±2.7	1:3 (p<0.05)
17-OHP (nmol/L)	5.1±2.7	8.1±5.2	6.3±2.8	HC
PRL (pmol/L)	18.7±11.0	18.8±8.5	17.6±7.6	HC
SHBG (nmol/L)	37.8±15.7	27.1±11.1	22.3±7.5	1:2; 1:3 (p<0.05)
OGTT-0' (mmol/L)	4.7±0.5	5.6±0.7	6.8±1.6	1:2; 1:3; 2:3 (p<0.05)
OGTT-120' (mmol/L)	5.8±1.0	8.7±0.9	11.8±0.2	1:2; 1:3; 2:3 (p<0.05)
Total lipids (mmol/L)	8.2±1.9	8.6±0.9	8.4±0.8	HC
Triglycerides (mmol/L)	1.31±0.6	1.69±0.70	2.33±0.58	1:3 (p<0.05)
T.Cholesterol (mmol/L)	4.8±1.0	4.82±0.78	4.83±0.40	HC
HDL-C (mmol/L)	1.1±0.2	1.13±0.36	1.0±0.14	HC
LDL-C (mmol/L)	3.2±1.1	3.20±1.05	2.75±0.91	HC

*Data are presented as mean±SD. Student T-tests were used for analyzing the differences between the groups.

**F-G scor: Ferriman and Gallwey score system; BMI: body mass index; FSH: folliculostimulating hormone; LH: luteinizing hormone; E2: estradiol; F testosterone: free testosterone; DHEAs: dehydroepiandrosterone sulfate ; 17-OHP: 17-hydroxyprogesterone; PRL: prolactin; SHBG: sex hormone-binding globulin; OGTT-0': fasting glucose; OGTT-120': 2-hr glucose after 75 g oral glucose load; T. Cholesterol: total cholesterol; HDL-C: high density cholesterol; LDL-C: low density cholesterol.

The Statistical Package Statistics, version 7.0 was used. Baseline characteristics were expressed as a mean \pm S.D. Shapiro-Wilk test, showing that all variables have normal distribution. Differences between groups were detected by unpaired Student's t test for continuous variables. The correlation between the tested parameters was determined using Pearson's R for correlation. A GLM multivariate analysis was used for the evaluation of the independent effect of the analyzed variables on fasting, and 2 hour glucose values from OGTT. The value of $p < 0.05$ was taken as statistically significant.

RESULTS

The demographic, anthropometric, and biochemical (hormonal and lipid parameters) characteristics of the 80 women with PCOS are presented in Table 1.

The prevalence of alterations in glucose tolerance was as follows: IGT 16/80 (23%) and DMT2 6/80 (9%).

The women who had normal glucose tolerance were significantly younger than the women with PCOS and altered glucose tolerance. BMI was lower in women with normal glucose tolerance compared to women with altered glucose tolerance, but the differences were not statistically significant. With regard to the hormonal profile, the only difference found between the women with normal glucose tolerance and the IGT group was the statistically significantly lower level of SHBG. Interestingly, there were significantly lower levels of total testosterone and DHEAs in

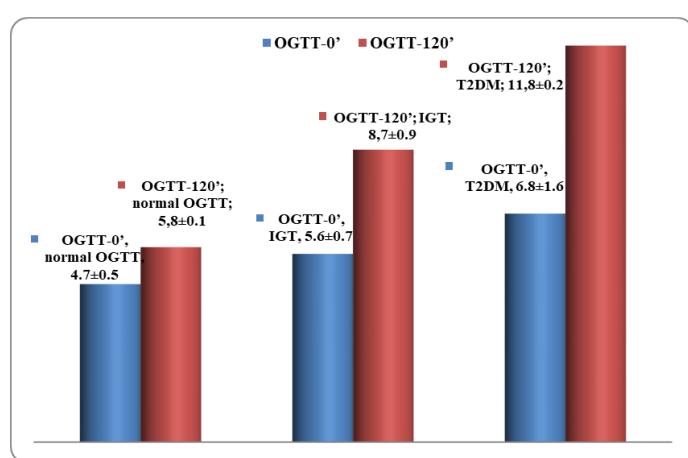
women with DMT2, than in women with normal glucose tolerance. Also, SHBG was significantly lower in the DMT2 group than in women with normal glucose tolerance (Table 1).

The glycemic values from OGTT of women with IGT and DMT2 were significantly higher compared to women with normal glucose tolerance (Table 1, Graph 1). The results from the lipid profile showed significantly higher triglyceride levels in women with DMT2 than in women with normal glucose tolerance (Table 1).

The results from the correlation revealed the following statistically significant correlation: a positive correlation between age and fasting glycaemia, and age with 2 hours post-load glucose from OGTT, a negative correlation between the SHBG and both glycemic values from OGTT, and a positive correlation between the 2 hours post-load glucose and triglycerides, and BMI.

Multivariate linear regression was used to determine the independent impact of the analyzed parameters on the OGTT-0' and OGTT-120' plasma glucose values. BMI, total testosterone, DHEAs, SHBG, and total cholesterol were shown to have an independent effect on the fasting glycaemia in PCOS women (Table 2). Age, BMI, total testosterone, DHEAs, SHBG, total lipids, total cholesterol, and HDL-C have an independent effect on 2 hour post-load glucose from OGTT in PCOS women (Table 3).

We compared our results with those from other countries, trying to explain the differences of IGT/DMT2 prevalence in our cohort to others, and we found mostly higher results, but also some lower prevalence which can partly be explained with the magnitude of BMI (Table 4) [12, 18–23].



Graph 1. Comparison of glycemic values (mmol/l) from OGTT between the women with normal glucose tolerance, IGT, and DMT2

Table 2. Independent effect of analyzed parameters on OGTT-0'

	df	F	p-value
Model	1	20.00037	0.000008
age	1	3.00378	0.083070
BMI	1	6.88429	0.008696
Testosteron	1	29.76036	0.000000
DEHAS	1	5.50194	0.018995
SHBG	1	14.94384	0.000111
Total lipids	1	0.03744	0.846578
Triglycerides	1	0.66487	0.414847
T. Ch	1	15.91711	0.000066
HDL-C	1	0.21245	0.644853
LDL-C	1	0.23702	0.626369

*DHEAs: dehydroepiandrosterone sulfate ; SHBG: sex hormone-binding globulin; OGTT-0': fasting glucose; T. Cholesterol: total cholesterol; HDL-C: high density cholesterol; LDL-C: low density cholesterol.

Table 3. Independent effect of analyzed parameters on OGTT-120'

	df	F	p-value
Model	1	49.78806	0.000000
age	1	5.87812	0.015330
BMI	1	19.67203	0.000009
Testosteron	1	14.62136	0.000131
DEHAS	1	16.32805	0.000053
SHBG	1	22.32290	0.000002
Total lipids	1	4.16304	0.041315
Triglycerides	1	1.99268	0.158061
T. Ch	1	42.07618	0.000000
HDL-C	1	5.35168	0.020702
LDL-C	1	2.43199	0.118882

*DHEAs: dehydroepiandrosterone sulfate ; SHBG: sex hormone-binding globulin; OGTT-0': fasting glucose; T. Cholesterol: total cholesterol; HDL-C: high density cholesterol; LDL-C: low density cholesterol.

Table 4. Comparison of prevalence of IGT and DMT2 in our study and the results from the other countries

Author and year	Ethnicity	N	Age (years) mean±SD (min–max)	BMI (kg/m²) mean±SD	IGT (%)	T2DM (%)
Ehrmann et al. (1999) [12]	52% Caucasian 36% African American USA 8% Asian, 4% Hispanic	122	25.5 ± 0.7 (14–40)	NGT 33.4 ± 1.1 IGT 36.9 ± 1.2 DMT2 41.0 ± 2.4	35	10
Legro et al. (1999) [18]	57% Caucasian USA	110	27 ± 5	29.9±8.1	30	7.3
		144	28 ± 6 (14–44)	35.9±8.0	31.9	7.6
Weerakient et al. (2001) [19]	Thai	79	28.2±6.2	27.2±5.9	20.3	17.7
Gambineri et al. (2004) [20]	Mediterranean	121	— (14–37)	84.3% >25kg/m ²	15.7	2.5
Dabadghao et al. (2007) [21]	Caucasian Australian	372	30.3 ± 5.6 (15–62)	35.1 ± 8.0	15.6	4
Apridonidze et al. (2005) [22]	92,4% Caucasian USA	46 60	— (20–40)	NMS* 33.7 (31.67– 35.85)** MS* 39.3 (36.8– 41.57)**	11	8
Carmina et al. (2006) [23]	Italian	282	24.9±0.1	27.2±0.3	12.4	-
Our study	Caucasian	80	27.5±7.9	30.3±7.4	23	9

*NMS– without metabolic syndrome, MS–with metabolic syndrome

** mean BMI (min–max values of BMI)

DISCUSSION

Studies have shown that abnormal glucose tolerance is present in overweight and obese women with PCOS, compared to women without PCOS [18, 24]. One recent review [25] confirms the original findings of an increased prevalence of IGT and DMT2 among PCOS women in comparison to normal controls. This study revealed that 23% (16/80 patients) of women with PCOS had IGT while 9% (6/80 patients) had DMT2. The finding is in line with the prevalence of impaired glucose tolerance in Italian and European women with PCOS [23]. Different studies from the literature show that IGT was present in 35% of US women and 47% in Asian obese women [19] and in low to moderate weight women from Europe, at first clinical examination [25]. The International Diabetes federation [26] identified PCOS women as a non-modifiable risk factor for DMT2.

Differences in the results may be due to different ages, BMI, ethnicity, the impact of environmental factors, particularly dietary habits, and number of enrolled patients. The prevalence of IGT/DMT2 in our study is lower than the prevalence found in women from the USA and Asia, and higher compared to Australian, Italian and Mediterranean women.

PCOS women show a tendency to develop IGT/DMT2 at an early age and the prevalence is higher when compared to the general population [14, 27]. In our study, IGT was detected in the third decades and DMT2 in the fourth decades. Furthermore, we demonstrated a statistically significant positive correlation between age and FPG, and age with 2 hour post-load glycaemia from OGTT. It is notable that age was the contributing factor to have IGT in the third decade and DMT2 in the fourth decades, meaning that clinicians should keep this in mind. Age has an independent effect on 2 hour post-load glucose from OGTT.

Obesity is common among PCOS women [28]. There is a great variability of overweight (25- 30 kg/m²) and obese (>30 kg/m²) in the PCOS women among different population. The proportion of PCOS women who are overweight is 10% in Italy and 37% in Kuwait. The studies from the USA and Australia reported the highest prevalence of obesity, from 61% to 76% in PCOS women [23]. Obesity has a crucial role in the de-

velopment and maintaining of PCOS [29], and it significantly influences the severity of metabolic abnormalities. Obesity is also a major modifiable risk factor for DMT2 in women with PCOS [30]. In our study, we have found that women with IGT and diabetic PCOS women are significantly more obese in comparison to those with normal glucose tolerance (31.7 ± 4.6 kg/m², 34.5 ± 5.6 kg/m², 29.1 ± 8.3 kg/m², respectively). Obesity has a major impact on the development of PCOS, even more so in the creation of the phenotype of PCOS. Menstrual irregularity, hirsutism, and hyperandrogenemia are associated with morbid obesity in PCOS women. A recent review [14] showed that American and Asian obese women are presented predominantly with metabolic syndrome or the metabolic PCOS phenotype. European women are prone to hirsutism, acne, androgenic alopecia or the hyperandrogenic phenotype. Otherwise lean women with PCOS are rarely diagnosed with DMT2 and only a few percent of normal-weight women have prediabetes. Therefore, regular screening is recommended, particularly in overweight or obese patients and in those with a family history of DMT2, in order to identify impaired glucose metabolism early on [31]. The lower prevalence of IGT/DM2 in our patients with PCOS is partly due to the lower BMI in our study, a finding similar to other Mediterranean countries.

According to the recent guidelines of the American Association of Clinical Endocrinologists, the American College of Endocrinology, and the Androgen Excess and PCOS Society, OGTT should be performed at the moment of diagnosis of PCOS and every 1 to 2 years in patients with PCOS based on a family history of DMT2 and BMI >30kg/m², whereas this test should be performed every year in patients with PCOS and IGT [32].

PCOS is the condition that most often causes elevated testosterone concentrations, and PCOS consensus criteria define hyperandrogenemia on the basis of serum testosterone. Hyperandrogenemia is strongly associated with a diabetes risk in PCOS women. An important pathogenic element for DMT2 is insulin resistance. It is well known that hyperinsulinemia stimulates ovarian theca cells, thereby increasing androgen production and synergistically via LH hypersecretion. Therefore, another contributing factor to abnormal glucose tolerance is the interrelation between insulin resistance and hyperandrogenemia [33]. Hyperandrogenemia has been reported to increase insulin

resistance through the inflammation pathway, which could contribute to hyperglycemia. The correlation between high testosterone levels and insulin concentrations during OGTT may be interpreted as a marker of insulin resistance without direct contribution to the development of diabetes, possibly through the inflammation pathway. This finding was documented by Ehrmann et al. in 1999 for the first time [12] and was confirmed by Shorakae et al. [34]. In our study, multiple linear regression analysis showed that total testosterone has an independent impact on fasting glycaemia and on 2 hour post-load glucose from OGTT in PCOS women. This data from our PCOS cohort shows that other factors associated with abnormal glucose tolerance included testosterone, as well as elevated age and obesity. It seems that the incidence of dysglucaemia, according to an oral glucose tolerance test, increased with severity of the androgen phenotype. However, co-measurement of both androstenedione and testosterone can help to discover the PCOS cohort which is highest for metabolic risk [35].

Insulin resistance (IR) is the prevalent finding in PCOS women and it is predominant in women with the classic and severe PCOS phenotype presented with hyperandrogenism and chronic anovulation. One protein that functionally links those two apparently unparalleled phenotypes is SHBG. Insulin has a direct inhibitory effect on SHBG production from the liver, thus PCOS patients often have the lowest levels of SHBG [36] and the high amount of circulating free androgens [37]. The Study of Women's Health Across the Nation (SWAN) shows that low SHBG and high free androgen index are strongly related to metabolic and cardiovascular risk factors: higher insulin, glucose, hemostatic and inflammatory markers and more adverse lipid profile [38]. In this study, we found statistically significant lower levels of SHBG in IGT and DMT2 groups compared to the group with normal glucose tolerance. There are statistically significant differences between normal glucose tolerance and IGT, and between normal glucose tolerance and DMT2 groups of PCOS women. We found, however, that SHBG shows a statistically significant negative correlation with both fasting and 2 hour post-load glycaemia from OGTT. This is consistent with the fact that SHBG has been found to predict the development of type 2 diabetes. Our finding demonstrated the need to perform OGTT in women with PCOS and low levels of SHBG.

Alteration in the lipid profile is a common finding in women with PCOS. A great reduction of high-density lipoproteins (HDL-C) with both increase of triglycerides and total cholesterol levels, has been observed in obese PCOS women and less in lean PCOS women in comparison to normal weight women [39, 40]. Overall, most investigators agree that PCOS women have levels of triglycerides that are twice as high and a 25% lower concentration of HDL. In our study we found high levels of triglycerides and low levels of HDL-C. Furthermore, we demonstrated a significant negative correlation between FPG and HDL-C, while triglycerides correlated positively with 2 hour post-load glycaemia. Those metabolic patterns are seen in people with DMT2.

CONCLUSIONS

It seems that the prevalence of IGT and DMT2 among PCOS women in our country is not as high as in Western countries. The prevalence rate of IGT and DMT2 increases with age and BMI. The major predictors for abnormal glucose metabolism in PCOS are age, BMI, testosterone and SHBG. Thus, close monitoring of older, obese women with low SHBG is needed because there is a higher risk of developing IGT and DMT2 in these kinds of patients.

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Резиме

ПРЕВАЛЕНЦИЈА И ПРЕДИКТОРИ НА НАРУШЕНА ГЛИКОЗНА ТОЛЕРАНЦИЈА И ДИЈАБЕТЕТ МЕЛИТУС ТИП 2 КАЈ ПАЦИЕНТКИ СО СИНДРОМ НА ПОЛИЦИСТИЧНИ ЈАЈНИЦИ

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Цел: Процена на преваленцијата на нарушка гликозна толеранција (IGT) и дијабетес мелитус тип 2 (DMT2), како и предикторите за нарушувања во метаболизмот на гликоза кај жени со синдром на полицистични јајници (PCOS).

Материјал и методи: Пресечна студија со 80 последователни пациенти со ново дијагностициран PCOS беа подложени на стандарден тест со 75 g оптоварување со орална гликоза (OGTT) и мерење на половите стероидни хормони и липидниот профил.

Резултати: Според резултатите од OGTT, 63 % имаа нормален тест (NT), 23 % имаа IGT и 9 % имаа DMT2. Групата NT беше помлада со понизок БМИ од групата IGT и DMT2 ($25,1 \pm 7,3$, $31,5 \pm 6,5$, $37,4 \pm 4,0$ години и $29,1 \pm 8,3$ кг/м², $31,7 \pm 4,6$ кг/м² и $34,5 \pm 5,6$ кг/м² соодветно). Нивото на тестостерон беше највисоко во групата со нормален тест ($2,7 \pm 0,8$ nmol/l) и најниско во групата DMT2 ($1,9 \pm 0,8$ nmol/L), со статистичко значење. Нивото наекс-хормон врзувачки глобулин (SHBG) беше ниско во сите три групи, со статистички значајни разлики меѓу NG и IGT и групите NT и DMT2. Мултиваријатниот линеарен регресивен модел ги идентификуваше возраста, БМИ, SHBG и тестостеронот како главни независни предиктори за абнормален метаболизам на гликоза.

Заклучок: Се чини дека преваленцијата на IGT и DMT2 кај жените со PCOS во нашата земја не е толку голема како во западните земји. Возраста, БМИ и SHBG го зголемуваат ризикот за развој на IGT и DMT2. Потребно е внимателно следење на постарите дебели жени со низок SHBG, поради поголем ризик за развој на IGT и DMT2 кај таквите пациентки.

Клучни зборови: синдром на полицистични јајници, орален глукозен толерантен тест, нарушка гликозна толеранција, дијабетес мелитус тип 2, тестостерон

'AGE IS JUST A NUMBER:' HOW CELEBRITY-DRIVEN MAGAZINES MISREPRESENT FERTILITY AT ADVANCED REPRODUCTIVE AGES. S. Willson,^a K. N. Goldman.^b ^aNew York University School of Medicine, New York, NY; ^bNew York University Langone Medical Center, New York, NY.



OBJECTIVE: Reproductive-aged women frequently overestimate the likelihood of fertility at advanced reproductive ages resulting in the devastating consequence of unintended childlessness. We hypothesize that popular media over-represents celebrity pregnancies at advanced reproductive ages and thus contributes to public misconceptions surrounding age-related fertility decline. We sought to characterize the depiction of fertility and pregnancy among celebrities in widely-consumed mainstream print media.

DESIGN: Quantitative and qualitative analysis of three top-read print magazines targeting reproductive-aged women.

MATERIALS AND METHODS: Three top-read print magazines targeting reproductive-aged women were identified using publicly available demographic data: *US Weekly*, *Cosmopolitan*, and *People Magazine*. All archived magazines from January 2010 to January 2014 were systematically reviewed for any mention in text or photo of pregnancy, infertility, use of assisted reproductive technology (ART), gestational carrier (GC), or adoption. Depictions of mothers with children under the age of 2y at the time of publication and mentions of pregnancy-related health risks were recorded.

RESULTS: In total, 416 print magazines met inclusion criteria and were analyzed, with a total of 1,894 mentions related to fertility, pregnancy, or motherhood. Fertility was highlighted on nearly 1/3 of magazine covers. 240 individual celebrities received at least one fertility-related mention, with a mean and median age at mention of 35 y. The majority (56%) of women mentioned were AMA. In total, only 2 subjects (<0.008%) were reported as having used ART; this number increased to 6 (0.03%) when including celebrities publicly known to have used ART. Among all AMA women (n=135), 10 (7%) were mentioned as having adopted children, and 5 (4%) used GC. There was no mention of infertility prior to adoption/GC. 45 women were over the age of 40 years (33%); 10 used adoption or GC, and only 2 women (4%) over 40 were mentioned as utilizing ART with autologous oocytes. 7 subjects over the age of 44 years were depicted as pregnant or having delivered healthy infants with no mention of ART. The use of donor gametes received no mention. All magazines contained \geq 1 mention of contraception through sponsored advertisements, while only 10 magazines (2%) mentioned any form of ART. There were no mentions of AMA pregnancy-related health risks.

CONCLUSIONS: Widely-consumed popular media downplays the impact of age on fertility and glamorizes pregnancy at advanced ages. Magazines concurrently advertise contraception contrasted with fertility at advanced reproductive ages, with rare or no mention of ART, donor gametes, or AMA-related health risks. Magazine content reflects a continued stigma surrounding the use of ART and further the public's misconceptions about fertility at advanced reproductive ages. This depiction perpetuates the general notion that fertility is 'flexible' and is highly damaging to young women.

O-155 Tuesday, October 31, 2017 12:00 PM

OPIOID PRESCRIBING PATTERNS AFTER EGG RETRIEVAL. P. Bortolotto,^a M. Prabhu,^b E. Garry,^c K. F. Huybrechts,^d R. M. Anchan,^a B. T. Bateman.^a ^aBrigham and Women's Hospital, Boston, MA; ^bMassachusetts General Hospital, Boston, MA; ^cUniversity of North Carolina at Chapel Hill, Chapel Hill, NC; ^dDivision of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA.



OBJECTIVE: We sought to describe opioid prescribing patterns following egg retrieval (ER).

DESIGN: A retrospective cohort of commercially insured patients from the Truven Marketscan database from 2003-2014.

MATERIALS AND METHODS: We identified a cohort of women who underwent egg retrieval (CPT code 58970) and had filled no more than 1 opioid prescription in the 12 weeks prior to ER (in order to exclude chronic opioid users). We also excluded women with a diagnosis of opioid or substance use disorders. We assessed for factors that might influence the decision to prescribe opioids including mood or anxiety disorder, smoking, use of SSRIs/TCA, pelvic pain or endometriosis. Patient age, region, and year of ER were also captured. The outcomes of interest were i) proportion who filled an opioid prescription within 3 days of ER and ii) quantity dispensed, expressed as oral morphine equivalents (median, interquartile range [IQR]). Differences in the frequency

of opioid fill by patient characteristics were tested using a chi-squared test.

RESULTS: A total of 57,727 women had an ER meeting criteria for analysis. Their mean age was 34.9 (standard deviation 4.8), 2.8% had a diagnosis of anxiety, 3.0% had a diagnosis of mood disorder, 5.7% used SSRI/TCA's, and 5.5% had a diagnosis of endometriosis. Among women having an ER, 11.9% (6,885/57,727) had a post-procedure opioid fill. The most frequently prescribed opioids were hydrocodone (48.8%), codeine (22.5%), and oxycodone (17.4%). The median (IQR) oral morphine equivalents prescribed after ER was 90 (50-125) mg, or 18 tablets of hydrocodone 5 mg. Women with mood disorders, smoking history, or SSRI/TCA use were more likely to fill an opioid prescription, compared to their counterparts without these diagnoses. The frequency of opioids filled over time varied from a low of 10.3% in 2003 to a high of 13.6% in 2006, and was 12.1% for the last year in the study period (2014). Opioids filled after ER varied significantly by region, from a high of 21.2% in the South to a low of 5.3% in the Northeast.

CONCLUSIONS: Whereas only a small proportion of women fill a prescription for opioids after ER, those who do receive a large quantity of opioids. This suggests a disconnect between expected procedural pain and provider prescribing patterns for this subgroup of patients. Patients with a concurrent diagnosis of mood disorder or users of antidepressants were more likely to fill opioid prescriptions, and significant differences existed by region. As most patients tolerate the procedure without using opioids, this should prompt physicians who routinely prescribe these medications to reevaluate this practice.

O-156 Tuesday, October 31, 2017 12:15 PM

QUALITY OF LIFE AND DEPRESSION IN POLYCYSTIC OVARY SYNDROME. E. A. Greenwood,^a

L. Pasch,^a R. S. Legro,^{b,c} M. Cedars,^d H. Huddleston.^a ^aUCSF, San Francisco, CA; ^bPenn State University College of Medicine; ^cReproductive Medicine Network, New Haven, CT; ^dUCSF, San Francisco, CA.



OBJECTIVE: Polycystic ovary syndrome (PCOS) has known pronounced quality of life effects in the domains of emotional, body hair, infertility, weight, and menstrual problems. The purpose of this study is to examine PCOS-related quality of life in depressed and non-depressed PCOS patients.

DESIGN: Secondary analysis of a randomized clinical trial

MATERIALS AND METHODS: 725 women ages 18-40 with PCOS-Rotterdam, desiring pregnancy, were enrolled in the Pregnancy in Polycystic Ovary Syndrome II (PPCOSII) clinical trial comparing letrozole and clomid. Anthropometric data and hirsutism assessment by modified Ferriman-Gallwey (mFG) scores were obtained. Depression was assessed by the self-administered Patient Health Questionnaire (PHQ), using a validated cutoff algorithm. The PCOS Health-Related Quality of Life (PCOSQ) survey, a validated 26-item questionnaire, was self-administered. PCOSQ scores were calculated for each of five domains: Emotional, Body Hair, Infertility, Weight, and Menstrual Problems. Domain scores range from 1-7, with 1 indicating poorest function and 7 optimal function. Two-sided t-tests compared PCOS QOL symptom scores between depressed and non-depressed patients. Linear regression models assessed the impact of a depression diagnosis on PCOSQ domain scores, controlling for age, BMI and mFG score.

RESULTS: 63/725 (8.7%) of women met the criteria for clinically significant depression. Depressed patients reported significantly lower scores (i.e. poorer function) on all five domains, compared to patients without depression: Emotions (3.1 vs 4.6), Weight (2.0 vs 3.5), Infertility (1.9 vs 3.0), Body Hair (3.5 vs 4.2), Menstrual Problems (3.2 vs 4.1); $p < 0.001$. Depressed PCOS patients reported greater sense of lacking of control over their PCOS than patients without depression. In a multivariate analysis controlling for age, BMI and mFG scores, women with depression reported lower quality of life in all domains.

Effect of depression on PCOS QOL domain scores. *Analysis controlled for age, BMI, hirsutism score.

Domain	Coefficient	95% CI	p-value
Emotions	-1.36	(-1.66, -1.07)	<0.001
Body Hair	-0.49	(-0.83, -0.15)	<0.001
Weight	-1.28	(-1.68, -0.89)	<0.001
Infertility	-1.00	(-1.35, -0.65)	<0.001
Menstrual Problems	-0.83	(-1.11, -0.56)	<0.001

CONCLUSIONS: Depression is associated with poor subjective quality of life from PCOS symptoms. This finding remained after controlling for objective measures of symptoms including weight and hirsutism. Although the direction of the effect cannot be determined, these findings may suggest that depression colors the subjective experience of PCOS symptoms. Treatment of depression may improve subjective assessment of symptoms and quality of life in patients with PCOS.

LEIOMYOMA 2

O-157 Tuesday, October 31, 2017 11:00 AM

REGULATION OF PD-1 AND LEPTIN RECEPTOR EXPRESSION BY ESTROGEN THROUGH AKT3 IN HUMAN UTERINE FIBROIDS. A. El Andaloussi,^a A. Al-Hendy,^b ^aOb/Gyn, Augusta University, Augusta, GA; ^bOB/GYN, Dept of Obstetrics & Gynecology, Augusta, GA.



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OBJECTIVE: To study the regulation of PD-1 expression by estrogen and its cross talk with Leptin receptor through AKT3 in human uterine fibroids.

DESIGN: In vitro laboratory study with the use of human uterine fibroid (UF) cells.

MATERIALS AND METHODS: To verify our hypothesis, we stimulated HuLM and primary UF patients cells (n=7) with E2 conjugated with BSA (E2-BSA, is too large to enter the cells and thus cannot bind to nuclear ER) at the following concentration (0.1 ; 1 and 10 nM) at three different time point (30 mn; 1h and 2h). The expression of PD-1, PD-L1, anti-TNF α and anti-TGF β by intracellular staining was analyzed by FACS. Q-PCR was used for RNA expression analysis for PD-1, PI3K, AKT isoforms and LepR used as marker of obesity.

RESULTS: To examine the cross-talk between ER and PD-1 through the non-genomic pathway of E2, Stimulation of UF cells with E2-BSA significantly induces the expression of PD-1 mRNA (5.7 ± 0.84) at the concentration of 0.1 nM after 1h compared to untreated control (2.2 ± 0.25) ($P = 0.016$). This effect reached a plateau and the concentrations of 1 and 10 nM doesn't induce further PD-1 induction. The ER-BSA treatment had no effect on the level of PD-L1 mRNA in UF cells. This observation was supported by FACS analysis based on the mean fluorescence intensity of PD-1 in UF cells (77136 ± 585.4) versus the untreated control (36183 ± 2917.5) ($P = 0.035$). Downstream of PD-1, the PI3K expression level was induced significantly after 30 mins at 0.1 nM of E2-BSA (0.084 ± 0.0014) vs. the control cells (0.029 ± 0.001) ($P = 0.0009$). For AKT, we analyzed the three isoforms AKT1, AKT2 and AKT3 separately. Surprisingly E2-BSA induced marked up-regulation (300 fold increase) of AKT3 after 30 mins of stimulation with 0.1 nM of E2-BSA (300.25 ± 106.6) vs. the unstimulated control (1.38 ± 0.24) ($P = 0.008$). E2 mediated modest induction of AKT1 and no effect on AKT2 ($P = 0.07$) compared to untreated control. E2-BSA induced a significant increase of LepR (14.68 ± 4.6) vs. (0.22 ± 0.01) under the same conditions. This results is suggesting the cross-talk of non-genomic ER, PD-1 and LepR through AKT3, which are eventually mediate proliferation of UF cells.

CONCLUSIONS: Our work presents novel immunomodulatory functions of estrogen in human UF. Our study introduces interconnection among three majors and important pathways in the pathogenesis of UF Targeting AKT3 directly or indirectly through PD-1, might represent a novel effective anti-fibroid immunotherapeutic strategy.

O-158 Tuesday, October 31, 2017 11:15 AM

A CONTROLLED TRIAL ON UTERINE FIBROIDS TREATMENT COMPARING AROMATASE INHIBITOR PLUS GnRH ANALOGUE VERSUS ULIPRISTAL ACETATE. F. Scarpellini,^a M. Sbracia,^b ^aCERM, Rome, Italy; ^bCERM-Hungaria, Roma, Italy.



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OBJECTIVE: We have previously showed that combined treatment of uterine fibroids with the aromatase inhibitor Anastrazole plus GnRH analogue (Goserelin) is an effective therapy in these women with a fast reduction of uterine volume and related symptoms especially uterine bleeding. In this controlled study we compared this treatment with Ulipristal acetate that recently has been introduced in the treatment of fibroids.

DESIGN: A controlled randomized trial on women with uterine fibroids

MATERIALS AND METHODS: 63 women with symptomatic uterine fibroids All patients did not undergo surgery and were medically treated. The mean age of women was 39.1 ± 2.0 . The women were assigned to the com-

bined treatment group or to the Ulipristal group by a computer generated sequence. 30 women were treated with Anastrazole 1 mg/die plus Goserelin 3.6 mg/month. 33 women were treated with Ulipristal acetate 5.0 mg/daily. The women of the two groups were followed up during the treatment, undergoing to serial the assessment ultrasound scan of uterine and fibroids dimensions as well as side effects record.

RESULTS: The two groups of patients did not show statistical significant differences for any of epidemiological data. The time of pain symptom disappearance was shorter in the group treated with the combined therapy than in the Ulipristal group (2.8 ± 0.9 vs 4.1 ± 1.2 , $P < 0.01$). After three months treatment there was a significantly bigger reduction in uterine and fibroids volume in the women treated with the combined therapy than in the Ulipristal group (41.8% vs 14.3% , $P < 0.01$). The side effects rate observed was significantly lower in the patients treated with the combined therapy than controls especially regarding uterine bleeding during treatment (3.3% vs 30.3% ; $P < 0.01$).

CONCLUSIONS: The combined treatment of uterine fibroids with Anastrazole plus GnRH analog showed better results than Ulipristal acetate group with a bigger fibroids reduction, in a shorter time and with lower side effects, especially for uterine bleeding. The combined treatment seems to be the treatment of choice in these women even though these data should be confirmed in larger study.

O-159 Tuesday, October 31, 2017 11:30 AM

SYNERGISTIC EFFECTS OF SIMVASTATIN AND ULIPRISTAL ACETATE ON UTERINE LEIOMYOMA. M. Malik,^a W. H. Catherino,^a



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OBJECTIVE: Human fibroids are highly prevalent uterine tumors composed of proliferating transformed myometrial cells and excessive disordered extracellular matrix (ECM). The gonadal hormone progesterone is known to induce and maintain leiomyoma growth. Simvastatin, primarily used to treat hyperlipidemia, was recently shown to have anti-proliferative and pro-apoptotic effect on leiomyoma cells and xenograft model. Moreover, simvastatin is thought to modulate progesterone levels. Our objectives are to examine effect of simvastatin on ECM production and leiomyoma stem cells, and evaluate the combined effect of simvastatin and ulipristal acetate (UPA), a progesterone receptor modulator.

DESIGN: In-vitro laboratory study

MATERIALS AND METHODS: Patient-derived leiomyoma cell lines were treated with simvastatin at different concentrations for 24 and 48 hours. Expression of ECM proteins and regulating pathways was determined using western blot. Patient-derived stro-1 $^+$ /CD44 $^+$ tumor initiating stem cells were treated with simvastatin, UPA and combinations for 48 hours. Proliferation was examined using MTT assay.

RESULTS: Simvastatin affected the expression of collagen 1A (COL1A) in leiomyoma cells, as early as 24hrs of treatment. A clear concentration dependent effect was observed at 48hr of exposure, with leiomyoma cells demonstrating a 2.5-fold (0.4 ± 0.03) reduction in COL1A at 10^{-7} M simvastatin, compared to untreated controls. At similar concentration and time point, versican (VCAN) was reduced by 1.25-fold whereas fibronectin (FN1) protein did not demonstrate a significant change. Fibromodulin (FMOD) demonstrated significant change at higher concentrations of simvastatin. A significant 2-fold decrease in transforming growth factor beta3 (TGF β 3) protein indicated that simvastatin may affect the production of the ECM proteins by inhibition of the fibrosis-inducing pathway. Its pro-apoptotic role was supported by a concentration-dependent increase in cleaved caspase-3, in treated cells. We have previously demonstrated that leiomyoma cells exposed to UPA demonstrated a decrease in expression of ECM proteins and various components of the TGF pathway. Treatment of leiomyoma stem cells by simvastatin or UPA for 48 hours inhibited proliferation with effects significant at 10^{-7} M ($81 \pm 4\%$ of control) and lower. With simvastatin/UPA combination, proliferation was significantly inhibited to $39 \pm 25\%$ of control at 10^{-7} M concentrations.

CONCLUSIONS: Simvastatin inhibits production of leiomyoma ECM and inhibits proliferation of leiomyoma cells. Simvastatin/ulipristal acetate synergism appears to be a promising approach in leiomyoma therapy. To improve efficacy, combination therapy may work by focusing on different steps in leiomyoma cell stimulation.

Article

Quality of Life of Women with Polycystic Ovary Syndrome

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Abstract: *Background and Objectives:* Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by multiple hormonal and metabolic abnormalities, including insulin resistance, hyperandrogenism, and disturbances in lipid and carbohydrate metabolism. The objective of this study is to assess the quality of life of women diagnosed with polycystic ovary syndrome (PCOS) and to identify any factors within the study group that may impact the scores related to quality of life. *Materials and Methods:* This research was carried out among women diagnosed with PCOS. An original questionnaire, developed through an online Google Forms survey, was utilized as the research instrument and distributed through social networks and support groups to women facing PCOS. This study encompassed a participant pool of 200 women with PCOS, aged 24 years or older. For the analytical component, Pearson's χ^2 test was employed—a nonparametric test designed to assess the relationship between two variables measured on a qualitative scale. The chosen level of statistical significance was set at $p < 0.05$. *Results:* The analysis revealed that the quality of life of the women under study was not linked to the duration of the disease or comorbidities. However, a significant association was observed with the inconvenience caused by PCOS symptoms. Women experiencing very bothersome symptoms of PCOS reported a lower quality of life compared to those with symptoms rated as not very bothersome. Despite the majority of women with PCOS rating their quality of life as good or very good, they often find the associated symptoms of PCOS bothersome. Women reporting lower quality of life tend to acknowledge the impact of PCOS on their lives, experience a sense of lack of control over the disease, struggle with depression, and do not accept their physical appearance. *Conclusions:* Hence, the support from specialists like endocrinologists, gynecologists, and nutritionists becomes crucial for many women dealing with PCOS. Adopting a healthy lifestyle, incorporating a balanced diet, and engaging in regular physical activity can assist in managing the troublesome symptoms of PCOS, thereby enhancing overall quality of life. In instances of emotional difficulties, seeking psychological support is equally important, and the significance of support and acceptance from loved ones should not be overlooked.



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1. Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by multiple hormonal and metabolic abnormalities, including insulin resistance, hyperandrogenism, and disturbances in lipid and carbohydrate metabolism [1–7]. Dysbiosis of gut microbiota may play a pathogenic role in the development of PCOS [8]. Several criteria exist for diagnosing PCOS, such as the National Institutes of Health (NIH) criteria, Androgen Excess Society (AES) criteria, and Rotterdam criteria. Among these, the Rotterdam criteria are the most widely utilized [9–12]. To receive a diagnosis of PCOS, a minimum of two of the three Rotterdam criteria must be satisfied: ultrasound evidence of polycystic ovaries (presence of at least 20 Graff follicles measuring 2–9 mm in diameter and/or ovarian volume >10 mL),

infrequent ovulation or absence of ovulation, and clinical and/or biochemical indications of hyperandrogenism [13]. When employing these criteria for PCOS diagnosis, it is essential to simultaneously rule out other endocrine causes [13]. Women grappling with PCOS frequently contend with symptoms that can be personally challenging. Therefore, the paramount approach involves providing them with support and understanding, creating a sense of safety. This approach not only facilitates effective interviews but also contributes to formulating a treatment plan geared toward mitigating or addressing the prevailing symptoms and achieving the desired outcomes for the patient. Consequently, it is essential to delve into the quality of life experienced by women with PCOS and the prevalent challenges they encounter [14–20]. This includes exploring aspects such as family life, social interactions, sexual well-being, professional engagements, parenthood, fertility treatments, and potential feelings of helplessness linked to issues like hirsutism or accompanying metabolic conditions.

The objective of this study was to conduct a self-assessment of the quality of life of women with PCOS and to analyze the factors influencing the aforementioned quality of life scores.

2. Materials and Methods

The research was carried out among women diagnosed with PCOS. An original questionnaire entitled “Assessment of the quality of life of women with polycystic ovary syndrome”, developed through an online Google Forms survey, was utilized as the research instrument and distributed through social networks and support groups to women with verified PCOS. The study included a group of 200 participants with PCOS.

The questionnaire consisted of 28 questions (including 4 multiple-choice ones). The first part of the questionnaire had questions related to general demographic information (age, place of residence, marital status, education, professional status, and socioeconomic conditions). The next questions concerned PCOS (when was the disease diagnosed, what are the symptoms and other diseases, and what is the treatment used) and fertility. The third part of the survey included questions regarding the assessment of quality of life and experienced emotions (depression/anxiety/sadness, a feeling of lack of control or acceptance of physical appearance, and support from family).

Data analysis was conducted using TIBCO Software Inc. (2017) Statistica, version 13, and Microsoft Excel, version 2019 (Microsoft Office). The analysis of the gathered data took the form of both descriptive and analytical statistics. Descriptive statistics were conducted through a Microsoft Excel spreadsheet, which included the creation of graphs based on the collected data. For the analytical component, Pearson’s χ^2 test was employed—a nonparametric test designed to assess the relationship between two variables measured on a qualitative scale. The chosen level of statistical significance was set at $p < 0.05$.

3. Results

The study cohort comprised 200 women diagnosed with PCOS, aged 24 years or older.

3.1. Characteristics of the Study Group of Women with Polycystic Ovary Syndrome

The predominant segment of the study group consisted of women aged 24 to 29, making up 53% of the participants. Geographically, 34.5% resided in large cities with populations exceeding 100,000, while 32% lived in rural areas. Among the participants, 41% were married. In terms of education, 60% of the women held higher education degrees, and a majority, accounting for 71%, were economically active. Assessing socioeconomic conditions, 57% rated them as good (see Table 1). Within the study group, 18% of the women had children, while the remaining 82% did not. Among those attempting to conceive, 55% made no efforts, 41.5% encountered difficulties, and 3.5% reported no problems. For women with children, the duration of attempts to conceive varied, with 38.6% lasting 1–2 years, 31.3% up to a year, 21.7% spanning 3–5 years, and 8.4% extending beyond 5 years. The manifestation of PCOS primarily presented as irregular menstrual cycles (80.5%) and the

characteristic ultrasound image of polycystic ovaries (71.5%). Other common manifestations included infrequent or absent ovulation (61%), insulin resistance/hyperinsulinemia (60.5%), hirsutism (50%), overweight/obesity (47%), difficulties in getting pregnant (45%), acne (44%), and bloating (41.5%). Less frequently reported symptoms included amenorrhea (32%), hyperandrogenism (26.5%), infertility (24%), and androgenetic alopecia (17.5%). Regarding comorbidities, 30.5% of women had hypothyroidism/Hashimoto's disease, 9% had lipid disorders, 7.5% experienced hypertension, 5.5% had diabetes, and 1.5% had hyperthyroidism.

Table 1. Characteristics of the study group.

Variable	Subgroup	%
Age	24–29 years	53%
	18–23 years	24.5%
	30–35 years	18.5%
	above 35 years	4%
Residence	large cities, >100 thousand residents	34.5%
	medium-sized cities, 50–100 thousand residents	15.5%
	small cities, <50 thousand residents	18%
	country	32%
Marital status	married	41%
	informal relationship	30.5%
	unmarried—maidens	27%
	widows	1%
Education	divorced	0.5%
	higher	60%
	secondary	34.5%
	vocational	3.5%
Job status	primary	2%
	active—working	71%
	studying	19.5%
	nonactive	9.5%
Socio-economic conditions	good	57%
	very good	30%
	sufficient	12%
	poor	1%

The women surveyed typically rated the severity of their symptoms as bothersome (40.5%), moderately bothersome (26.5%), or very bothersome (24%). Less frequently, respondents rated their symptoms associated with PCOS as not very bothersome (8.5%) or not bothersome at all (0.5%). Of the women surveyed, 79% were undergoing treatment for PCOS-related symptoms, while 21% were not receiving treatment for PCOS. A total of 96% of the surveyed women were under the regular care of a gynecologist, and 50.5% were under the regular care of an endocrinologist. A smaller percentage of women surveyed were under the regular care of a nutritionist (13%), psychologist (11%), dermatologist (8.5%), psychiatrist (8%), or diabetologist (7.5%) (see Table 2).

Table 2. Clinical symptoms and treatment options for polycystic ovary syndrome.

Variable	Subgroup	%
Diagnosis of PCOS	1–3 years	31.5%
	up to 1 year	24%
	4–6 years	22%
	up to 10 years	10%
	above 10 years	12.5%
Severity of symptoms	bothersome	40.5%
	moderately bothersome	26.5%
	very bothersome	24%
	little bothersome	8.5%
	nondisruptive	0.5%
Under constant care	gynecologist	96%
	endocrinologist	50.5%
	dietician	13%
	psychologist	11%
	dermatologist	8.5%
Treatment undertaken	psychiatrist	8%
	diabetologist	7.5%
	yes	79%
	no	21
Forms of treatment	hormonal contraception/yes	26%
	no	74%
	metformin/yes	39.5%
	no	60.5%
	diet/yes	53.5%
	no	46.5%
	physical activity/yes	51%
	no	49%

3.2. Self-Assessment of Quality of Life of Women with Polycystic Ovary Syndrome

The women who participated in the survey generally assessed their quality of life as good (self-assessment of quality of life), rated by 61.5%. Following this, 20% rated their quality of life as very good, while 15% indicated a satisfactory quality of life. A small percentage of respondents, 2.5%, rated their quality of life poorly, and 1% rated it very poorly. The presence of PCOS affected “some sphere” of life for 84% of the surveyed women, whereas 16% acknowledged that PCOS had no impact on their lives. Within the study group, PCOS predominantly affected the sexual sphere for 79.2% and, to a lesser extent, the family (61.9%), social (50.6%), and occupational (24.4%) spheres. Sadness attributed to PCOS was reported by 79% of the surveyed women, with only 21% indicating that they experienced no sadness or anxiety due to PCOS. A feeling of being out of control due to PCOS was experienced by 75% of the women, and 26% struggled with depression. Acceptance of their physical appearance was noted by only 40.5% of the surveyed women, while 59.5% did not accept their appearance. Furthermore, 67.5% of the women admitted to having low self-esteem due to the presence of PCOS, with 32.5% reporting no perceived impact. Regarding family support, the surveyed women typically rated it as medium (43%)

or good (32%), with fewer respondents rating it as very good (14%), bad (9%), or very bad (2%) (see Table 3).

Table 3. Self-assessment of quality of life in women with polycystic ovary syndrome.

Variable	Subgroup	%
Self-assessment of quality of life	good quality of life	61.5%
	very good quality of life	15%
	poor quality of life	2.5%
	very bad quality of life	1%
Sadness	yes	79%
	no	21%
Depression	diagnosed	26%
	no depression	74%
Accept of their appearance	yes	40.5%
	no	59.5%
Self-esteem	low	67.5%
	not affected	32.5%
Influence on spheres of life	sexual sphere	79.2%
	family sphere	61.9%
	social sphere	50.6%
	professional sphere	24.4%

3.3. Assessment of Factors Affecting the Quality of Life of Women with Polycystic Ovary Syndrome

The analysis revealed that the quality of life of the women under study was not linked to the duration of the disease ($\chi^2 = 8.98; p = 0.344$) or comorbidities ($\chi^2 = 4.04; p = 0.401$). However, a significant association was observed with the inconvenience caused by PCOS symptoms ($\chi^2 = 22.25; p < 0.01$). Women experiencing very bothersome symptoms of PCOS reported a lower quality of life compared to those with symptoms rated as not very bothersome (refer to Table 4).

Table 4. Relationship between quality of life assessment, duration of illness, severity of symptoms, and comorbidities.

	How Is Your Quality of Life?			χ^2	<i>p</i>
	Very Good	Good	Sufficient/Poor		
How long ago were you diagnosed with polycystic ovarian syndrome (PCOS)?	Less than a year ago	25.0%	58.3%	16.7%	8.98 0.344
	1–3 years ago	11.1%	73.0%	15.9%	
	4–6 years ago	22.7%	61.4%	15.9%	
	7–10 years ago	20.0%	50.0%	30.0%	
	11 or more years ago	28.0%	48.0%	24.0%	

Table 4. Cont.

		How Is Your Quality of Life?			χ^2	<i>p</i>
		Very Good	Good	Sufficient/ Poor		
How do you assess the annoyance of the symptoms present?	Little bothersome	33.3%	66.7%	0.0%	22.25	0.001
	Moderately bothersome	24.5%	69.8%	5.7%		
	Bothersome	21.0%	58.0%	21.0%		
	Very bothersome	8.3%	56.3%	35.4%		
Have you been diagnosed with any of the conditions that accompany PCOS?	One	22.9%	61.8%	15.3%	4.04	0.401
	Two	12.2%	65.4%	22.4%		
	More	21.2%	54.6%	24.2%		

χ^2 : Chi-square statistics; *p*: statistical significance level.

Likewise, the correlation between the assessment of quality of life and factors such as treatment, adherence to diet, and physical activity was investigated through Pearson's χ^2 test analyses. The outcomes of these analyses are presented in Table 5, but they proved to be statistically insignificant (*p* > 0.05). Only the connection between quality of life and dietary adherence approached statistical significance ($\chi^2 = 5.67$; *p* = 0.059). Women following a diet tended to give lower ratings of their quality of life.

Table 5. Relationship between quality of life assessment, treatment, diet, and physical activity.

		How Is Your Quality of Life?			χ^2	<i>p</i>
		Very Good	Good	Sufficient/ Poor		
Are you being treated (for symptoms related to polycystic ovary syndrome?)	No	19.0%	57.2%	23.8%	1.00	0.607
	Yes	20.3%	62.6%	17.1%		
Do you use hormonal contraception?	No	23.0%	58.1%	18.9%	3.63	0.162
	Yes	11.5%	71.2%	17.3%		
Do you take metformin?	No	20.7%	61.1%	18.2%	0.09	0.956
	Yes	19.0%	62.0%	19.0%		
Do you follow any kind of diet?	No	14.0%	69.9%	16.1%	5.67	0.059
	Yes	25.2%	54.2%	20.6%		
Do you take care of regular physical activity (at least three times a week)?	No	16.3%	64.3%	19.4%	1.62	0.445
	Yes	23.5%	58.9%	17.6%		

χ^2 : Chi-square statistics; *p*: statistical significance level.

Additionally, through Pearson's χ^2 test analyses, the relationship between the assessment of quality of life and factors such as having children and experiencing negative emotions was explored. The results of these analyses are detailed in Table 6. No significant association was found between quality of life and having children ($\chi^2 = 1.66$; *p* = 0.436) or experiencing sadness ($\chi^2 = 3.40$; *p* = 0.183). However, quality of life was observed to be linked with the impact of the disease on one's life ($\chi^2 = 13.14$; *p* < 0.01), feeling out of control ($\chi^2 = 10.17$; *p* < 0.01), and depression ($\chi^2 = 19.16$; *p* < 0.001). Women who acknowledged that PCOS had an impact on their lives, those feeling out of control due to the disease, and those struggling with depression reported lower quality of life.

Table 6. Relationship between quality of life assessment, having children, and experiencing negative emotions.

	How Is Your Quality of Life?			χ^2	<i>p</i>
	Very Good	Good	Sufficient/ Poor		
Do you have any children?	No	18.3%	62.8%	18.9%	1.66 0.436
	Yes	27.8%	55.6%	16.8%	
Does the presence of PCOS affect any area of your life?	No	40.6%	56.3%	3.1%	13.14 0.001
	Yes	16.1%	62.5%	21.4%	
Do you experience anxiety/sadness due to PCOS?	No	26.2%	64.3%	9.5%	3.40 0.183
	Yes	18.4%	60.8%	20.8%	
Do you feel a lack of control over the situation with PCOS?	No	28.0%	68.0%	4.0%	10.17 0.006
	Yes	17.3%	59.4%	23.3%	
Do you have depression?	No	23.0%	65.5%	11.5%	19.16 0.000
	Yes	11.5%	50.0%	38.5%	

χ^2 : Chi-square statistics; *p*: statistical significance level.

This study also investigated whether the quality of life of women with PCOS was linked to the impact of the disease on self-esteem. To explore this, a series of analyses were conducted using Pearson's χ^2 test, and the results, detailed in Table 7, were found to be statistically significant (*p* < 0.05). The findings indicated that women who did not accept their physical appearance, had low self-esteem, and lacked family support tended to rate their quality of life as lower.

Table 7. Relationship between quality of life assessment and self-esteem.

	How Is Your Quality of Life?			χ^2	<i>p</i>
	Very Good	Good	Sufficient/ Poor		
Do you accept your appearance (physical)?	No	13.5%	58.8%	27.7%	20.19 0.000
	Yes	29.7%	65.4%	4.9%	
Do you have low self-esteem due to polycystic ovary syndrome?	No	27.7%	63.1%	9.2%	7.36 0.025
	Yes	16.3%	60.7%	23.0%	
How do you assess the support from your family?	Very good	39.3%	53.6%	7.1%	22.13 0.001
	Good	21.9%	67.2%	10.9%	
	Moderate	15.1%	64.0%	20.9%	
	Poor	9.0%	45.5%	45.5%	

χ^2 : Chi-square statistics; *p*: statistical significance level.

4. Discussion

PCOS stands as the most prevalent endocrine disorder among women of reproductive age. The range of clinical manifestations associated with PCOS are substantial, encompassing hormonal, metabolic, lipid, and carbohydrate metabolism disorders [16]. These conditions collectively exert a significant impact on the quality of life for affected women [1]. Given the diverse array of clinical symptoms and the associated dependencies on the occurrence of additional diseases, it is imperative to approach each patient with PCOS on an individual basis. Tailoring the treatment to encompass the patient's symptoms, concurrent conditions, and expectations for therapeutic outcomes is crucial for quality of life.

Women with PCOS suffer more from depression and sexual dysfunction than healthy patients [21,22]. In our study, the majority of women in the sample rated their quality of life (self-assessment of quality of life) as good, accounting for 61.5%, while 20% of respondents perceived themselves as having a very good quality of life. Unfortunately, a significant portion, 79% of the surveyed women, experienced feelings of sadness related to the disease. Additionally, 75% declared a lack of control over PCOS, and 26% of the women reported struggling with depression. Moreover, 67.5% of the surveyed women admitted to experiencing low self-esteem due to the presence of PCOS, with only 40.5% accepting their physical appearance.

Women dealing with PCOS contend with various health challenges that manifest to varying degrees across different aspects of their lives. The predominant symptoms of PCOS include irregular menstrual cycles [23] and hirsutism [16]. Sidra et al. [24] noted that irregular menstrual cycles (71.8%) and hirsutism (68.7%) were the most commonly mentioned symptoms by women with PCOS [24]. Hirsutism, identified by Bazarganipour et al. [25], is frequently reported by women with PCOS, with Mohammad et al. [16] stating that it affects nearly 70% of women, often impacting their sense of femininity [16]. Rzońca et al. [26] reported that the longer the duration of the PCOS, the lower the overall quality of life of affected women, affecting various spheres such as social, physical, and environmental well-being [26]. Conversely, Stańczyk et al. [27] observed a prevalence of lowered self-esteem among most women with PCOS, particularly those grappling with hirsutism and lacking robust social support [27]. Contrary to some previous findings, our study did not establish a correlation between the duration of illness or the presence of additional diseases and the quality of life. However, it did reveal a noteworthy association between the severity of PCOS symptoms and the overall quality of life. Women with highly bothersome PCOS symptoms tended to rate their quality of life as lower.

Struggling with issues such as excessive body hair, challenging-to-control acne, increased hair loss, or heightened sebum production can significantly diminish a woman's self-esteem, particularly in terms of her physical attractiveness, leading to embarrassment and potentially contributing to the development of psychosocial disorders [1,2]. Additionally, conditions like overweight, obesity, insulin resistance, and hyperinsulinemia can either be a cause or consequence of metabolic disorders, substantially impacting the deterioration of quality of life and self-perception [28,29]. For women with PCOS, excessive body weight and the prolonged effort to shed it can also negatively affect their self-esteem [27,30]. A study by Moghadam et al. [20] highlighted obesity as a significant contributor to poor quality of life, particularly due to its association with negative psychological symptoms [20]. In addressing most symptoms linked to PCOS, lifestyle modification is often recommended. This involves adopting a diet that supports weight maintenance or reduction, alongside regular exercise—considered the primary nonpharmacological treatment for women with PCOS. Lifestyle modifications yield substantial improvements in metabolism, reproductive function, and a reduction in insulin resistance [17,31]. A reduction in body weight has been found to primarily enhance insulin sensitivity in target tissues. This weight loss leads to increased sex hormone binding globulin (SHBG) and decreased testosterone levels, thereby alleviating symptoms of hyperandrogenism. This mechanism also contributes to rectifying endocrine dysfunction, regulating menstrual cycles, and enhancing ovulation frequency, thereby improving fertility [32–34]. In the context of lifestyle modification, maintaining an appropriate diet is crucial. This involves primarily reducing the intake of high glycemic index carbohydrates, adopting a low-calorie diet, increasing fiber and polyunsaturated fat consumption, and decreasing saturated fats [3,18,35,36]. Another vital aspect of modifying the lifestyle of women with PCOS is regular physical exercise, which, when combined with an appropriate diet, can lead to a reduction in excessive body weight and alleviate bothersome PCOS-related symptoms, ultimately contributing to enhanced well-being. Regular physical activity is recommended at least three times a week, with each session lasting at least 30 min. The selection of suitable physical activities depends on individual needs and preferences, ensuring alignment with a woman's current capabilities [29]. Although our

study did not confirm a direct correlation between physical activity and quality of life, it did highlight that women who did not accept their physical appearance, had low self-esteem, and lacked family support tended to rate their quality of life as lower. Intriguingly, there was a noteworthy trend in quality of life among those adhering to dietary recommendations, approaching statistical significance. Specifically, women on a diet tended to rate their quality of life more negatively.

Women with PCOS often face challenges in conceiving or may be diagnosed with infertility. This contributes to a decline in the quality of life for these women, as the desire to have a child holds significant importance in the lives of a certain proportion of women. It represents the realization of their dreams and a strengthening of family ties with their partners. According to Sulaiman et al. [29], infertility affects 38.4% of women with PCOS [29]. Additionally, Barnard et al. [23] associate PCOS with elevated levels of depression [23]. Sidra et al. [24] share a similar perspective, reporting an increasing incidence of depression among women with PCOS, with a result of 61.8% [24]. In our study, a slightly different result was obtained, with 26% of surveyed women confirming the presence of depression. Given the gravity of depression in the context of this condition, further investigation into its prevalence among women with PCOS, involving a larger sample, would be valuable. Our study did not establish a direct relationship between quality of life and the experience of having offspring or feelings of sadness. Instead, it revealed that lower quality of life was associated with women who acknowledged that PCOS was impacting their lives, women with a sense of lack of control over the disease, and women grappling with depression.

The treatment of PCOS is contingent upon the predominant symptoms and the individual patient's expectations regarding therapeutic outcomes. Consequently, PCOS treatment should be comprehensive and tailored to the specific needs of each woman. In cases of insulin resistance and hyperinsulinemia, when nonpharmacological approaches like a proper diet and regular exercise prove insufficient, pharmacological treatment becomes necessary. Metformin, a widely utilized drug, is commonly prescribed. It enhances insulin sensitivity in target tissues and has a positive impact on the lipid profile. Metformin's mechanism involves inhibiting hepatic gluconeogenesis, subsequently reducing intestinal glucose absorption, and later increasing peripheral glucose uptake and metabolism. Despite its side effects, metformin significantly improves tissue insulin sensitivity and contributes to weight loss. As an alternative to metformin, inositol supplementation is increasingly recommended [37–41]. Conversely, for women not planning to conceive but contending with irregular menstrual cycles and excessive hairiness, oral contraceptives are the preferred form of therapy. Their primary role is to regulate menstrual cycles and reduce hyperandrogenemia. Hormonal contraception inhibits excessive secretion of luteinizing hormone (LH) and lowers free androgens. It is crucial to note that the effects of hirsutism therapy may only become evident after 3–6 months due to the hair follicle development cycle. However, these effects may reverse upon discontinuation of treatment. Some women with PCOS are turning to cosmetic procedures like laser hair removal. Given the potential risk of embolic complications with oral contraceptives, it is essential to approach patients individually, selecting the safest contraception type while considering contraindications and assessing risk factors for heart disease [42–46]. Therefore, comprehensive care is vital, tailoring treatment based on accompanying symptoms, conditions, and expected outcomes. Early diagnosis and appropriately selected treatment can help prevent more serious consequences associated with untreated PCOS [1,27,29]. Unfortunately, in our study, we did not observe an impact of treatment on the assessed quality of life of women with PCOS.

5. Conclusions

Despite the majority of women with PCOS rating their quality of life as good or very good, they often find the associated symptoms of PCOS bothersome. Women reporting a lower quality of life tend to acknowledge the impact of PCOS on their lives, experience a sense of lack of control over the disease, struggle with depression, and do not accept

their physical appearance. Hence, the support from specialists like endocrinologists, gynecologists, and nutritionists becomes crucial for many women dealing with PCOS. Adopting a healthy lifestyle, incorporating a balanced diet, and engaging in regular physical activity can assist in managing the troublesome symptoms of PCOS, thereby enhancing overall quality of life. In instances of emotional difficulties, seeking psychological support is equally important, and the significance of support and acceptance from loved ones should not be overlooked.

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Racial differences in anxiety, depression, and quality of life in women with polycystic ovary syndrome

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Objective: To evaluate racial differences in the anxiety and depression prevalence and scores in women with polycystic ovary syndrome (PCOS).

Design: Cross-sectional.

Setting: Academic institution.

Patient(s): Reproductive-aged women with PCOS ($n = 272$) and controls ($n = 295$).

Intervention(s): Hospital anxiety and depression scale and modified PCOS quality-of-life survey (MPCOS-Q).

Main Outcome Measure(s): Differences in depression and anxiety scores and quality-of-life score measured using the hospital anxiety and depression scale and MPCOS-Q were determined between White and Black women with PCOS. Multivariable correlation regressions assessed the association of the Ferriman-Gallwey score, total testosterone, body mass index (BMI), and homeostatic model assessment of insulin resistance with anxiety, depression, and quality-of-life scores.

Result(s): Multivariable regression controlling for age, BMI, and socioeconomic status showed that White women with PCOS had a significantly higher prevalence of anxiety than Black women with PCOS (75.9% vs. 61.3%) and significantly higher anxiety scores (mean \pm SD, 10.3 ± 4.1 vs. 8.7 ± 4.6). The prevalence of depression (24.4% vs. 29%) and depression scores (4.8 ± 3.6 vs. 5.1 ± 4.0) was not significantly different. In multivariable correlation regressions, the interaction between BMI and race in its association with anxiety scores was significant. The association of race with Ferriman-Gallwey score, total testosterone, or homeostatic model assessment of insulin resistance was not significant. In multivariable models, although the total MPCOS-Q scores were similar, the infertility domain was significantly lower in Black women with PCOS (mean \pm SD, 12.6 ± 7.8 vs. 17.5 ± 6.8) indicating a lower quality of life related to infertility.

Conclusion: Racial differences identified in the prevalence of anxiety and MPCOS-Q domains suggest the importance of routine screening and provide an opportunity for targeted interventions based on race. (Fertil Steril Rep® 2021;■:■-■. ©2021 by American Society for Reproductive Medicine.)

Key Words: Anxiety, depression, PCOS, quality of life, racial differences

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting reproductive-aged women (1). Its prev-

alence ranges from 8% to 13% depending on the diagnostic criteria used and the race and ethnicity of the population studied (2). For example, although the

prevalence of PCOS in the United States ranges from 5% to 7% (3), it is as low as 2.2% in China (4) and as high as 14.1% in Iran (5). The prevalence of different phenotypes of PCOS also varies depending upon race or ethnicity. In a cross-sectional retrospective study in the United Kingdom ($n = 1,310$), South Asian women were significantly more likely to have hyperandrogenic symptoms compared with White women (6). Similar differences in phenotypes have been described in other populations, including African Americans and Hispanics (7, 8), leading recent international guidelines to suggest

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ethnicity-based cutoffs for Ferriman-Gallwey (FG) scores (2).

In addition, metabolic risk in women with PCOS also varies with ethnicity. In an international study, Norwegian women with PCOS were more likely to have metabolic syndrome, Indian women were more likely to have impaired glucose tolerance, and Brazilian women were more likely to have low high-density lipoprotein (HDL) compared with White women residing in the United States (9). In the United States, Black adolescents and young adults have been reported to have a higher prevalence of metabolic syndrome and its components compared with their White counterparts (relative risk 2.65, 95% confidence interval [CI]: 1.29–5.4) (10, 11).

Although racial disparities in phenotype and metabolic risk have been studied, there is no data on racial differences in emotional wellness in the PCOS population. It is important to consider the effect of racial disparities and differences on mental health, including the emerging evidence that racial experiences in minority populations can affect multiple aspects of mental health care, including distress due to anxiety, access to care, and the use of treatment (12–16). In the US general population, the lifetime prevalence of generalized anxiety disorder (GAD) is higher in White women (8.6%) compared with that in Black women (5.1%) (17). A survey-based study reported higher 12-month odds of GAD diagnosis (odds ratio [OR] 2.9, 95% CI: 2.1–4.1) and social anxiety disorders diagnosis (OR 2.4, 95% CI: 1.8–3.2) in White adults compared with African Americans after controlling for socio-demographic variables (18). Another survey of 43,093 adults found that Black adults had significantly lower lifetime odds of social anxiety disorder compared with White adults (OR 0.6, 95% CI: 0.5–0.73) (19). The prevalence of depression has also been shown to be influenced by race, although the 2013–2016 National Health and Nutrition Examination Survey found no significant differences in the prevalence of major depression between White ($10.5\% \pm 0.9\%$) and Black ($11.0\% \pm 0.8\%$) women (20). Despite the evidence in the non-PCOS population, there are no studies directly comparing the racial differences in anxiety and depression within the PCOS population. Understanding these differences is important as it could influence screening guidelines, counseling tools, or allocation of resources when evaluating mental health in PCOS.

Therefore, the aim of our study was to evaluate the racial differences in the prevalence of anxiety and depression between Black and White women with PCOS and to determine if physical and biochemical attributes of PCOS correlate with anxiety, depression, and quality of life.

MATERIALS AND METHODS

Subjects

This was a retrospective, cross-sectional study conducted at the University of Pennsylvania from November 2015 to October 2018 that included nonpregnant women of 18–50 years of age. Women seen at the Penn PCOS center meeting the Rotterdam criteria (21) were approached for participation. Data on clinical and biochemical measures related to PCOS were obtained by chart review. The homeostatic model

assessment of insulin resistance (HOMA-IR) was calculated by multiplying fasting glucose levels (mg/dL) times fasting insulin levels (mIU/mL) divided by 405. Women without PCOS were recruited from the gynecology clinic as controls and were excluded if they reported both hirsutism and irregular menses on the demographic questionnaires. The University of Pennsylvania Institutional Review Board approved this study.

Surveys

Demographic questionnaires containing items on race, socioeconomic status (SES), and psychiatric, menstrual, and pregnancy history, the hospital anxiety and depression scale (HADS) survey, and the modified-PCOSQ (MPCOS-Q) survey were administered. White or Black race was self-reported. The HADS is a validated 14-item questionnaire with 7 questions dedicated to the assessment of anxiety and 7 to the assessment of depressive symptoms (22, 23). HADS is scored on a Likert scale, and scores ≥ 8 were considered clinical cutoffs as described in other studies (24). The MPCOS-Q is a 30-item questionnaire containing the following domains: emotions, body hair, weight, infertility, menstruation, and acne (25). Questions relate to the impact of each domain on the quality of life, with answers presented on Likert scales, for example, none of the time to all of the time. Higher values in each domain and in total scores indicate a higher quality of life. The study data were collected and managed using REDCap (Vanderbilt University, Nashville, TN) (26) electronic data capture tools.

Outcomes

The primary outcome was the differences in the prevalence of anxiety and depression in women with PCOS as well as differences in anxiety, depression, and quality-of-life scores between White and Black women with PCOS. The secondary outcomes included the same comparisons in White and Black controls and correlations between anxiety, depression, quality-of-life scores and FG scores, body mass index (BMI), testosterone levels, and HOMA-IR between races in women with PCOS.

Statistical Analyses

Continuous outcomes were compared using either rank-sum or student *t*-test as dictated by normality assessments. Normality assessments were based on graphical displays as well as quantitatively through the Shapiro-Wilk test. Categorical outcomes were compared using Pearson chi-square tests or Fisher's exact test. For correlation analyses, FG score, BMI, total testosterone levels, and HOMA-IR were included.

Multivariable logistic regression modeling was used to examine differences in the prevalence of anxiety and depression between White and Black women with PCOS. Multivariable linear regression modeling was used to examine differences in continuous HADS scores and MPCOS-Q scores between White and Black women with PCOS. Covariates to include in the model were determined

TABLE 1**Demographic characteristics of women with PCOS and controls.**

	PCOS (n = 272)			Controls (n = 295)		
	White (n = 202)	Black (n = 70)	P value	White (n = 109)	Black (n = 186)	P value
Median age in years (range)	28.7 (24.5–32.2)	29.2 (25.2–32.2)	.36	32.6 (27.9–40.7)	31.6 (26.5–39.3)	.22
Median BMI in kg/m ² (range)	31.1 (25.5–38.4)	36.5 (31.0–41.8)	<.001	25.2 (22.3–31.5)	31.8 (26.1–39.3)	<.001
Highest degree, n (%)			.006			<.001
Some high school	1 (0.5%)	2 (2.9%)		1 (0.9%)	12 (6.6%)	
High school	6 (3.0%)	7 (10.1%)		8 (7.3%)	53 (29.3%)	
Some college	45 (22.4%)	25 (36.2%)		14 (12.8%)	53 (29.3%)	
College	78 (38.8%)	20 (29.0%)		36 (33.0%)	38 (21.0%)	
Some professional	16 (8.0%)	3 (4.4%)		7 (6.4%)	6 (3.3%)	
Professional	55 (27.4%)	12 (17.4%)		43 (39.5%)	19 (10.3%)	
Employment, n (%)			.228			.004
Full time	152 (75.3%)	52 (75.4%)		79 (73.2%)	117 (64.6%)	
Part time	12 (5.9%)	2 (2.9%)		10 (9.3%)	11 (6.1%)	
Unemployed, not looking for job	35 (17.3%)	11 (15.9%)		16 (14.8%)	25 (13.8%)	
Unemployed, looking for job	3 (1.5%)	4 (5.8%)		3 (2.8%)	28 (15.5%)	
Income in dollars, n (%)			<.001			<.001
<20,000	26 (13.2%)	10 (14.5%)		9 (8.3%)	58 (33.0%)	
20,001–50,000	37 (18.8%)	32 (46.4%)		28 (25.9%)	72 (40.9%)	
50,001–100,000	63 (32.0%)	22 (31.9%)		35 (32.4%)	29 (16.5%)	
100,001–150,000	41 (20.8%)	4 (5.8%)		19 (17.6%)	13 (7.4%)	
>150,000	30 (15.2%)	1 (1.5%)		17 (15.7%)	4 (2.3%)	
Marital status, n (%)			.034			<.001
Single, never married	130 (64.4%)	49 (70.0%)		56 (51.4%)	140 (76.1%)	
Married or domestic partnership	71 (35.2%)	18 (25.7%)		46 (42.2%)	35 (19.0%)	
Divorced or separated	1 (0.5%)	3 (4.3%)		7 (6.4%)	9 (4.9%)	
Antidepressant use, n (%)	22 (10.8%)	5 (7.1%)	.366	16 (14.7%)	18 (9.7%)	.194

Note: BMI = body mass index; PCOS = polycystic ovary syndrome.

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a priori as well as assessment of confounding using a backward elimination strategy and included patient age, BMI, and SES. Linear regression with interaction terms as well as Pearson's correlation were employed to evaluate racial differences in association between FG scores, BMI, testosterone levels, and HOMA-IR, HADS, and MPCOS-Q scores. For comparative purposes, the preceding analyses were replicated for the controls, including examining for interactive effects for race between women with PCOS and controls.

RESULTS

Demographic Characteristics

The demographic characteristics of the 272 women with PCOS and 295 controls are shown in Table 1. Black women with PCOS had a significantly higher BMI ($P < .001$), were less likely to have a college degree or higher ($P = .006$), had lower incomes ($P < .001$), and were less likely to be married or in a domestic partnership ($P = .034$) than White women with PCOS. FG score, total testosterone, and free testosterone did not differ significantly between Black and White women with PCOS (Table 2).

Racial Differences in Anxiety and Depression Prevalence

White women with PCOS had a significantly higher prevalence of anxiety (defined as HADS > 8) than Black women

(75.9% vs. 61.3%), and the odds of anxiety in multivariable logistic regression models controlling for age, BMI, and SES (adjusted odds ratio [aOR] 2.21, 95% CI: 1.17–4.19) was also higher in White versus Black women with PCOS ($P = .014$). However, the prevalence of depression (defined as HADS > 8) and the odds of depression were not significantly different (White women 24.4% vs. Black women 29.0%) in adjusted models (aOR 1.03, 95% CI: 0.50–2.14, $P = .933$) (Table 3, Fig. 1A).

In multivariable logistic regression models controlling for age, BMI, and SES, White controls had a significantly higher prevalence of anxiety and odds of anxiety than Black controls (59.6% vs. 47.1%; aOR 2.04, 95% CI: 1.17–3.53, $P = .011$). The prevalence of depression and odds of depression were not significantly different between White and Black controls in models adjusted for age, BMI, and SES (18.5% vs. 13.2%; aOR 1.46, 95% CI: 0.65–3.28, $P = .361$) (Table 3, Fig. 1B).

Thus, in both women with PCOS and controls, a higher prevalence of anxiety was seen among White women compared with Black women. To determine if the differences between White women and Black women varied significantly between women with PCOS and controls, the data were combined and the above models extended to include the interaction between groups. Both interaction models were nonsignificant ($P = .839$ for anxiety prevalence; $P = .514$ for depression prevalence) indicating that there were no racial differences in prevalence when comparing the PCOS cohort with the control cohort.

TABLE 2**Phenotypic characteristics and biochemical data in White versus Black women with PCOS.**

	White women with PCOS (n = 202)	Black women with PCOS (n = 70)	P value
Measures of androgen excess			
FG score	10 (4–15)	12 (5–17)	.128
Total testosterone (ng/dL)	49 (32–60)	48 (44–74)	.055
Free testosterone (pg/mL)	4.9 (2.5–8)	6.3 (3.7–9.7)	.086
DHEAS (μ g/dL)	222.5 (136.0–307.0)	177.5 (118.0–264.8)	.036
SHBG (nmol/L)	53.5 (31.6–100.9)	38 (24–67)	.031
Measures of hyperlipidemia			
Total cholesterol (mg/dL)	179.5 (162–204)	164 (149–177)	<.001
Triglycerides (mg/dL)	103.5 (75.5–163.5)	68 (51–92)	<.001
LDL (mg/dL)	100 (83–118)	97 (86–110)	.584
HDL (mg/dL)	54 (45–67)	50 (41.5–59)	.043
Measures of insulin resistance			
HgbA1c	5.3 \pm 0.4	5.6 \pm 0.4	<.001
HOMA-IR	2.8 (1.5–5.6)	3.7 (1.8–6.2)	.334
Fasting glucose	85 (78–91)	85 (81–90)	.730
Measures of ovarian reserve			
AMH (ng/mL)	6.0 (3.1–9.1)	7.0 (4.4–10.4)	.251
Total AFC	37 (27–40)	40 (31–55)	.044

Note: Data are presented as median (IQR) and mean \pm SD. AFC = antral follicle count; AMH = antimüllerian hormone; DHEAS = dehydroepiandrosterone sulfate; FG = Ferriman-Gallwey score; HDL = high-density lipoprotein; HgbA1c = hemoglobin A1c; HOMA-IR = homeostatic model assessment of insulin resistance; IQR = interquartile range; LDL = low-density lipoprotein; PCOS = polycystic ovary syndrome; SHBG = sex hormone-binding globulin.

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Racial Differences in Anxiety and Depression Scores

In multivariable linear regression models controlling for age, BMI, and SES, White women with PCOS had significantly higher anxiety scores (mean \pm SD 10.3 \pm 4.1 vs. 8.7 \pm 4.6, β = 1.80, P = .006). Depression scores were not significantly different in adjusted models for comparisons of White and Black women with PCOS (mean 4.8 \pm 3.6 vs. 5.1 \pm 4.0, β = 0.23, P = .659) (Table 3).

In multivariable linear regression models adjusted for age, BMI, and SES, White controls did not have significantly different anxiety scores compared with those of Black controls (mean 8.1 \pm 3.8 vs. 7.5 \pm 4.8, β = 1.03, P = .083). In models adjusted for age, BMI, and SES, White controls did not have significantly different depression scores compared with those of Black controls (mean 3.6 \pm 3.3 vs. 4.1 \pm 3.5, β = 0.77, P = .105) (Table 3).

Combining the PCOS and controls data, interaction models yielded nonsignificant interactions for both anxiety (P = .363) and depression (P = .425) scores, indicating that there were no racial differences in scores when comparing the PCOS cohort with the controls.

Correlation Between Anxiety, Depression, and FG Scores, Total Testosterone, BMI, and HOMA-IR

In multivariable correlation regressions of anxiety and depression, within the PCOS sample, the interaction term between BMI and race in its association with anxiety scores was significant (P = .031), indicating that the relationship between BMI and anxiety varied differentially between White and Black women. Further evaluation of correlation estimates separately within White and Black women with PCOS revealed a direct relationship in White women in whom higher

TABLE 3**Racial differences in anxiety and depression in White versus Black women with PCOS and controls.**

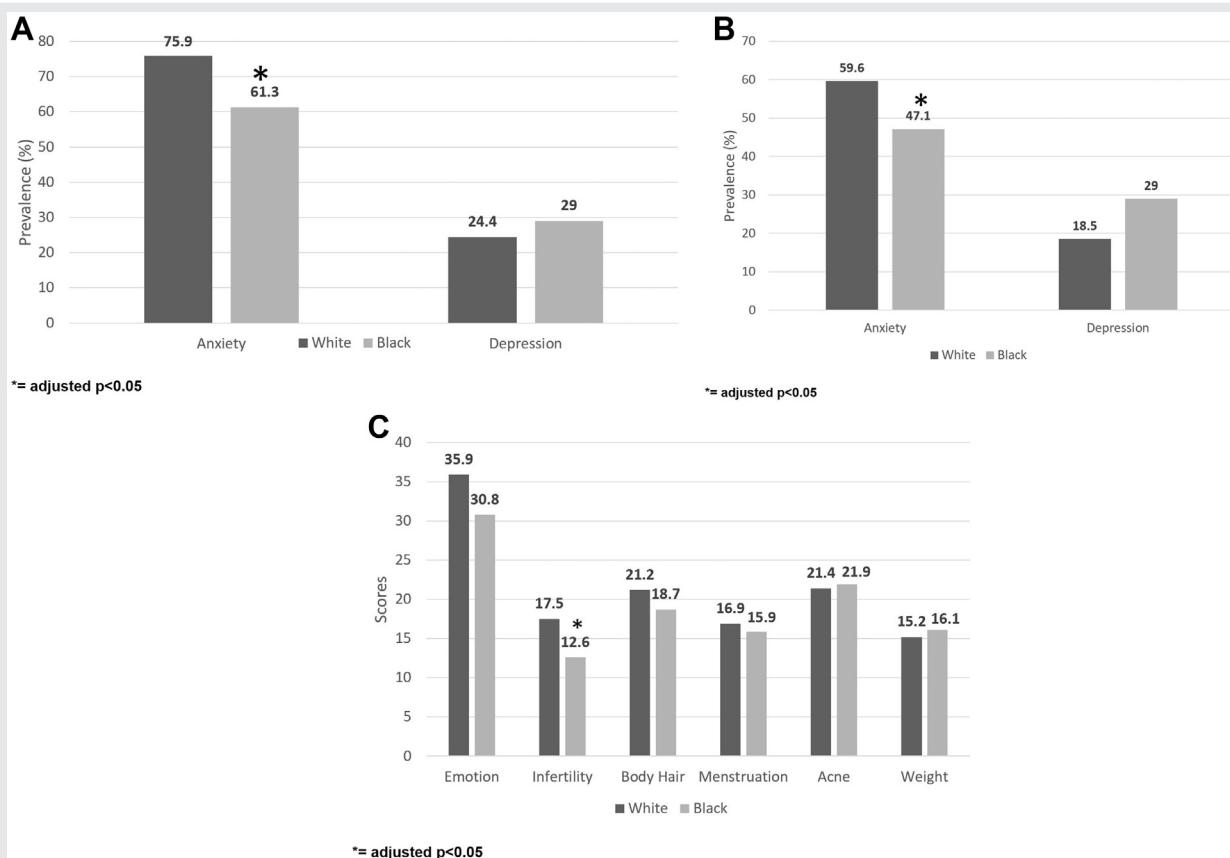
	White vs. Black PCOS (n = 272)		White vs. Black controls (n = 295)		
	aOR ^b	P value	aOR ^b	P value	Interaction P value
HADS anxiety prevalence ^a	2.21 (1.17, 4.19)	.014	2.04 (1.17, 3.53)	.011	.839
HADS depression prevalence ^a	1.03 (0.50, 2.14)	.933	1.46 (0.65, 3.28)	.361	.514
Mean HADS anxiety score	Coefficient	P value	Coefficient	P value	
Mean HADS depression score	1.80 (0.51, 3.10)	.006	1.03 (−0.13, 2.19)	.083	.363
	0.23 (−0.80, 1.27)	.659	0.77 (−0.16, 1.70)	.105	.425

Note: aOR = adjusted odds ratio; BMI = body mass index; HADS = hospital anxiety and depression scale; PCOS = polycystic ovary syndrome.

^a Defined as HADS score >8.

^b Adjusted for age, BMI, and socioeconomic status variables.

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FIGURE 1

(A) Racial differences in the prevalence of anxiety and depression symptoms in women with PCOS. (B) Racial differences in the prevalence of anxiety and depression symptoms in controls. (C) Racial differences in the quality-of-life domain scores in women with PCOS. PCOS = polycystic ovary syndrome.

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BMI was associated with higher anxiety scores ($r = 0.11, P = .147$) but an inverse relationship in Black women in whom higher BMI was associated with lower anxiety scores ($r = -0.17, P = .184$). The interaction term between race and FG score, total testosterone, and HOMA-IR was not significant.

Racial Differences in Quality-of-Life Scores

In unadjusted analyses, Black women with PCOS had significantly lower total MPCOS-Q scores compared with those of White women (98.6 vs. 110.7, $P = .009$). In multivariable linear regression models adjusted for age, BMI, and SES, there was no difference in the total MPCOS-Q score ($\beta = 2.75, P = .572$). When broken down by domain, in unadjusted analyses the emotions domain and infertility domain scores were significantly lower in Black women with PCOS compared with those in White women with PCOS ($P = .002$ and $P < .001$, respectively), meaning that Black women had lower quality of life related to emotional well-being and infertility concerns. In multivariable linear regression models adjusted for age, BMI, and SES, the infertility domain score remained significantly lower in Black women with PCOS (mean 12.6

vs. 17.5, $\beta = 3.51, P = .001$) (Fig. 1C). In correlation regressions of total quality-of-life scores in women with PCOS, the interaction terms between race and FG score, total testosterone, and HOMA-IR were not significant ($P = .644$, $P = .276$, and $P = .300$, respectively).

DISCUSSION

Racial differences in PCOS phenotypes and long-term metabolic risk are well recognized. In our study, the prevalence of anxiety after adjusting for age, BMI, and SES and the anxiety levels were significantly higher in adult White women with PCOS compared with those in Black women with PCOS. There were no significant differences in the prevalence of depression or depressive symptoms between the 2 groups.

In keeping with the literature, we found that White controls had a significantly higher prevalence of anxiety compared with that of Black controls, with no difference in the prevalence of depression. In addition, although the finding that higher BMI was associated with higher anxiety in White women with PCOS but lower anxiety in Black women with PCOS did not reach statistical significance, this

may relate in part to a lack of power and warrants further investigation. Examination of quality-of-life scores showed that infertility had the most significant impact on lowering quality of life, with Black women with PCOS having lower infertility domain scores compared with those of White women with PCOS.

Anxiety disorders contribute significantly to the financial burden related to health care (27) such that GAD is associated with 1.5–5.4 days of work impairment in 1 month and 5 times greater likelihood of moderate/severe occupational dysfunction and physical disability (28, 29). Women with PCOS are at an increased risk of anxiety compared with controls as seen in a large meta-analysis of >1,400 women (OR 5.62; 95% CI: 3.22–9.80) (30). Thus, understanding the risk factors that mediate the relationship between PCOS and anxiety is vital.

Although our study was not designed to determine causative factors, potential causes for the lower anxiety scores in Black women include greater resilience to stressors secondary to strong social support and religiosity (18). Also, preexisting substance-abuse disorders, known to be more common in White adults, may contribute to an increase in certain forms of anxiety (18). Further, higher body image dissatisfaction in White compared with Black adults (31) has also been linked to mood disorders (32–34). Of note, body image dissatisfaction is a known mediator for anxiety in women with PCOS. In contrast, other studies have emphasized that sociocultural differences in beliefs and attitudes may affect the expression and assessment of anxiety in Black adults, thus advising caution in the interpretation of observed differences (35). The impact of racial experiences on mental health cannot be understated. Unconscious bias and other race-related factors have been associated with differences in access to care, the use of treatment, and stress (12–16). It is possible that differences in mental health are also driven by cultural and systemic differences as well as structural racism (36). Although our study was not constructed to evaluate this, the contribution and interplay of these factors must not be ignored.

The underlying etiology for increased anxiety and depression in women with PCOS is unclear; in 1 study, women with PCOS and concurrent depression had higher BMI and hirsutism scores, whereas women with PCOS and concurrent anxiety had higher BMI, hirsutism scores, and free testosterone levels, although the effect sizes were small (30). The association between BMI and anxiety has been studied in the general population (37), with a recent meta-analysis of 25 studies reporting increased anxiety in obese individuals (pooled OR 1.30, 95% CI: 1.20–1.41) (38). Dysregulated biological pathways, including neurotransmitter imbalances, oxidative stress, and hypothalamus-pituitary-adrenal axis disturbances, have been implicated in the association between psychiatric disorders and obesity (39). In addition, anxiety has been associated with disordered eating, which can affect obesity, and obese women may be at a higher risk of facing stigma and discrimination leading to dissatisfaction (38). Another study demonstrated that insulin resistance was associated with increased odds of depression in women with PCOS after controlling for age and BMI (40). To understand

the etiology for increased anxiety in White women with PCOS, we examined the association with the previously described risk factors and found a significant interaction between race and BMI as it associates with anxiety scores.

Racial differences in the health-related quality of life in women with PCOS have been described with varying results (41, 42). In our study, Black women with PCOS were noted to have significantly lower scores on the emotion and infertility domains of the quality-of-life survey. With regards to the relationship between infertility and quality of life, several studies have shown that infertile women suffer from poor quality of life scores. An Iranian matched case-control study of 180 infertile and 540 fertile women found that infertility affected the women's physical health, mental health, and social health significantly (43). A cross-sectional study of US women veterans also found that of the 996 veterans studied, those reporting a history of infertility had worse perceived physical health and higher rates of depression in analyses adjusted for age (44). In a meta-analysis of studies comparing racial differences in in vitro fertilization treatment outcomes in the general infertile population, Black women had lower live birth rates compared with those of White women, although there was considerable heterogeneity (45). In addition to differences in access to infertility services, Black and Hispanic women use infertility services far less frequently compared with White women (46). Black women have a higher prevalence of uterine fibroids and tubal disease, which affect miscarriage and live birth rates even in equal access settings (47). These studies underscore the complex relationship between infertility and race and may provide insights into our findings of lower quality-of-life scores related to infertility. In our population, Black women were less likely to be married or in a domestic partnership, which could have also contributed to lower quality-of-life scores related to fertility. As the majority of women with anovulatory infertility have PCOS (48), practitioners should be sensitive to the impact that infertility has on overall quality of life, particularly in Black populations.

Cognitive behavioral therapy combined with nutritional counseling, lifestyle changes and the use of continuous hormonal contraceptives improve anxiety scores in women with PCOS (49, 50). Cognitive behavioral therapy is a form of psychotherapy that focuses on changing the dysfunctional thoughts that lead to negative mood states and is recommended by the American Psychological Association as a first-line treatment for several mental health disorders (51, 52). Although most of these studies were small, they suggested that targeting weight and hyperandrogenism improved anxiety symptoms. Our findings of an interaction between race and BMI also suggested that BMI may play a role in the differences observed. As it is estimated that 80% of women with PCOS in the United States are obese (53), future trials should examine if the impact of lifestyle modifications and hormonal contraceptives on anxiety and depression symptoms is modified by race.

Our study is the first to examine differences in anxiety and depressive symptoms and health-related quality-of-life scores between White and Black women with PCOS residing in the United States. Relatively large sample sizes and

interaction assessment with clinical parameters in women with PCOS add to the strengths of this study. We were unable to examine racial differences in anxiety and depression based on PCOS phenotypes, and our findings may not be generalizable to adolescents. Although women with hirsutism and irregular menses were excluded from the control group, it is possible that some controls were incorrectly labeled; however, we would expect this to result in more conservative estimates. Hormonal contraceptive use data, which can impact mood, was not available, although antidepressant use was not significantly different between the populations. In addition, although the focus of this paper was on Black and White women, exploration of other races is also necessary. Although there were insufficient numbers and power to evaluate additional races in this analysis, future studies evaluating a larger cohort of races should be conducted. They should also examine the impact of factors such as substance abuse or body image distress on the relationship between race and anxiety in these populations.

CONCLUSION

White women with PCOS are more likely to have anxiety symptoms and higher anxiety scores compared with Black women. Black women with PCOS also had lower quality-of-life scores, particularly in the infertility domain, compared with those of White women with PCOS. The Androgen Excess-Polycystic Ovary Syndrome Society recommends screening all women with PCOS for anxiety and depression and having adequate resources for follow-up, referral, and ongoing care (54). Understanding the factors that contribute to differences in the prevalence of anxiety may provide an opportunity for improved individualized counseling. Currently, there appears to be a role for recommending lifestyle management as studies in the general population suggest that exercise, such as resistance training or Pilates, can lead to significant reductions in anxiety levels both in obese individuals and those with anxiety disorders (55–57). Further, routine management of women with PCOS must include assessment of quality-of-life symptoms, and research trials should continue to evaluate the contribution of race and race-related factors to these findings. Management of long-term comorbidities in this young, reproductive age population may be best addressed by multidisciplinary teams, including physicians, nutritionists, mental health therapists, and psychologists, as proposed in the international guidelines (2).

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Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome[†]

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ABSTRACT

STUDY QUESTION: What is the recommended assessment and management of those with polycystic ovary syndrome (PCOS), based on the best available evidence, clinical expertise, and consumer preference?

SUMMARY ANSWER: International evidence-based guidelines address prioritized questions and outcomes and include 254 recommendations and practice points, to promote consistent, evidence-based care and improve the experience and health outcomes in PCOS.

WHAT IS KNOWN ALREADY: The 2018 International PCOS Guideline was independently evaluated as high quality and integrated multidisciplinary and consumer perspectives from six continents; it is now used in 196 countries and is widely cited. It was based on best available, but generally very low to low quality, evidence. It applied robust methodological processes and addressed shared priorities. The guideline transitioned from consensus based to evidence-based diagnostic criteria and enhanced accuracy of diagnosis, whilst promoting consistency of care. However, diagnosis is still delayed, the needs of those with PCOS are not being adequately met, evidence quality was low and evidence-practice gaps persist.

STUDY DESIGN, SIZE, DURATION: The 2023 International Evidence-based Guideline update reengaged the 2018 network across professional societies and consumer organizations, with multidisciplinary experts and women with PCOS directly involved at all stages. Extensive evidence synthesis was completed. Appraisal of Guidelines for Research and Evaluation-II (AGREEII)-compliant processes were followed. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was applied across evidence quality, feasibility, acceptability, cost, implementation and ultimately recommendation strength and diversity and inclusion were considered throughout.

PARTICIPANTS/MATERIALS, SETTING, METHODS: This summary should be read in conjunction with the full Guideline for detailed participants and methods. Governance included a six-continent international advisory and management committee, five guideline development groups, and paediatric, consumer, and translation committees. Extensive consumer engagement and guideline experts informed the update scope and priorities. Engaged international society-nominated panels included paediatrics, endocrinology, gynaecology, primary care, reproductive endocrinology, obstetrics, psychiatry, psychology, dietetics, exercise physiology, obesity care, public health and other experts, alongside consumers, project management, evidence synthesis, statisticians and translation experts. Thirty-nine professional and consumer organizations covering 71 countries engaged in the process. Twenty meetings and five face-to-face forums over 12 months addressed 58 prioritized clinical questions involving 52 systematic and 3 narrative reviews. Evidence-based recommendations were developed and approved via consensus across five guideline panels, modified based on

international feedback and peer review, independently reviewed for methodological rigour, and approved by the Australian Government National Health and Medical Research Council (NHMRC).

MAIN RESULTS AND THE ROLE OF CHANCE: The evidence in the assessment and management of PCOS has generally improved in the past five years, but remains of low to moderate quality. The technical evidence report and analyses (~6000 pages) underpins 77 evidence-based and 54 consensus recommendations, with 123 practice points. Key updates include: i) further refinement of individual diagnostic criteria, a simplified diagnostic algorithm and inclusion of anti-Müllerian hormone (AMH) levels as an alternative to ultrasound in adults only; ii) strengthening recognition of broader features of PCOS including metabolic risk factors, cardiovascular disease, sleep apnea, very high prevalence of psychological features, and high risk status for adverse outcomes during pregnancy; iii) emphasizing the poorly recognized, diverse burden of disease and the need for greater healthcare professional education, evidence-based patient information, improved models of care and shared decision making to improve patient experience, alongside greater research; iv) maintained emphasis on healthy lifestyle, emotional wellbeing and quality of life, with awareness and consideration of weight stigma; and v) emphasizing evidence-based medical therapy and cheaper and safer fertility management.

LIMITATIONS, REASONS FOR CAUTION: Overall, recommendations are strengthened and evidence is improved, but remains generally low to moderate quality. Significantly greater research is now needed in this neglected, yet common condition. Regional health system variation was considered and acknowledged, with a further process for guideline and translation resource adaptation provided.

WIDER IMPLICATIONS OF THE FINDINGS: The 2023 International Guideline for the Assessment and Management of PCOS provides clinicians and patients with clear advice on best practice, based on the best available evidence, expert multidisciplinary input and consumer preferences. Research recommendations have been generated and a comprehensive multifaceted dissemination and translation program supports the Guideline with an integrated evaluation program.

STUDY FUNDING/COMPETING INTEREST(S): This effort was primarily funded by the Australian Government via the National Health Medical Research Council (NHMRC) (APP1171592), supported by a partnership with American Society for Reproductive Medicine, Endocrine Society, European Society for Human Reproduction and Embryology, and European Society for Endocrinology. The Commonwealth Government of Australia also supported Guideline translation through the Medical Research Future Fund (MRFCRI000266). HJT and AM are funded by NHMRC fellowships. JT is funded by a Royal Australasian College of Physicians (RACP) fellowship. Guideline development group members were volunteers. Travel expenses were covered by the partnering organizations. Disclosures of interest were strictly managed according to NHMRC policy and are available with the full guideline, technical evidence report, peer review and responses (www.monash.edu/medicine/mchri/pcos). Of named authors HJT, CTT, AD, LM, LR, JBoyle, AM have no conflicts of interest to declare. JL declares grant from Ferring and Merck; consulting fees from Ferring and Titus Health Care; speaker's fees from Ferring; unpaid consultancy for Ferring, Roche Diagnostics and Ansh Labs; and sits on advisory boards for Ferring, Roche Diagnostics, Ansh Labs, and Gedeon Richter. TP declares a grant from Roche; consulting fees from Gedeon Richter and Organon; speaker's fees from Gedeon Richter and Exeltis; travel support from Gedeon Richter and Exeltis; unpaid consultancy for Roche Diagnostics; and sits on advisory boards for Roche Diagnostics. MC declares travels support from Merck; and sits on an advisory board for Merck. JBoivin declares grants from Merck Serono Ltd.; consulting fees from Ferring B.V; speaker's fees from Ferring Arzneimittel GmbH; travel support from Organon; and sits on an advisory board for the Office of Health Economics. RJJ has received speaker's fees from Merck and sits on an advisory board for Ferring. AJoham has received speaker's fees from Novo Nordisk and Boehringer Ingelheim. The guideline was peer reviewed by special interest groups across our 39 partner and collaborating organizations, was independently methodologically assessed against AGREEII criteria and was approved by all members of the guideline development groups and by the NHMRC.

Keywords: Polycystic ovary syndrome / guideline / evidence-based / assessment / management / GRADE

What does this mean for those with PCOS?

Building on the 2018 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome (PCOS), this Guideline updates and expands clinical questions, aiming to ensure that women with PCOS receive optimal, evidence-based care that meets their needs and improves health outcomes. The guideline and translation program were developed with full consumer participation at all stages including priority topics and outcomes for those with PCOS. The aim is to support women and their healthcare providers to optimize diagnosis, assessment and management of PCOS. There is an emphasis on improved education and awareness of healthcare professionals, partnership in care, and empowerment of women with PCOS. Personal characteristics, preferences, culture and values are considered, in addition to resource availability across different settings. With effective translation, the Guideline will address priorities identified by women with PCOS, upskill healthcare professionals, empower consumers, improve care and outcomes, identify key research gaps, and promote vital future research.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting reproductive-aged women, with impacts across the lifespan from adolescence to post menopause. PCOS prevalence is between 10 to 13%, as confirmed in the guideline process (Teede et al., 2010; Azziz et al., 2016). PCOS aetiology is complex; and clinical presentation is heterogeneous with reproductive,

metabolic, and psychological features (Teede et al., 2010; Azziz et al., 2016). Women internationally experience delayed diagnosis and dissatisfaction with care (Gibson-Helm et al., 2017; Dokras et al., 2017; Teede et al., 2014). Clinical practice in the assessment and management of PCOS remains inconsistent, with ongoing key evidence-practice gaps. Following on from the 2018 International Evidence-based Guideline for the Assessment and

Management of Polycystic Ovary Syndrome (Teede et al., 2018a; Teede et al., 2018b), independently evaluated as high quality, this extensive update integrates current literature with previous systematic reviews and extends to new clinical questions prioritized by consumers. Ultimately, we aim to update, extend and translate rigorous, comprehensive evidence-based guidelines for diagnosis, assessment and treatment, to improve the lives of those with PCOS worldwide.

To do so, the Guideline leverages substantive government and society investment and brings together extensive consumer engagement and international collaboration with leading societies and organizations, multidisciplinary experts, and primary care representatives. This comprehensive evidence-based Guideline is constructed from a rigorous, Appraisal of Guidelines for Research and Evaluation-II (AGREE-II)-compliant, evidence-based guideline development process. It provides a single source of international evidence-based recommendations to guide clinical practice, with the opportunity for adaptation in relevant health systems. Together with an extensive translation program, the aim is to reduce worldwide variation in care and promote high quality clinical service provision to improve health outcomes and quality of life in women with PCOS. The Guideline is supported by a multi-faceted international translation program with co-designed resources to enhance the skills of healthcare professionals and to empower women with PCOS, with an integrated comprehensive evaluation program. Here, we summarize recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of PCOS.

Materials and methods

Best practice evidence-based guideline development methods were applied and are detailed in the full Guideline and the technical report, which are available online (www.monash.edu/medicine/mchri/pcos) (Misso and Teede, 2012). In brief, extensive healthcare professional and consumer or patient engagement informed the Guideline priority areas. International society-nominated panels from across three leading entities, four partner organizations and thirty-two collaborating entities, included consumers and experts in paediatrics, endocrinology, gynaecology, primary care, reproductive endocrinology, psychology, dietetics, exercise physiology, sleep, bariatric/metabolic surgery, public health, other co-opted experts, project management, evidence synthesis and translation. Governance included an international advisory and a management committee, five guideline development groups (GDGs) with 56 members, and paediatric, consumer, and translation committees. The five GDGs covered i) Screening, diagnostic and risk assessment and life stage; ii) Psychological features and models of care; iii) Lifestyle management; iv) Management of nonfertility features; and v) Assessment and management of infertility. The leading entities; the Australian National Health and Medical Research Council (NHMRC) Centres for Research Excellence in Women's Health in Reproductive Life and in Polycystic Ovary Syndrome, led by Monash University, partnered with the American Society for Reproductive Medicine, the Endocrine Society, the European Society of Endocrinology and the European Society of Human Reproduction and Embryology and collaborated with 32 other entities. With international meetings over 12 months fifty-five prioritized clinical questions involved 52 systematic and three narrative reviews, generating evidence-based and consensus recommendations with accompanying practice points. Committee members nominated by partner and collaborator organizations provided international peer

review, and independent experts reviewed methods, which were then submitted to NHMRC for independent review. The target audience includes multidisciplinary healthcare professionals, consumers or patients, policy makers, and educators. The Guideline includes a focus on equity, cultural and ethnic diversity, avoidance of stigma and inclusivity (see full guideline for details).

Processes aligned with all elements of the AGREE-II tool for quality guideline assessment (Brouwers et al., 2010), with extensive evidence synthesis and meta-analysis. Integrity assessment was integrated into guideline evidence synthesis processes and followed the Research Integrity in Guideline Development (RIGID) framework, with studies assessed against criteria from the Research Integrity Assessment (RIA) tool and the Trustworthiness in Randomised Controlled Trials (TRACT) checklist (Mousa et al., 2023; Weibel et al., 2023; Mol et al., 2023). Evidence synthesis methods are outlined in the full guideline and followed best practice (Brouwers et al., 2010; National Health and Medical Research Council, 2009; National Health and Medical Research Council, 2007). Guideline recommendations are presented by category, terms used, evidence quality and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework considerations. Category includes evidence-based (sufficient evidence in PCOS) or consensus (insufficient evidence in PCOS, also evidence in general or relevant populations was considered) recommendations and accompanying practice points (implementation considerations) (Table 1).

The terms include "should", "could" and "should not", which are informed by the nature of the recommendation (evidence or consensus), the GRADE framework and the evidence quality and are independent descriptors reflecting GDG judgement. They refer to overall interpretation and practical application of the recommendation, balancing benefits and harms. "Should" is used where benefits of the recommendation exceed harms and where the recommendation can be trusted to guide practice. Conditional recommendations are reflected using the terms "could" or "should/could consider" which are used where evidence quality was limited or available studies demonstrate little clear advantage of one approach over another, or the balance of benefits to harms was unclear. "Should not" applies when there is a lack of appropriate evidence, or harms may outweigh benefits.

Evidence quality was categorized according to the GRADE framework, with judgments about the quality of the included studies and/or synthesized evidence incorporating risk of bias, inconsistency, indirectness, imprecision and any other considerations (e.g., publication bias) that may influence evidence quality. These judgments considered study number and design, statistical data and importance of outcomes (Table 2). The quality of evidence reflects the confidence that the estimate of the effect is

Table 1. Categories of PCOS guideline recommendations

EBR	Evidence Based Recommendations: Evidence sufficient to inform a recommendation made by the guideline development group.
CR	Consensus Recommendations: In the absence of adequate evidence, a consensus recommendation has been made by the guideline development group, also informed by evidence from the general population.
PP	Practice Points: Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or consensus recommendations.

PCOS, polycystic ovary syndrome.

Table 2. Quality (certainty) of evidence categories (adapted from GRADE)

High	⊕⊕⊕⊕	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	⊕⊕⊕○	Moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different.
Low	⊕⊕○○	Limited confidence in the effect estimate. The true effect may be substantially different from the estimate of the effect.
Very Low	⊕○○○	Very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

adequate to support each recommendation (National Health and Medical Research Council, 2009), largely determined by the expert evidence synthesis team. GRADE acknowledges that evidence quality is a continuum; any discrete categorization involves some arbitrary decisions; nevertheless, the advantages of simplicity, transparency, and clarity outweigh these limitations (National Health and Medical Research Council, 2009).

The GRADE framework enabled structured and transparent consideration across evidence quality, feasibility, acceptability, cost, implementation, and ultimately recommendation strength (National Health and Medical Research Council, 2009) and was completed at face to face guideline group meetings for all clinical questions (Table 3) (GRADE).

Notably, certainty of evidence varied across outcomes within each question. Here evidence certainty reflects the lowest certainty for the critical outcomes. Evidence was often stronger for the top ranked outcome, and high quality randomized controlled trials (RCTs) were often present, despite overall low quality of evidence. These nuances were considered by the GDG for all question as per the technical report, with any apparent discrepancy between recommendation strength and evidence certainty justified in the full Guideline. Finally, we note that this is a living Guideline with annual evidence review in rapidly evolving areas.

The recommendations (Table 4) apply the category, descriptive terms, GRADE of the recommendations and the quality of the evidence. The full Guideline, technical evidence and administrative reports are available online (www.monash.edu/medicine/mchri/pcos). The Guideline outlines the clinical need for the question, the clinical question, the evidence summary, the recommendations and practice points, and a summary of the justification developed by the GDGs using the GRADE framework. Extensive international peer review from across the 39 organizations was then considered by each GDG and recommendations were reconsidered applying the GRADE framework if justified. The comprehensive evidence reviews, profiles, and GRADE frameworks supporting each recommendation can be found in the Technical Report. The administrative report on guideline development, disclosure of interest process and declarations, peer review feedback and responses can also be found online. Here, we present the evidence-based and consensus recommendations and practice points (Table 4). This summary, the full Guideline and technical reports are supported by a comprehensive co-designed translation program to optimize dissemination and impact with resources freely available online (www.monash.edu/medicine/mchri/pcos).

Table 3. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework recommendation strength

❖	Conditional recommendation against the option.
❖❖	Conditional recommendation for either the option or the comparison.
❖❖❖	Conditional recommendation for the option.
❖❖❖❖	Strong recommendation for the option.

Two algorithms are provided to support recommendations on diagnosis (Figure 1) and infertility management (Figure 2).

Discussion

The International Evidence-based Guideline for the Assessment and Management of PCOS and the related translation program aims to provide a high quality, reliable source of international evidence-based recommendations to guide consistent clinical practice and to empower women with evidence-based information. All recommendations were formulated after an assessment of the best available evidence, multidisciplinary clinical expertise, consumer preferences and structured review by five GDGs. The guideline provides 77 evidence-based and 54 consensus recommendations, with 123 practice points underpinned by a technical report on evidence synthesis and GRADE detailed considerations (~6000 pages). The evidence has generally improved over the past five years but remains of low to moderate quality, requiring significant research investment into this neglected, yet common condition.

Key recommendations and updates include that PCOS should be diagnosed using the 2018 International Evidence-based Guideline criteria, which built on the consensus based 2003 Rotterdam criteria. This requires the presence of two of the following: i) clinical/biochemical hyperandrogenism; ii) ovulatory dysfunction; and iii) polycystic ovaries on ultrasound; and here in 2023, alternatively anti-Müllerian hormone (AMH) can now be used instead of ultrasound. Exclusion of other aetiologies is needed. Importantly, where irregular menstrual cycles and hyperandrogenism are present, diagnosis is simplified and ultrasound or AMH are not required for diagnosis. In adolescents, both hyperandrogenism and ovulatory dysfunction are required, with ultrasound and AMH not recommended due to poor specificity. AMH was highlighted as a rapidly evolving area in 2018 and evidence is now strong enough to make this new recommendation. This will significantly change practice and offers women a low cost, convenient option, without evidence of overdiagnosis.

Insulin resistance is recognized as a key feature of PCOS, yet routinely available measures of insulin resistance are inaccurate and clinical measurement is not currently recommended. Once diagnosed, assessment and management should address reproductive, metabolic, cardiovascular, dermatologic, sleep, and psychological features. A lifelong health plan is recommended including a focus on healthy lifestyle, prevention of excess weight gain, optimization of fertility and preconception risk factors, and prevention and treatment of diverse clinical features. These include metabolic risk factors, diabetes, cardiovascular disease, and sleep disorders, which are all increased in PCOS. PCOS should be considered a high-risk condition in pregnancy with women identified and monitored. An increased premenopausal risk of endometrial cancer should also be recognized, whilst absolute risks remain low.

Table 4. Recommendations for the assessment and management of polycystic ovary syndrome (PCOS). © Monash University on behalf of the NHMRC Centre for Research Excellence in Women's Health in Reproductive Life 2023.

NO.	TYPE	RECOMMENDATION	GRADE/QUALITY
1		Screening, diagnostic and risk assessment and life-stages	
		General principles	
	PP	All diagnostic assessments are recommended for use in accordance with the diagnostic algorithm (Algorithm 1).	
1.1		Irregular cycles and ovulatory dysfunction	
1.1.1	CR	Irregular menstrual cycles are defined as:	♦♦♦♦
		<ul style="list-style-type: none"> • Normal in the first year post menarche as part of the pubertal transition. • 1 to < 3 years post menarche: < 21 or > 45 days. • 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year. • 1 year post menarche > 90 days for any one cycle. • Primary amenorrhea by age 15 or > 3 years post thelarche (breast development). <p>When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to these PCOS Guidelines.</p>	
1.1.2	PP	The mean age of menarche may differ across populations.	
1.1.3	PP	In adolescents with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient and their parent/s or guardian/s, considering diagnostic challenges at this life stage and psychosocial and cultural factors.	
1.1.4	PP	For adolescents who have features of PCOS, but do not meet diagnostic criteria, an "increased risk" could be considered and reassessment advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before combined oral contraceptive pill (COC) commencement, those with persisting features and those with significant weight gain in adolescence.	
1.1.5	PP	Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.	
1.2		Biochemical hyperandrogenism	
1.2.1	EBR	Healthcare professionals should use total and free testosterone to assess biochemical hyperandrogenism in the diagnosis of PCOS; free testosterone can be estimated by the calculated free androgen index.	♦♦♦♦ ⊕○○○
1.2.2	EBR	If testosterone or free testosterone is not elevated, healthcare professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), noting their poorer specificity and greater age associated decrease in DHEAS.	♦♦♦ ⊕○○○
1.2.3	EBR	Laboratories should use validated, highly accurate tandem mass spectrometry (LC-MS/MS) assays for measuring total testosterone and if needed, for androstenedione and DHEAS. Free testosterone should be assessed by calculation, equilibrium dialysis or ammonium sulfate precipitation.	♦♦♦♦ ⊕⊕○○
1.2.4	EBR	Laboratories should use LC-MS/MS assays over direct immunoassays (e.g., radiometric, enzyme-linked, etc.) for assessing total or free testosterone, which have limited accuracy and demonstrate poor sensitivity and precision for diagnosing hyperandrogenism in PCOS.	♦♦♦♦ ⊕⊕○○
1.2.5	PP	For the detection of hyperandrogenism in PCOS, the assessment of biochemical hyperandrogenism is of greatest value in patients with minimal or no clinical signs of hyperandrogenism (i.e., hirsutism).	
1.2.6	PP	It is very difficult to reliably assess for biochemical hyperandrogenism in women on the combined oral contraceptive pill (COC) as the pill increases sex hormone-binding globulin and reduces gonadotrophin-dependent androgen production. If already on the COCP, and assessment of biochemical androgens is imperative, the pill should be withdrawn for a minimum of three months and contraception should be managed otherwise during this time.	
1.2.7	PP	Repeated androgen measures for the ongoing assessment of PCOS in adults have a limited role.	
1.2.8	PP	In most adolescents, androgen levels reach adult ranges at 12-15 years of age	
1.2.9	PP	If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenaemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis (after menopause), iatrogenic causes, and syndromes of severe insulin resistance, should be considered. However, some androgen-secreting neoplasms are associated with only mild to moderate increases in androgen levels. The clinical history of time of onset and/or rapid progression of symptoms is critical in assessing for an androgen-secreting tumour.	

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUALITY
1.2.10	PP	Reference ranges for different methods and laboratories vary widely, and are often based on an arbitrary percentile or variances of the mean from a population that has not been fully characterized and is highly likely to include women with PCOS. Normal values should be determined either by the range of values in a well characterized healthy control population or by cluster analysis of general population values.	
1.2.11	PP	Laboratories involved in androgen measurements in females should consider: <ul style="list-style-type: none"> Determining laboratory normal values by either the range of values in a well characterized healthy control population or by cluster analysis of the values of a large general population. Applying the most accurate methods where available. Using extraction/chromatography immunoassays as an alternative to mass spectrometry only where adequate expertise is available. Future improvements may arise from measurement of 11-oxygenated androgens, and from establishing cut-off levels or thresholds based on large-scale validation in populations of different ages and ethnicities. 	
1.3 Clinical hyperandrogenism			
1.3.1	EBR	The presence of hirsutism alone should be considered predictive of biochemical hyperandrogenism and PCOS in adults.	♦♦♦ ⊕○○○
1.3.2	EBR	Healthcare professionals could recognize that female pattern hair loss and acne in isolation (without hirsutism) are relatively weak predictors of biochemical hyperandrogenism.	♦♦♦ ⊕○○○
1.3.3	CR	A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, female pattern hair loss and hirsutism in adults, and severe acne and hirsutism in adolescents.	♦♦♦♦
1.3.4	CR	Healthcare professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism and should consider the reporting of unwanted excess hair growth and/or female pattern hair loss as being important, regardless of apparent clinical severity.	♦♦♦
1.3.5	CR	A modified Ferriman Gallwey score (mFG) of 4 – 6 should be used to detect hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment.	♦♦♦♦
1.3.6	CR	Healthcare professionals should consider that the severity of hirsutism may vary by ethnicity but the prevalence of hirsutism appears similar across ethnicities.	♦♦♦
1.3.7	PP	Healthcare professionals should: <ul style="list-style-type: none"> Be aware that standardized visual scales are preferred when assessing hirsutism, such as the mFG scale in combination with a photographic atlas. Consider the Ludwig or Olsen visual scales for assessing female pattern hair loss. Note that there are no universally accepted visual instruments for assessing the presence of acne. Recognize that women commonly treat clinical hyperandrogenism cosmetically, diminishing their apparent clinical severity. Appreciate that self-assessment of unwanted excess hair growth, and possibly acne and female pattern hair loss, has a high degree of validity and merits close evaluation, even if overt clinical signs of hyperandrogenism are not readily evident on examination. Note that only terminal hairs need to be considered in defining hirsutism, and these can reach >5 mm if untreated, vary in shape and texture, and are generally pigmented. Note that new-onset severe or worsening hyperandrogenism, including hirsutism, requires further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis. Monitor clinical signs of hyperandrogenism, including hirsutism, acne and female pattern hair loss, for improvement or treatment adjustment during therapy. 	
1.4 Ultrasound and polycystic ovarian morphology			
1.4.1	EBR	Follicle number per ovary (FNPO) should be considered the most effective ultrasound marker to detect polycystic ovarian morphology (PCOM) in adults.	♦♦♦♦ ⊕○○○
1.4.2	EBR	Follicle number per ovary (FNPO), follicle number per cross-section (FNPS) and ovarian volume (OV) should be considered accurate ultrasound markers for PCOM in adults.	♦♦♦♦ ⊕○○○
1.4.3	CR	PCOM criteria should be based on follicle excess (FNPO, FNPS) and/or ovarian enlargement.	♦♦♦♦
1.4.4	CR	Follicle number per ovary (FNPO) ≥ 20 in at least one ovary should be considered the threshold for PCOM in adults.	♦♦♦♦

(continued)

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUAITY
1.4.5	CR	Ovarian volume (OV) ≥ 10 ml or follicle number per section (FNPS) ≥ 10 in at least one ovary in adults should be considered the threshold for PCOM if using older technology or image quality is insufficient to allow for an accurate assessment of follicle counts throughout the entire ovary.	♦♦♦♦
1.4.6	PP	There are no definitive criteria to define polycystic ovary morphology (PCOM) on ultrasound in adolescents, hence it is not recommended in adolescents.	
1.4.7	PP	When an ultrasound is indicated, if acceptable to the individual, the transvaginal approach is the most accurate for the diagnosis of PCOM.	
1.4.8	PP	Transabdominal ultrasound should primarily report ovarian volume (OV) with a threshold of ≥ 10 ml or follicle number per section (FNPS) ≥ 10 in either ovary in adults given the difficulty of assessing follicle counts throughout the entire ovary with this approach.	
1.4.9	PP	In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis.	
1.4.10	PP	Thresholds for PCOM should be revised regularly with advancing ultrasound technology, and age-specific cut-off values for PCOM should be defined.	
1.4.11	PP	There is a need for training in careful and meticulous follicle counting per ovary and clear standardized protocols are recommended for PCOM reporting on ultrasound including at a minimum: <ul style="list-style-type: none"> • Last menstrual period (or stage of cycle). • Transducer bandwidth frequency. • Approach/route assessed. • Total number of 2–9 mm follicles per ovary. • Measurements in three dimensions (in cm) or volume of each ovary. • Other ovarian features and/or pathology including ovarian cysts, corpus lutea, dominant follicles (≥ 10 mm) (which should not be included in ovarian volume calculations). • Reliance on the contralateral ovary FNPO for diagnosis of PCOM, where a dominant follicle is noted. • Uterine features and/or pathology including endometrial thickness and pattern. 	
1.5	Anti-Müllerian Hormone in the diagnosis of PCOS		
1.5.1	EBR	Serum anti-Müllerian hormone (AMH) could be used for defining PCOM in adults.	♦♦♦ ⊕⊕⊕○
1.5.2	EBR	Serum AMH should only be used in accordance with the diagnostic algorithm, noting that in patients with irregular menstrual cycles and hyperandrogenism, an AMH level is not necessary for PCOS diagnosis.	♦♦♦♦ ⊕⊕⊕○
1.5.3	EBR	We recommend that serum AMH should not be used as a single test for the diagnosis of PCOS.	♦♦♦♦ ⊕⊕⊕○
1.5.4	EBR	Serum AMH should not yet be used in adolescents.	♦♦♦♦ ⊕⊕⊕○
1.5.5	PP	Either serum AMH or ultrasound may be used to define PCOM; however, both tests should not be performed to limit overdiagnosis.	
1.5.6	PP	Laboratories and healthcare professionals need to be aware of factors that influence AMH in the general population including: <ul style="list-style-type: none"> • Age: Serum AMH generally peaks between the ages of 20–25 years in the general population. • Body mass index (BMI): Serum AMH is lower in those with higher BMI in the general population. • Hormonal contraception and ovarian surgery: Serum AMH may be suppressed by current or recent COCP use. • Menstrual cycle day: Serum AMH may vary across the menstrual cycle. 	
1.5.7	PP	Laboratories involved in AMH measurements in females should use population and assay specific cut-offs.	
1.6	Ethnic variation		
1.6.1	EBR	Healthcare professionals should be aware of the high prevalence of PCOS in all ethnicities and across world regions, ranging from 10–13% globally using the Rotterdam criteria.	♦♦♦♦ ⊕⊕○○
1.6.2	EBR	Healthcare professionals should be aware that PCOS prevalence is broadly similar across world regions, but may be higher in South East Asian and Eastern Mediterranean regions.	♦♦♦♦ ⊕⊕○○

(continued)

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUALITY
1.6.3	PP	Healthcare professionals should be aware that the presentation of PCOS may vary across ethnic groups.	
1.7	Menopause life stage		
1.7.1	CR	A diagnosis of PCOS could be considered as enduring / lifelong.	♦♦♦
1.7.2	CR	Healthcare professionals could consider that both clinical and biochemical hyperandrogenism persist in the postmenopause for women with PCOS.	♦♦♦
1.7.3	CR	PCOS diagnosis could be considered postmenopause if there is a past diagnosis, or a long-term history of oligo-amenorrhoea with hyperandrogenism and/or PCOM, during the earlier reproductive years (age 20–40).	♦♦♦
1.7.4	CR	Further investigations should be considered to rule out androgen-secreting tumours and ovarian hyperthecosis in postmenopausal women presenting with new-onset, severe or worsening hyperandrogenism including hirsutism.	♦♦♦
1.8	Cardiovascular disease risk		
1.8.1	EBR	Women with PCOS should be considered at increased risk of cardiovascular disease and potentially of cardiovascular mortality, acknowledging that the overall risk of cardiovascular disease in pre-menopausal women is low.	♦♦♦ ⊕○○○
1.8.2	EBR	All women with PCOS should be assessed for cardiovascular disease risk factors.	♦♦♦♦ ⊕○○○
1.8.3	CR	All women with PCOS, regardless of age and BMI, should have a lipid profile (cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level) at diagnosis. Thereafter, frequency of measurement should be based on the presence of hyperlipidaemia and additional risk factors or global cardiovascular risk.	♦♦♦♦
1.8.4	CR	All women with PCOS should have blood pressure measured annually and when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities.	♦♦♦♦
1.8.5	CR	Funding bodies should recognize that PCOS is highly prevalent with multisystem effects including cardiometabolic disease and should diversify and increase research support accordingly.	♦♦♦♦
1.8.6	CR	Cardiovascular general population guidelines could consider the inclusion of PCOS as a cardiovascular risk factor.	♦♦♦
1.8.7	CR	Healthcare professionals, women with PCOS and other stakeholders should all prioritize preventative strategies to reduce cardiovascular risk.	♦♦♦♦
1.8.8	PP	Consideration should be given to the differences in cardiovascular risk factors, and cardiovascular disease, across ethnicities (see 1.6.1) and age, when determining frequency of risk assessment.	
1.9	Impaired glucose tolerance and type 2 diabetes risk		
1.9.1	EBR	Healthcare professionals and women with PCOS should be aware that, regardless of age and BMI, women with PCOS have an increased risk of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes.	♦♦♦♦ ⊕○○○
1.9.2	EBR	Glycaemic status should be assessed at diagnosis in all adults and adolescents with PCOS.	♦♦♦♦ ⊕○○○
1.9.3	CR	Glycaemic status should be reassessed every one to three years, based on additional individual risk factors for diabetes.	♦♦♦♦
1.9.4	CR	Healthcare professionals, women with PCOS and other stakeholders should prioritize preventative strategies to reduce type 2 diabetes risk.	♦♦♦♦
1.9.5	CR	Funding bodies should recognize that PCOS is highly prevalent, has significantly higher risk for diabetes, and should be funded accordingly.	♦♦♦♦
1.9.6	CR	Diabetes general population guidelines should consider the inclusion of PCOS as an independent risk factor for diabetes.	♦♦♦♦
1.9.7	PP	Healthcare professionals, adults and adolescents with PCOS and their first-degree relatives, should be aware of the increased risk of diabetes and the need for regular glycaemic assessment.	
1.9.8	PP	Women with type 1 and type 2 diabetes have an increased risk of PCOS and screening should be considered in individuals with diabetes.	

(continued)

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUAITY
Glycaemic testing			
1.9.9	EBR	Healthcare professionals and women with PCOS should recommend the 75-g oral glucose tolerance test (OGTT) as the most accurate test to assess glycaemic status in PCOS, regardless of BMI.	♦♦♦♦ ⊕○○○
1.9.10	EBR	If an OGTT cannot be performed, fasting plasma glucose and/or glycated haemoglobin (HbA1c) could be considered, noting significantly reduced accuracy.	♦♦♦ ⊕○○○
1.9.11	EBR	An OGTT should be considered in all women with PCOS and without pre-existing diabetes, when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed preconception, an OGTT could be offered at the first prenatal visit and all women with PCOS should be offered the test at 24–28 weeks gestation.	♦♦♦ ⊕○○○
1.9.12	PP	Insulin resistance is a pathophysiological factor in PCOS, however, clinically available insulin assays are of limited clinical relevance and are not recommended in routine care (refer to 3.1.10).	
1.10 Obstructive Sleep Apnea			
1.10.1	EBR	Healthcare professionals should be aware that women with PCOS have significantly higher prevalence of obstructive sleep apnea compared to women without PCOS, independent of BMI.	♦♦♦♦ ⊕⊕⊕○
1.10.2	EBR	Women with PCOS should be assessed for symptoms of obstructive sleep apnea (i.e., snoring in combination with waking unrefreshed from sleep, daytime sleepiness or fatigue) and if present, screen with validated tools or refer for assessment.	♦♦♦♦ ⊕⊕⊕○
1.10.3	PP	Simple obstructive sleep apnea screening questionnaires (such as the Berlin questionnaire, validated in the general population) can assist in identifying obstructive sleep apnea in women with PCOS, noting that diagnosis requires a formal sleep study.	
1.10.4	PP	Goals of treatment should target obstructive sleep apnea related symptom burden.	
1.11 Endometrial hyperplasia and cancer			
1.11.1	EBR	Healthcare professionals should be aware that premenopausal women with PCOS have markedly higher risk of developing endometrial hyperplasia and endometrial cancer.	♦♦♦♦ ⊕○○○
1.11.2	PP	Women with PCOS should be informed about the increased risk of endometrial hyperplasia and endometrial cancer, acknowledging that the overall chance of developing endometrial cancer is low, therefore routine screening is not recommended.	
1.11.3	PP	Long-standing untreated amenorrhea, higher weight, type 2 diabetes and persistent thickened endometrium are additional to PCOS as risk factors for endometrial hyperplasia and endometrial cancer.	
1.11.4	PP	Women with PCOS should be informed of preventative strategies including weight management, cycle regulation and regular progestogen therapy.	
1.11.5	PP	When excessive endometrial thickness is detected, consideration of a biopsy with histological analysis and withdrawal bleed is indicated.	
1.12 Risks in first degree relatives			
1.12.1	EBR	Healthcare professionals could consider that fathers and brothers of women with PCOS may have an increased prevalence of metabolic syndrome, type 2 diabetes, and hypertension.	♦♦♦ ⊕○○○
1.12.2	PP	The cardiometabolic risk in female first degree relatives of women with PCOS remains inconclusive.	
2 Prevalence, screening and management of psychological features and models of care			
General principles			
PP Psychological features are common and important components of PCOS that all healthcare professionals should be aware of.			
PP Funding bodies should recognize that PCOS is highly prevalent, and has significantly higher psychological disorders which should be prioritized and funded accordingly.			
2.1 Quality of Life			
2.1.1	EBR	Healthcare professionals and women should recognize the adverse impact of PCOS and/or PCOS features on quality of life in adults.	♦♦♦♦ ⊕⊕○○

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUALITY
2.1.2	PP	Women with PCOS should be asked about their perception of PCOS related-symptoms, impact on quality of life, key concerns, and priorities for management.	
2.2	Depression and Anxiety		
2.2.1	EBR	Healthcare professionals should be aware of the high prevalence of moderate to severe depressive symptoms and depression in adults and adolescents with PCOS and should screen for depression in all adults and adolescents with PCOS, using regionally validated screening tools.	♦♦♦♦ ⊕⊕⊕⊕
2.2.2	EBR	Healthcare professionals should be aware of the high prevalence of moderate to severe anxiety symptoms and anxiety disorders in adults and should screen for anxiety in all adults with PCOS, using regionally validated screening tools.	♦♦♦♦ ⊕⊕⊕⊕
2.2.3	CR	If moderate or severe depressive or anxiety symptoms are detected, practitioners should further assess, refer appropriately, or offer treatment.	♦♦♦♦
2.2.4	PP	Severity of symptoms and clinical diagnosis of depression or anxiety should guide management. The optimal interval for anxiety and depression screening is not known. A pragmatic approach could include screening at diagnosis with repeat screening based on clinical judgement, risk factors, comorbidities, and life events, including the perinatal period. Screening for mental health disorders comprises assessment of risk factors, symptoms, and risk of self-harm and suicidal intent.	
2.3	Psychosexual function		
2.3.1	CR	Healthcare professionals could consider the multiple factors that can influence psychosexual function in PCOS including higher weight, hirsutism, mood disorders, infertility and PCOS medications.	♦♦♦
2.3.2	CR	Permission to discuss psychosexual function should be sought noting that the diagnosis of psychosexual dysfunction requires both low psychosexual function combined with related distress.	♦♦♦♦
2.4	Body Image		
2.4.1	EBR	Healthcare professionals should be aware that features of PCOS can have a negative impact on body image.	♦♦♦♦ ⊕⊕○○
2.5	Eating disorders		
2.5.1	EBR	Eating disorders and disordered eating should be considered in PCOS, regardless of weight, especially in the context of weight management and lifestyle interventions (see sections 2.4 and 3.6).	♦♦♦ ⊕⊕○○
2.5.2	PP	If disordered eating or eating disorders are suspected, appropriately qualified practitioners should further assess via a full diagnostic interview. If an eating disorder or disordered eating is detected, appropriate management and support should be offered.	
2.6	Information resources, models of care, cultural and linguistic considerations		
2.6.1	Information needs		
2.6.1.1	EBR	Tailored information, education and resources that are high-quality, culturally appropriate and inclusive should be provided to all with PCOS.	♦♦♦♦ ⊕⊕⊕○
2.6.1.2	EBR	Information, education and resources are a high priority for patients with PCOS and should be provided in a respectful and empathic manner.	♦♦♦♦ ⊕⊕⊕○
2.6.1.3	CR	Entities responsible for healthcare professional education should ensure that information and education on PCOS is systemically embedded at all levels of healthcare professional training to address knowledge gaps.	♦♦♦♦
2.6.1.4	PP	The diversity of the population should be considered when adapting practice paradigms. Healthcare professional education opportunities should be optimised at all stages of graduate and postgraduate training and continuing professional development and in practice support resources.	
2.6.1.5	PP	Women should be counselled on the risk of misinformation and guided to evidence-based resources.	
2.6.2	Models of care		
2.6.2.1	CR	Models of care should prioritize equitable access to evidence-based primary care with pathways for escalation to integrated specialist and multidisciplinary services as required.	♦♦♦♦

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUAITY
2.6.2.2	PP	Strategies to deliver optimal models of care could include healthcare professional education, care pathways, virtual care, broader health professional engagement (e.g., nurse practitioners) and coordination tools.	
2.6.3	Support to manage PCOS		
2.6.3.1	CR	Public health actors should consider increasing societal awareness and education on PCOS to reduce stigma and marginalization.	❖❖❖
2.6.3.2	PP	Culturally appropriate resources and education on PCOS across the life span for families of those with the condition should be considered.	
2.6.4	Patient care		
2.6.4.1	EBR	Healthcare professionals should employ shared decision-making and support patient agency or ability to take independent actions to manage their health and care.	❖❖❖ ⊕⊕⊕○
2.6.4.2	EBR	The importance of being knowledgeable about PCOS, of applying evidence-based practices when sharing news on diagnosis, treatment, and health implications, and of ascertaining and focusing on patient priorities, should be recognized.	❖❖❖ ⊕⊕⊕○
2.6.4.3	CR	Healthcare system leaders should enable system wide changes to support healthcare professional training, knowledge and practice in sharing news optimally, shared decision making and patient agency, including ensuring adequate consultation time and accessible resources.	❖❖❖
2.6.4.4	PP	Evidence-based strategies for shared decision making and for sharing news (such as the SPIKES framework) are readily available and should be used to inform PCOS care. All healthcare professionals partnering with women with PCOS should be knowledgeable in sharing news, in shared decision-making, and in supporting patient self-management. Evidence-based strategies and resources can be used to support patient activation, which refers to modifiable knowledge, skills, ability, confidence, and willingness to self-manage one's own health and care.	
2.7	Psychological therapy		
2.7.1	CR	Women with PCOS diagnosed with depression, anxiety, and/or eating disorders should be offered psychological therapy guided by regional general population guidelines and the preference of the woman with PCOS.	❖❖❖
2.7.2	CR	Women with PCOS with disordered eating, body image distress, low self-esteem, problems with feminine identity, or psychosexual dysfunction should be offered evidence-based treatments (e.g., cognitive behaviour therapy) where appropriate.	❖❖❖
2.8	Antidepressant and anxiolytic treatment		
2.8.1	CR	Psychological therapy could be considered first-line management, and antidepressant medications considered in adults where mental health disorders are clearly documented and persistent, or if suicidal symptoms are present, based on general population guidelines.	❖❖
2.8.2	PP	Lifestyle intervention and other therapies (e.g., COCP, metformin, laser hair removal) that target PCOS features should be considered, given their potential to improve psychological symptoms. Where pharmacological treatment for anxiety and depression is offered in PCOS, healthcare professionals should apply caution: <ul style="list-style-type: none"> • to avoid inappropriate treatment with antidepressants or anxiolytics. • to limit use of agents that exacerbate PCOS symptoms, including weight gain. Healthcare professionals should be aware that not managing anxiety and depression may impact adherence to PCOS treatment / management.	
3	Lifestyle management		
3.1		Effectiveness of lifestyle interventions	
3.1.1	EBR	Lifestyle intervention (exercise alone or multicomponent diet combined with exercise and behavioural strategies) should be recommended for all women with PCOS, for improving metabolic health including central adiposity and lipid profile.	❖❖❖ ⊕○○○
3.1.2	CR	Healthy lifestyle behaviours encompassing healthy eating and/or physical activity should be recommended in all women with PCOS to optimize general health, quality of life, body composition and weight management (maintaining weight, preventing weight gain and/or modest weight loss).	❖❖❖

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUALITY
3.1.3	PP	Healthcare professionals should be aware that lifestyle management is a core focus in PCOS management.	
3.1.4	PP	Lifestyle management goals and priorities should be co-developed in partnership with women with PCOS, and value women's individualized preferences.	
3.1.5	PP	There are benefits to a healthy lifestyle even in the absence of weight loss.	
3.1.6	PP	In those with higher weight, weight management can be associated with significant clinical improvements and the following key points need to be considered including:	
		<ul style="list-style-type: none"> • A lifelong focus on prevention of further weight gain. • If the goal is to achieve weight loss, a tailored energy deficit could be prescribed for women, considering individual energy requirements, body weight and physical activity levels. • The value of improvement in central adiposity (e.g., waist circumference, waist-hip ratio) or metabolic health. • The need for ongoing assessment and support. 	
3.1.7	PP	Healthcare professionals should be aware of weight stigma when discussing lifestyle management with women with PCOS (see 3.6).	
3.1.8	PP	Healthy lifestyle and optimal weight management, in the context of structured, intensive, and ongoing clinical support, appears equally effective in PCOS as in the general population.	
3.1.9	PP	In those who are not overweight, in the adolescent and at key life points, the focus should be on healthy lifestyle and the prevention of excess weight gain.	
3.1.10	PP	Insulin resistance is a pathophysiological factor in PCOS, however, clinically available insulin assays are of limited clinical relevance and should not be used in routine care (refer to 1.9.12).	
3.2 Behavioural Strategies			
3.2.1	CR	Lifestyle interventions could include behavioural strategies such as goal-setting, self-monitoring, problem solving, assertiveness training, reinforcing changes, and relapse prevention, to optimize weight management, healthy lifestyle and emotional wellbeing in women with PCOS.	♦♦♦
3.2.2	PP	Behavioural support could include: goal-setting, problem solving, self-monitoring and reviewing, or SMART goals (Specific, Measurable, Achievable, Realistic and Timely).	
3.2.3	PP	Comprehensive healthy behavioural or cognitive behavioural interventions could be considered to increase support, engagement, retention, adherence, and maintenance of healthy lifestyle and improve health outcomes in women with PCOS.	
3.3 Dietary Intervention			
3.3.1	EBR	Healthcare professionals and women should consider that there is no evidence to support any one type of diet composition over another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.	♦♦♦ ⊕〇〇〇
3.3.2	CR	Any diet composition consistent with population guidelines for healthy eating will have health benefits and, within this, healthcare professionals should advise sustainable healthy eating tailored to individual preferences and goals.	♦♦♦♦
3.3.3	PP	Tailoring of dietary changes to food preferences, allowing for a flexible, individual and co-developed approach to achieving nutritional goals, and avoiding unduly restrictive and nutritionally unbalanced diets, are important, as per general population guidelines.	
3.3.4	PP	Barriers and facilitators to optimize engagement and adherence to dietary change should be discussed, including psychological factors, physical limitations, socioeconomic and sociocultural factors, as well as personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied healthcare professionals needs to be considered when women with PCOS need support with optimizing their diet.	
3.4 Exercise Intervention			
3.4.1	EBR	Healthcare professionals and women could consider that there is a lack of evidence supporting any one type and intensity of exercise being better than another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.	♦♦♦ ⊕〇〇〇

(continued)

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUAITY
3.4.2	CR	Any physical activity consistent with population guidelines will have health benefits and, within this, healthcare professionals should advise sustainable physical activity based on individual preferences and goals.	♦♦♦♦
3.4.3	CR	Healthcare professionals should encourage and advise the following in concordance with general population physical activity guidelines: <ul style="list-style-type: none"> • All adults should undertake physical activity as doing some physical activity is better than none. • Adults should limit the amount of time spent being sedentary (e.g., sitting, screen time) as replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits. • For the prevention of weight gain and maintenance of health, adults (18–64 years) should aim for a minimum of 150 to 300 minutes of moderate intensity activities or 75 to 150 minutes of vigorous intensity aerobic activity per week or an equivalent combination of both spread throughout the week, plus muscle strengthening activities (e.g., resistance/flexibility) on two non-consecutive days per week. • For promotion of greater health benefits including modest weight-loss and prevention of weight-regain, adults (18–64 years) should aim for a minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensities or an equivalent combination of both, plus muscle strengthening activities (e.g., resistance/flexibility) ideally on two non-consecutive days per week. • Adolescents should aim for at least 60 minutes of moderate- to vigorous-intensity physical activity per day, including activities that strengthen muscle and bone at least three times per week. 	♦♦♦♦
3.4.4	PP	Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure. It includes leisure time physical activity, transportation (e.g., walking or cycling), occupational (i.e., work), household chores, playing games, sports or planned exercise, or activities in the context of daily, family and community activities.	
3.4.5	PP	Aerobic activity is best performed in bouts of at least 10 minutes duration, aiming to achieve at least 30 minutes daily on most days.	
3.4.6	PP	Barriers and facilitators to optimize engagement and adherence to physical activity should be discussed, including psychological factors (e.g., body image concerns, fear of injury, fear of failure, mental health), personal safety concerns, environmental factors, physical limitations, socioeconomic factors, sociocultural factors, and personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied healthcare professionals needs to be considered for optimizing physical activity in women with PCOS.	
3.4.7	PP	Self-monitoring, including with fitness tracking devices and technologies for step count and exercise intensity, could be considered as an adjunct to support and promote active lifestyles and minimize sedentary behaviours.	
3.5 Factors affecting weight gain in PCOS			
3.5.1	EBR	Healthcare professionals and women with PCOS could consider that there is a lack of consistent evidence of physiological or behavioural lifestyle differences, related to weight, in women with PCOS compared to women without PCOS.	♦♦♦ ⊕○○
3.5.2	PP	Whilst the specific mechanisms are unclear, it is recognized that many women with PCOS will have underlying mechanisms that drive greater longitudinal weight gain and higher BMI which may: <ul style="list-style-type: none"> • Underpin greater challenges with weight management. • Highlight the importance of lifelong healthy lifestyle strategies and prevention of excess weight gain. • Assist women with PCOS and healthcare professionals in forming realistic, tailored life-style goals. 	
3.6 Weight Stigma			
3.6.1	EBR	Many women with PCOS experience weight stigma in healthcare and other settings and the negative biopsychosocial impacts of this should be recognized.	♦♦♦♦ ⊕○○
3.6.2	CR	Healthcare professionals should be aware of their weight biases and the impact this has on their professional practice and on women with PCOS.	♦♦♦♦
3.6.3	CR	Health policy makers, managers and educators should promote awareness of weight stigma and invest in weight stigma education and minimization strategies.	♦♦♦♦

(continued)

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUALITY
3.6.4	PP	<p>Healthcare professionals should be aware of weight-inclusive practices which promote acceptance of and respect for body size diversity and focus on improvement of health behaviours and health outcomes for people of all sizes. In PCOS this includes:</p> <ul style="list-style-type: none"> Acknowledging that whilst higher weight is a risk factor for PCOS and its complications, it is only one indicator of health and broader factors should be assessed. Asking permission to discuss and measure weight and using strategies to minimize discomfort (e.g., blind weighing). Recognizing that the terms "overweight" and "obese/obesity" can be stigmatizing with suggested alternatives including "higher weight". If weighing, explaining how weight information will be used to inform risks, prevention and treatment and how not knowing may impact on recommendations. Ensuring appropriate equipment is available for women of all sizes. Offering options of weight-centric care (promoting intentional weight loss) or weight-inclusive care (promoting healthy lifestyle change without focusing on intentional weight loss) tailored to individual goals and preferences. Offering all women best practice assessment, treatment and support regardless of weight, acknowledging that weight may be a non-modifiable risk factor when using lifestyle modification alone. 	
3.6.5	PP	Increasing awareness of weight stigma among family members of women and adolescents with PCOS should be considered.	
4 Management of non-fertility features			
4.1 Pharmacology treatment principles in PCOS			
	PP	Shared decision making between the patient (and parent/s or guardian/s, if the patient is a child) and the healthcare professional is required.	
	PP	An individual's characteristics, preferences and values must be elicited and considered when recommending any intervention alone or in combination.	
	PP	Understanding how individual adults and adolescents value treatment outcomes is essential when prescribing medications.	
	PP	Medical therapy is generally not approved for use specifically in PCOS and recommended use is therefore evidence-based, but off-label. Healthcare professionals need to inform adults, adolescents and their parents/s or guardian/s and discuss the evidence, possible concerns and side effects. Regulatory agencies should consider approval of evidence-based medications for use in PCOS.	
4.2 Combined Oral Contraceptive Pills			
4.2.1	EBR	Combined oral contraceptive pills (COCP) could be recommended in reproductive age adults with PCOS for management of hirsutism and/or irregular menstrual cycles.	❖❖❖ ⊕○○○
4.2.2	EBR	The COCP could be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles.	❖❖❖ ⊕○○○
4.2.3	EBR	Healthcare professionals could consider that there is no clinical advantage of using high dose ethinylestradiol ($\geq 30 \mu\text{g}$) versus low dose ethinylestradiol ($< 30 \mu\text{g}$) when treating hirsutism in adults with PCOS.	❖❖❖ ⊕○○○
4.2.4	EBR	General population guidelines should be considered when prescribing COCP in adults and adolescents with PCOS as specific types or doses of progestins, estrogens or combinations of COCP cannot currently be recommended.	❖❖❖ ⊕○○○
4.2.5	EBR	The 35 μg ethinyl estradiol plus cyproterone acetate preparations should be considered as second-line therapy, versus other COCPs, balancing benefits and adverse effects, including venous thromboembolic risks.	❖❖❖ ⊕○○○
4.2.6	EBR	Progestin only oral contraceptives may be considered for endometrial protection, based on general population guidelines, acknowledging that evidence in women with PCOS is limited.	❖❖❖ ⊕○○○
4.2.7	PP	<p>When prescribing COCPs in adults and adolescents with PCOS, and adolescents at risk of PCOS</p> <ul style="list-style-type: none"> It is important to address main presenting symptoms and consider other treatments such as cosmetic therapies. Shared decision-making (including accurate information and reassurance on the efficacy and safety of COCP) is recommended and likely to improve adherence. Natural estrogen preparations and the lowest effective estrogen doses (such as 20–30 μg of ethinyl estradiol or equivalent), need consideration, balancing efficacy, metabolic risk profile, side effects, cost, and availability. 	

(continued)

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUAITY
		<ul style="list-style-type: none"> The relatively limited evidence on COCPs specifically in PCOS needs to be appreciated with practice informed by general population guidelines. The relative and absolute contraindications and side effects of COCPs need to be considered and be the subject of individualized discussion. PCOS specific features, such as higher weight and cardiovascular risk factors, need to be considered. 	
4.3		Metformin	
4.3.1	EBR	Metformin alone should be considered in adults with PCOS and a BMI $\geq 25 \text{ kg/m}^2$ for anthropometric, and metabolic outcomes including insulin resistance, glucose, and lipid profiles.	♦♦♦ ⊕○○○
4.3.2	EBR	Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence.	♦♦♦ ⊕○○○
4.3.3	CR	Metformin alone may be considered in adults with PCOS and BMI $< 25 \text{ kg/m}^2$, acknowledging limited evidence.	♦♦♦
4.3.4	PP	Where metformin is prescribed the following need to be considered: <ul style="list-style-type: none"> Shared decision making needs to consider feasibility and effectiveness of active lifestyle intervention. Women should be informed that metformin and active lifestyle intervention have similar efficacy. Mild adverse effects, including gastrointestinal side-effects are generally dose dependent and self-limiting. Starting at a low dose, with 500 mg increments 1–2 weekly and extended-release preparations may minimize side effects and improve adherence. Suggested maximum daily dose is 2.5 g in adults and 2g in adolescents. Use appears safe long-term, based on use in other populations, however indications for ongoing requirement needs to be considered. Use may be associated with low vitamin B12 levels, especially in those with risk factors for low vitamin B12 (e.g., diabetes, post bariatric / metabolic surgery, pernicious anaemia, vegan diet etc.), where monitoring should be considered. 	
4.4		Metformin and combined oral contraceptive pills	
4.4.1	EBR	COCP could be used over metformin for management of hirsutism in irregular menstrual cycles in PCOS.	♦♦♦ ⊕○○○
4.4.2	EBR	Metformin could be used over COCP for metabolic indications in PCOS.	♦♦♦ ⊕○○○
4.4.3	EBR	The combination of COCP and metformin could be considered to offer little additional clinical benefit over COCP or metformin alone, in adults with a BMI $\leq 30 \text{ kg/m}^2$.	♦♦♦ ⊕○○○
4.4.4.	PP	In combination with the COCP, metformin may be most beneficial in high metabolic risk groups including those with a BMI $>30 \text{ kg/m}^2$, diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.	
4.4.5	PP	Where COCP is contraindicated, not accepted or not tolerated, metformin may be considered for irregular menstrual cycles. For hirsutism, other interventions may be needed.	
4.5		Anti-obesity pharmacological agents	
4.5.1	CR	Anti-obesity medications including liraglutide, semaglutide, both glucagon-like peptide-1 (GLP-1) receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines.	♦♦♦
4.5.2	PP	Healthcare professionals should ensure concurrent effective contraception when pregnancy is possible for women who take GLP-1 receptor agonists, as pregnancy safety data are lacking.	
4.5.3	PP	Gradual dose escalation for GLP-1 receptor agonists is recommended to reduce gastrointestinal adverse effects.	
4.5.4	PP	Shared decision making, when discussing GLP-1 receptor agonist use with women with PCOS, needs to consider side effects, and the potential need for long-term use in weight management, given the high risk for weight regain after discontinuation, and the lack of long-term safety data.	
4.6		Anti-androgen pharmacological agents	
4.6.1	EBR	In combination with effective contraception, anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of six months of COCP and/or cosmetic therapy.	♦♦♦ ⊕○○○

(continued)

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUALITY
4.6.2	CR	Given the negative psychological impact of female pattern hair loss, anti-androgens in combination with COCP could be trialed, acknowledging the lack of evidence in the PCOS population.	❖❖❖
4.6.3	PP	Whenever pregnancy is possible, healthcare professionals must educate and counsel women and adolescents, parents/s or guardian/s, regarding the risks of incomplete development of external genital structures of male fetuses (undervirilization) when anti-androgens are used. To prevent this, women who can get pregnant should be strongly counselled to use effective contraception (e.g., intrauterine device or COCPs).	
4.6.4	PP	Anti-androgens could be considered to treat hirsutism, in the presence of another effective form of contraception, for women with contraindications for COCP therapy or when COCPs are poorly tolerated.	
4.6.5	PP	When prescribing anti-androgens, based on general population recommendations, healthcare professionals should consider that: <ul style="list-style-type: none"> • Spironolactone at 25–100 mg/day appears to have lower risks of adverse effects. • Cyproterone acetate at doses ≥ 10 mg is not advised due to an increased risk including for meningioma. • Finasteride has an increased risk of liver toxicity. • Flutamide and bicalutamide have an increased risk of severe liver toxicity. • The relatively limited evidence on anti-androgens in PCOS needs to be appreciated with small numbers of studies and limited numbers of participants. 	
4.7	Inositol		
4.7.1	EBR	Inositol (in any form) could be considered in women with PCOS based on individual preferences and values, noting limited harm, potential for improvement in metabolic measures, yet with limited clinical benefits including in ovulation, hirsutism or weight.	❖❖ ⊕○○○
4.7.2	EBR	Metformin should be considered over inositol for hirsutism and central adiposity, noting that metformin has more gastrointestinal side effects than inositol.	❖❖ ⊕○○○
4.7.3	PP	Women taking inositol and other complementary therapies are encouraged to advise their healthcare professional.	
4.7.4	PP	Specific types, doses or combinations of inositol cannot currently be recommended in adults and adolescents with PCOS, due to a lack of quality evidence.	
4.7.5	PP	Shared decision making should include discussion that regulatory status and quality control of inositol in any form (like other nutrient supplements) can differ from those for pharmaceutical products and doses and qualities may vary.	
4.7.6	PP	Policy makers and healthcare professionals have a responsibility to ensure women have access to unconflicted, evidence-based information to inform shared-decision making, whilst also acknowledging and respecting individual values and preferences, including for complementary therapies.	
4.8	Mechanical laser and light therapies for hair reduction		
4.8.1	EBR	Mechanical laser and light therapies should be considered for reducing facial hirsutism and for related depression, anxiety, and quality of life in women with PCOS.	❖❖ ⊕○○○
4.8.2	EBR	A greater number of laser treatment sessions may be required in women with PCOS, compared to women with idiopathic hirsutism, to achieve hair reduction.	❖❖ ⊕○○○
4.8.3	CR	Adverse effects appear limited in the hands of experienced and suitably qualified providers, and women should be encouraged to seek hair reduction therapies from such providers.	❖❖❖
4.8.4	PP	Where laser hair removal is prescribed, the following need to be considered: <ul style="list-style-type: none"> • Wavelength and delivery of laser treatment varies by skin and hair colour. • Laser is relatively ineffective in women with blond, grey or white hair. • The addition of combined oral contraceptive pills (COCP), with or without anti-androgens, to laser treatment may provide greater hair reduction and maintenance compared to laser alone. • Low and high fluence laser appear to have similar efficacy in reducing facial hair, while low fluence laser has reduced associated pain. 	
4.8.5	PP	Mechanical hair removal with Intense Pulse Light (IPL) could be considered, albeit benefits may be less pronounced compared to laser treatment. There is no evidence to support the efficacy of home-based IPL kits.	
4.8.6	PP	Policy makers should consider funding this evidence-based effective therapy for women with PCOS to alleviate distressing symptoms of hirsutism, and related negative impact on quality of life, body image, and psychological health.	

(continued)

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUAITY
4.9	Bariatric/ metabolic surgery		
4.9.1	CR	Bariatric/ metabolic surgery could be considered to improve weight loss, hypertension, diabetes (prevention and treatment), hirsutism, irregular menstrual cycles, ovulation, and pregnancy rates in women with PCOS.	♦♦♦
4.9.2	CR	Bariatric/ metabolic surgery in women with PCOS should be informed by general population guidelines.	♦♦♦♦
4.9.3	CR	PCOS is a metabolic condition and could be considered an indication at a lower BMI threshold for bariatric/ metabolic surgery similarly to other metabolic conditions including diabetes.	♦♦♦
4.9.4	CR	Women should be strongly counselled on the likelihood of rapid return of fertility and the need to commit to effective contraception, ideally prior to surgery. Even when pregnancy is desired, contraception should be continued until a stable weight is achieved, usually after one year, to avoid significantly increased risk of growth restriction, prematurity, small for gestational age, pregnancy complications, and prolonged hospitalization of the infant.	♦♦♦♦
4.10	Pregnancy outcomes		
4.10.1	EBR	Women with PCOS have higher risk pregnancies, and healthcare professionals should ensure that PCOS status is identified during antenatal care, and appropriate monitoring and support is provided.	♦♦♦♦ ⊕○○○
4.10.2	EBR	Healthcare professionals should recognize that pregnant women with PCOS have an increased risk of: <ul style="list-style-type: none"> • Higher gestational weight gain. • Miscarriage. • Gestational diabetes. • Hypertension in pregnancy and preeclampsia. • Intrauterine growth restriction, small for gestational age babies and low birth weight. • Preterm delivery. • Caesarean section. 	♦♦♦♦ ⊕○○○
4.10.3	EBR	Assisted reproductive technology in women with PCOS should be considered as not conferring additional risk of miscarriage, preterm birth, impaired fetal growth, and caesarean section, over that observed in women without PCOS.	♦♦♦ ⊕○○○
4.10.4	EBR	Women with PCOS should be considered as not having an increased risk of large for gestational age babies, macrosomia and instrumental delivery.	♦♦♦ ⊕○○○
4.10.5	PP	Early lifestyle intervention should be offered to pregnant women with PCOS, given the risk of higher baseline weight, excess gestational weight gain and pregnancy complications.	
4.10.6	PP	Blood pressure measurement should be performed when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities in women with PCOS.	
4.10.7	PP	An OGTT should be offered to all women with PCOS when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed in the preconception phase, an OGTT should be offered at the first antenatal visit and repeated at 24–28 weeks gestation.	
4.11	Metformin in pregnancy		
4.11.1	EBR	Healthcare professionals should be aware that metformin in pregnant women with PCOS has not been shown to prevent: <ul style="list-style-type: none"> • Gestational diabetes. • Late miscarriage (12 weeks + 1 day to 21 weeks + 6 days gestational age). • Hypertension in pregnancy. • Pre-eclampsia. • Macrosomia or birthweight ≥ 4000 g. 	♦♦♦♦ ⊕○○○
4.11.2	EBR	Metformin could be considered in some circumstances (e.g., risk for preterm birth) to reduce preterm delivery and limit excess gestational weight gain, in pregnant women with PCOS.	♦♦♦ ⊕⊕○○
4.11.3	PP	Women should be counselled that the consequences of metformin exposure on long-term offspring health remain unclear and there is a suggestion of increased childhood weight, although causality is not certain.	
4.11.4	PP	Side effects of metformin are mostly mild, transient gastrointestinal symptoms and are not worse in pregnancy.	

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUALITY
5		Assessment and treatment of infertility	
		General principles	
	PP	All fertility treatment in PCOS should be guided by the fertility treatment algorithm (Algorithm 2).	
	PP	Those with PCOS should be reassured that pregnancy can often be successfully achieved either naturally or with assistance.	
	PP	Prenatal vitamins supplementation should be commenced with ovulation induction therapy aligned to routine preconception care.	
	PP	Pregnancy should be excluded prior to ovulation induction therapy.	
	PP	The use of ovulation induction agents, including letrozole, metformin and clomiphene citrate, is off-label in many countries. Where off-label use of ovulation induction agents is allowed, healthcare professionals need to inform women and discuss the evidence, possible concerns, and side effects.	
	PP	There should be ongoing monitoring of patients for adverse effects, and infants for congenital anomalies, in all studies conducted with ovulation induction agents and these should be reported in any published papers.	
5.1		Preconception risk factors	
5.1.1	EBR	Women with PCOS should be counselled on the adverse impact of excess weight on clinical pregnancy, miscarriage, and live birth rates, following infertility treatment.	♦♦♦♦ ⊕○○○
5.1.2	CR	Consistent with routine preconception care, in women with PCOS planning pregnancy, weight, blood pressure, smoking, alcohol, diet and nutritional status, folate supplementation (higher dose in those with BMI >30 kg/m ²), exercise, sleep and mental, emotional and sexual health should be considered and optimized to improve reproductive and pregnancy outcomes and overall health.	♦♦♦♦
5.1.3	PP	A reproductive life plan and age-appropriate education on optimizing reproductive health is recommended in adolescents and women with PCOS, including healthy lifestyle, prevention of excess weight gain, and optimizing preconception risk factors.	
5.1.4	PP	Healthcare professionals are encouraged to seek permission and, if given, to assess weight and BMI and initiate a dialogue on the importance of weight and lifestyle on women's health before pregnancy. This requires caution to avoid weight stigma and needs to consider the cultural, social, and environmental determinants of health (see 3.6).	
5.1.5	PP	Chronic conditions such as diabetes, high blood pressure, anxiety, depression and other mental health conditions, should be optimally managed and women should be counselled regarding the risk of adverse pregnancy outcomes.	
5.2		Tubal patency testing	
5.2.1	CR	In women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing and techniques of tubal patency testing in relation to the cost and complexity of the treatment, should be considered on an individual basis, depending on personal history and population prevalence, prior to starting ovulation induction with timed intercourse or intrauterine insemination.	♦♦♦
5.3		Letrozole	
5.3.1	EBR	Letrozole should be the first-line pharmacological treatment for ovulation induction in infertile anovulatory women with PCOS, with no other infertility factors.	♦♦♦♦ ⊕○○○
5.3.2	PP	The use of letrozole is still off-label in many countries. Where it is not allowed, clinicians could use other ovulation induction agents.	
5.3.3	PP	Letrozole should not be given where there is any possibility of a pre-existing pregnancy, though there is no evidence for increased teratogenicity compared to other ovulation induction agents.	
5.4		Clomiphene citrate and metformin	
5.4.1		Metformin versus placebo	
5.4.1.1	EBR	Metformin could be used alone, in women with PCOS with anovulatory infertility and no other infertility factors, to improve clinical pregnancy and live birth rates, whilst informing women that there are more effective ovulation agents.	♦♦♦ ⊕○○○

(continued)

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUAITY
5.4.1.2	PP	Women should be counselled as to potential mild gastrointestinal side-effects with metformin.	
5.4.1.3	PP	Healthcare and resource burden including monitoring, travel and costs are lower with metformin.	
5.4.1.4	PP	Consideration of age and screening for other fertility factors needs to be discussed before prescribing metformin.	
5.4.2 Clomiphene citrate verses metformin			
5.4.2.1	EBR	Clomiphene citrate could be used in preference to metformin in women with PCOS with anovulatory infertility and no other infertility factors, to improve ovulation, clinical pregnancy and live birth rates.	♦♦♦ ⊕○○
5.4.2.2	PP	The risk of multiple pregnancy is increased with clomiphene citrate use (alone or in combination with metformin) and therefore clomiphene cycles may require ultrasound monitoring.	
5.4.3 Clomiphene citrate and metformin verses clomiphene citrate alone			
5.4.3.1	EBR	Clomiphene citrate combined with metformin could be used rather than clomiphene citrate alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and clinical pregnancy rates.	♦♦♦ ⊕○○
5.4.4 Clomiphene citrate and metformin versus metformin alone			
5.4.4.1	EBR	Clomiphene citrate combined with metformin could be used rather than metformin alone in women with PCOS with anovulatory infertility and no other infertility factors to improve live birth rates.	♦♦♦ ⊕○○
5.4.4.2	PP	Monitoring of combined cycles will need to be equivalent to clomiphene citrate alone.	
5.4.5 Clomiphene citrate versus Letrozole			
5.4.5.1	EBR	Letrozole should be used rather than clomiphene citrate in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy and live birth rates.	♦♦♦♦ ⊕○○
5.4.5.2	PP	Current evidence demonstrates no difference in fetal abnormality rates between letrozole or clomiphene citrate ovulation induction or natural conception.	
5.5 Gonadotrophins			
5.5.1	EBR	Gonadotrophins alone could be considered rather than clomiphene citrate in therapy naïve women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy and live birth rates (refer to PP 5.5.6).	♦♦♦ ⊕○○
5.5.2	EBR	Gonadotrophins alone could be used over gonadotrophins combined with clomiphene citrate in women with PCOS who are anovulatory and infertile with clomiphene citrate resistance or failure, and no other infertility factors.	♦♦♦ ⊕○○
5.5.3	EBR	Gonadotrophins could be considered rather than the combination of clomiphene citrate and metformin in women with PCOS who are anovulatory and infertile, with clomiphene citrate-resistance and no other infertility factors.	♦♦♦ ⊕○○
5.5.4	EBR	Either gonadotrophins or laparoscopic ovarian surgery could be used in women with PCOS who are anovulatory and infertile, with clomiphene citrate-resistance and no other infertility factors, following counselling on higher live birth rate and higher multiple pregnancy rates with gonadotrophins.	♦♦ ⊕○○
5.5.5	EBR	Gonadotrophins could be second-line pharmacological therapy for women with PCOS who are anovulatory and infertile, with no other infertility factors and who have failed first line oral ovulation induction.	♦♦♦ ⊕○○
5.5.6	PP	Where gonadotrophins are to be prescribed, the following should be considered: <ul style="list-style-type: none"> • Cost of the intervention for ovulation induction. • Expertise required for the use of the intervention for ovulation induction. • The degree of intensive ultrasound monitoring that is required. • A low dose step-up gonadotrophin protocol should be used to optimize the chance of monofollicular development. • Implications of potential multiple pregnancy. 	
5.5.7	PP	There appears to be no difference in the clinical efficacy of the available gonadotrophin preparations.	
5.5.8	PP	When using gonadotrophins, best clinical practice is to avoid multiple pregnancy. Considerations here include cancelling cycles when there is more than a total of two follicles greater than 14mm in diameter and advising avoidance of unprotected intercourse.	

(continued)

Table 4. Continued

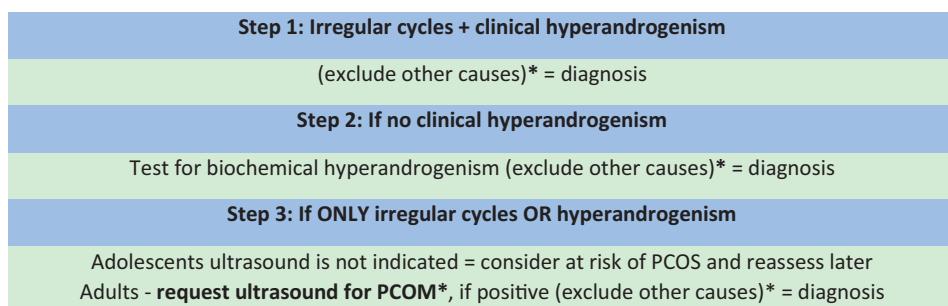
NO.	TYPE	RECOMMENDATION	GRADE/QUALITY
5.5.9	PP	Live birth rate, clinical pregnancy rate per patient and ovulation rate per cycle are higher with gonadotrophins than with clomiphene citrate.	
5.5.10	PP	A low dose gonadotrophin protocol should be used to optimize the chance of monofollicular growth and minimize multiple pregnancy.	
5.5.11	PP	Cycle monitoring and drug costs coupled with multiple injection will influence choice in gonadotrophin use.	
5.6		Laparoscopic ovarian surgery	
5.6.1	EBR	Laparoscopic ovarian surgery could be second-line therapy for women with PCOS who are anovulatory and infertile, with clomiphene citrate resistance and no other infertility factors.	♦♦♦ ⊕○○
5.6.2	PP	When using laparoscopic ovarian surgery, the following should be considered: <ul style="list-style-type: none"> Comparative cost of the intervention for ovulation induction. Expertise required for the safe use of the intervention for ovulation induction. Both intraoperative and postoperative risks, which are higher in women who are above healthy weight. 	
5.7		In vitro fertilization and in vitro maturation	
5.7.0.1	CR	In the absence of an absolute indication for in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI), IVF could be offered in women with PCOS and anovulatory infertility, if first- or second-line ovulation induction therapies have failed.	♦♦♦
5.7.0.2	PP	In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used, multiple pregnancies can be minimized.	
5.7.0.3	PP	Women with PCOS undergoing IVF/ICSI treatment should be counselled prior to starting treatment about the increased risk of ovarian hyperstimulation syndrome and options to reduce the risk should be offered.	
5.7.1		Gonadotrophin releasing hormone protocol	
5.7.1.1	PP	Gonadotrophin releasing hormone (GnRH) antagonist protocol cannot be recommended over GnRH agonist long protocol for women with PCOS undergoing IVF/ICSI to improve clinical pregnancy or live birth rate.	
5.7.1.2	PP	The use of a GnRH antagonist protocol for women with PCOS undergoing IVF/ICSI is recommended as it enables the use of an agonist trigger, with the freezing of all embryos generated if required, without compromising the cumulative live birth rate, to reduce the risk of significant ovarian hyperstimulation syndrome.	
5.7.2		Trigger type	
5.7.2.1	CR	Triggering final oocyte maturation with a GnRH agonist and freezing all suitable embryos is recommended, in an IVF/ICSI cycle with a GnRH antagonist protocol, where a fresh embryo transfer is not intended or where there is an increased risk of ovarian hyperstimulation syndrome.	♦♦♦♦
5.7.3		Choice of follicle stimulating hormone	
5.7.3.1	CR	Either urinary or recombinant follicle stimulating hormone (FSH) could be used in women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, with insufficient evidence to recommend a particular type of FSH preparation.	♦♦♦
5.7.4		Exogenous luteinising hormone	
5.7.4.1	CR	Exogenous recombinant luteinising hormone (LH) treatment should not be routinely used in combination with FSH therapy in women with PCOS undergoing controlled ovarian hyperstimulation for IVF/ ICSI.	♦
5.7.5		Adjunct metformin	
5.7.5.1	EBR	Adjunct metformin therapy could be used before and/or during FSH ovarian stimulation in women with PCOS undergoing IVF/ICSI treatment with GnRH agonist long protocol, to reduce the risk of developing ovarian hyperstimulation syndrome and miscarriage.	♦♦♦ ⊕○○
5.7.5.2	PP	Good practice in PCOS and IVF is the use of a GnRH antagonist protocol as it gives the flexibility of using a GnRH agonist trigger, freeze all strategy to reduce the risk of ovarian hyperstimulation syndrome. However, if using a GnRH agonist long protocol then metformin could be considered. If using metformin, the following could be considered: <ul style="list-style-type: none"> Commence metformin at the start of GnRH agonist treatment. Gradually titrate metformin up to a dose of between 1000mg to 2500mg daily in order to minimize side effects. Stopping metformin therapy at the time of the pregnancy test or period, unless the metformin therapy is otherwise indicated. 	

Table 4. Continued

NO.	TYPE	RECOMMENDATION	GRADE/QUAITY
5.7.6	In vitro maturation		
5.7.6.1	EBR	The use of in vitro maturation (IVM) and ICSI could be considered in women with PCOS as an alternative to a stimulated IVF/ICSI cycle, where an embryo is frozen and replaced in a subsequent embryo transfer cycle, acknowledging there is no risk of ovarian hyperstimulation syndrome, but a lower cumulative live birth rate.	❖❖ ⊕⊕⊕○
5.7.6.2	CR	The use of IVM and ICSI could be considered prior to stimulated IVF/ ICSI cycles acknowledging both benefits and limitations.	❖❖
5.7.6.3	PP	IVM should only be considered in services with sufficient expertise, and advocacy is needed for regional or national centres of expertise.	
5.7.6.4	PP	IVM could be offered as an option in women with prior severe ovarian hyperstimulation syndrome and where the risk of severe ovarian hyperstimulation syndrome is deemed unacceptably high, provided that expertise in IVM techniques exists.	
5.7.6.5	PP	Evidence suggests that IVM/ICSI is less effective than standard IVF/ICSI in terms of clinical pregnancy per patient and live birth rate per patient.	
5.8	Inositol		
5.8.1	EBR	Inositol in any form alone, or in combination with other therapies, should be considered experimental therapy in women with PCOS with infertility, with benefits and risks currently too uncertain to recommend the use of these agents as fertility therapies.	❖❖ ⊕○○○
5.8.2	PP	There is limited evidence with uncertain results, on the effect of inositol on ovulation, clinical pregnancy and live birth rates.	
5.8.3	PP	Side effects and safety are not known for inositol.	
5.8.4	PP	Women need to be aware that these agents can have limited regulation with variable dose, quality, consistency, and combination with other agents.	
5.8.5	PP	Women's personal goals and preferences should be considered when discussing complementary therapies.	
5.9	Anti-obesity pharmacological agents		
5.9.1	CR	We recommend using anti-obesity agents in PCOS for reproductive outcomes only in research settings to establish efficacy and safety.	

See [Table 1](#) for definition of CR, EBR and PP. © International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2023, Helena Teede et al. Monash University (monash.edu/medicine/mchri/pcos), 2023, by permission of Monash University, on behalf of the NHMRC Centre for Research Excellence in Women's Health in Reproductive Life. This image/content is not covered by the terms of the Creative Commons licence of this publication. For permission re reuse, please contact the rights holder.

Algorithm 1: Diagnostic algorithm for polycystic ovary syndrome (PCOS)



* Exclusion of other causes = TSH, prolactin, 17-OH progesterone, FSH or if clinically indicated exclude other causes (e.g. Cushing's Syndrome, adrenal tumours). For hypogonadotropic hypogonadism, usually due to low body fat or intensive exercise, exclude clinically and with LH/ FSH. PCOM = polycystic ovarian morphology on ultrasound

Figure 1. Algorithm 1 - Diagnostic algorithm for polycystic ovary syndrome (PCOS). © Monash University on behalf of the NHMRC Centre for Research Excellence in Women's Health in Reproductive Life, 2023. © International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2023, Helena Teede et al. Monash University (monash.edu/medicine/mchri/pcos), 2023, by permission of Monash University, on behalf of the NHMRC Centre for Research Excellence in Women's Health in Reproductive Life. This image/content is not covered by the terms of the Creative Commons licence of this publication. For permission re reuse, please contact the rights holder.

Algorithm 2: Infertility algorithm for polycystic ovary syndrome (PCOS)
Central Blue Pathway follows best practice evidence and is preferred

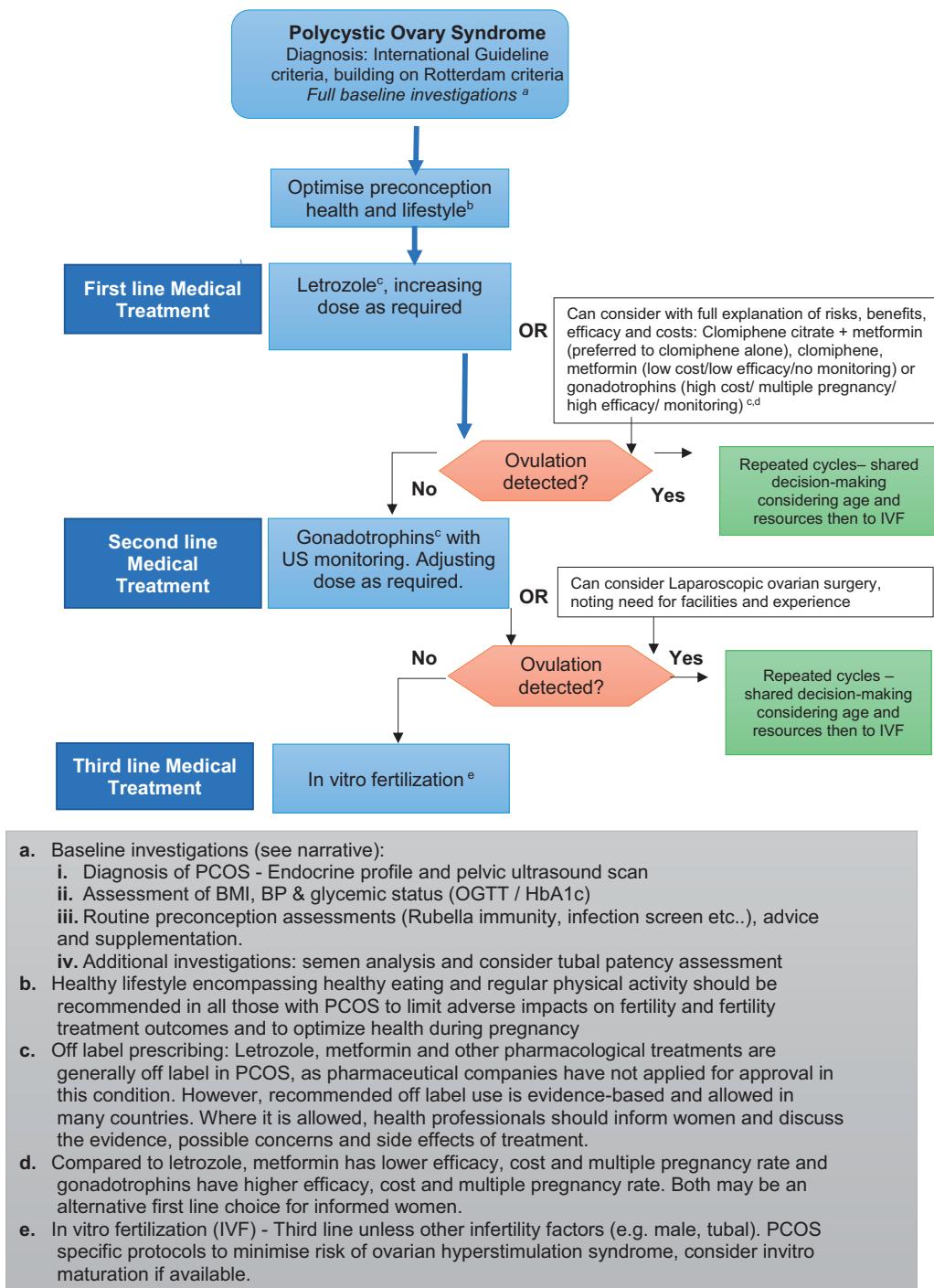


Figure 2. Algorithm 2 - Infertility algorithm for polycystic ovary syndrome (PCOS). © Monash University on behalf of the NHMRC Centre for Research Excellence in Women's Health in Reproductive Life, 2023. © International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2023, Helena Teede et al. Monash University (monash.edu/medicine/mchri/pcos), 2023, by permission of Monash University, on behalf of the NHMRC Centre for Research Excellence in Women's Health in Reproductive Life. This image/content is not covered by the terms of the Creative Commons licence of this publication. For permission re reuse, please contact the rights holder.

Symptoms of depression and anxiety are significantly increased and should be screened for in all women with PCOS, with psychological assessment and therapy as indicated. Greater awareness of psychological features including eating disorders and impacts on body image and quality of life is needed.

Dissatisfaction with PCOS diagnosis and care is high and significant improvement in education and awareness is

strongly recommended for women and healthcare professionals including high quality, evidence-based resources. Shared decision making and self-empowerment are fundamental and integrated models of care should be codesigned, funded and evaluated.

Supported healthy lifestyle remains vital throughout the lifespan in PCOS, with a strong focus on overall health, prevention of

weight gain and, if required, on weight management. Recognizing the benefits of many diet and physical activity regimens, there is no one specific regimen that has benefits over others in PCOS. Weight bias and stigma should be minimized and healthcare professionals should seek permission to weigh women, with explanation of weight-related risks.

Combined oral contraceptive pills are the first line pharmacological treatment for menstrual irregularity and hyperandrogenism, with no specific recommended preparation and a preference for lower ethinyl estradiol dose preparations and those with less side-effects. Metformin is recommended primarily for metabolic features and has greater efficacy than inositol, which offers limited clinical benefits in PCOS. Metformin is not routinely recommended for use in pregnant women with PCOS. Mechanical laser therapy is effective for hair reduction in some subgroups, whilst anti-androgens have a limited role where other therapies are ineffective or contraindicated. Anti-obesity agents and bariatric/metabolic surgery may be considered based on general population guidelines, balancing potential for benefits and side effects.

Letrozole is the preferred first line pharmacological infertility therapy, with clomiphene in combination with metformin; gonadotrophins or ovarian surgery primarily having a role as second line therapy. *In vitro* fertilization (IVF) could be offered, potentially with *in vitro* maturation, as third line therapy, where other ovulation induction therapies have failed and in the absence of an absolute indication for IVF in women with PCOS and anovulatory infertility. Given the underlying risk for pregnancy complications in PCOS, single embryo transfer should be preferred.

Overall, evidence in PCOS is low to moderate quality. Based on high prevalence and significant health impact, greater priority, education, models of care, funding, and research are recommended. Guideline translation will be extensive including multilingual education outputs and evidence-based resources for consumers (the ASKPCOS app), healthcare professionals and policy makers.

The guideline recommendations are protected under copyright, however a clear process for adaption of guideline recommendations to regional context is available by contacting the author for correspondence (www.monash.edu/medicine/mchri/pcos). The translation program will be free and internationally accessible, building on the existing range of codesigned resources including the patient focused, evidence-based PCOS APP (AskPCOS), used in 186 countries and based on a rigorously developed question prompt list. Multi-faceted patient codesigned resources will aim to enhance health literacy with comprehensive PCOS-related health information available in multiple formats and in 15-20 languages. Internationally accessible resources include education modules for healthcare professionals at different career stages and disciplines, healthcare professional accredited courses, practice resources and tools, webinars with international expert panels, and e-health information resources that will be available online (www.monash.edu/medicine/mchri/pcos). Importantly, the Guideline and translation of the Guideline is expected to improve patient experiences through the provision of timely and accurate diagnosis, of accessible evidence-based information and of improved multi-disciplinary support. Ultimately, this international initiative may serve as an exemplar for large scale collaborative engagement, pooling of resources, avoidance of duplication and inconsistency with consensus-based statements, and codesign of best quality consistent guidelines with processes for local adaption and healthcare impact. Key elements include extensive collaboration, broad stakeholder representation, consumer partnership, distributive leadership, adequate

funding, robust project management and governance, adherence to best practice and integrated comprehensive translation, and evaluation. We sincerely thank the partner and collaborating organizations, consumer groups and members of the GDGs for their substantive commitment to the international partnership to optimize health outcomes for women with this common, heterogeneous, and much neglected condition.

Data availability

All data extracted and analyzed in the guideline is available in a repository and can be accessed via <https://doi.org/10.26180/23625288.v1>

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- American Society for Reproductive Medicine (ASRM)
- Endocrine Society (ENDO)
- European Society for Endocrinology (ESE)
- European Society of Human Reproduction and Embryology (ESHRE)

Collaborating and engaged societies and consumer providing in-kind support include:

- Androgen Excess and Polycystic Ovary Syndrome Society (AEPPOS)
- Asia Pacific Paediatric Endocrine Society (APPES)
- Asia Pacific Initiative on Reproduction (ASPIRE)
- Australia and New Zealand Society for Paediatric Endocrinology and Diabetes (ANZSPED)
- Australian Diabetes Society (ADS)
- Brazilian Society of Endocrinology and Metabolism (SBEM)
- British Fertility Society (BFS)
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- European Society for Paediatric Endocrinology (ESPE)
- Exercise and Sports Science Australia (ESSA)
- Fertility Society Australia and New Zealand (FSA)
- International Federation of Fertility Societies (IFFS)
- International Federation of Gynecology and Obstetrics (FIGO)
- International Society of Endocrinology (ISE) - 40 partner societies
- Italian Society of Gynaecology and Obstetrics
- Japanese Society for Paediatric Endocrinology (JSPE)
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 Society for Endocrinology
 Verity UK
 Victorian Assisted Reproductive Technology Association (VARTA)

Other relevant organizations are welcome to apply to partner in guideline translation.

Authors' roles

HJT led the guidelines from funding, engaging partners, coordinating processes, prioritizing clinical questions, co-chairing guideline meetings, coordinating peer review responses and leading writing, approval and publication processes. Listed authors held senior leadership roles as chair or deputy chair of the five GDGs or leadership of the evidence team with roles from the management committee, chair/co-chair of GDG or the early career evidence network, involvement at all stages, responding to feedback, providing input into and endorsing the guideline. All other included authors were actively engaged as partner nominees and multidisciplinary GDG or consumer experts. The evidence synthesis network was led by CTT and AM across search strategies, training, Covidence processes, quality appraisal and GRADE, meta-analysis, evidence integrity processes (with BM) and preparing the technical report. The listed members of this network led evidence synthesis across the clinical questions and had input into the technical report.

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Conflict of interest

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Appendix

Members of the PCOS Network

The international advisory panel, guideline technical team, paediatric, consumer and translation committees, the Indigenous cultural advisor and the extended early career support network who assisted with evidence synthesis, can be found online (www.monash.edu/medicine/mchri/pcos).

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Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome

The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group

Rotterdam, The Netherlands

Received October 22, 2003; revised and accepted October 22, 2003.
May 1–3, 2003, Rotterdam, The Netherlands.
Congress chairmen: Tarlatzis (Gr), Fauser (Ni).
Scientific committee: J. Chang (USA), R. Azziz (USA), R. Legro (USA), D. Dewailly (Fr), S. Franks (UK), R. Tarlatzis (Gr), B. Fauser (Ni).
Invited discussants: A. Balen (UK), Ph. Bouchard (Fr), E. Dahlgren (Sw), L. Devoto (Chi), E. Diamanti (Gr), A. Dunai (USA), M. Filicori (It), R. Homburg (Is), L. Ibanez (Sp), J. Laven (Ni), D. Magoffin (USA), J. Nestler (USA), R. Norman (Aus), R. Pasquale (It), M. Pugeat (Fr), J. Strauss (USA), S. Tan (Can), A. Taylor (USA), R. Wild (USA), S. Wild (UK).

Invited discussants not present during the meeting: J. Chang (USA), D. Guzick (USA), D. Ehrmann (USA), R. Lobo (USA).

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Since the 1990 National Institutes of Health-sponsored conference on polycystic ovary syndrome (PCOS), it has become appreciated that the syndrome encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria. The 2003 Rotterdam consensus workshop concluded that PCOS is a syndrome of ovarian dysfunction along with the cardinal features hyperandrogenism and polycystic ovary (PCO) morphology. PCOS remains a syndrome, and as such no single diagnostic criterion (such as hyperandrogenism or PCO) is sufficient for clinical diagnosis. Its clinical manifestations may include menstrual irregularities, signs of androgen excess, and obesity. Insulin resistance and elevated serum LH levels are also common features in PCOS. PCOS is associated with an increased risk of type 2 diabetes and cardiovascular events. (Fertil Steril® 2004;81:19–25. ©2004 by American Society for Reproductive Medicine.)

Nearly 15 years have passed since the first international conference on polycystic ovary syndrome (PCOS) was held. During that initial meeting at the National Institutes of Health (NIH) in Bethesda, Maryland, there was considerable discussion with little consensus, although a questionnaire led to the current diagnostic criteria that stand today (see Table 1). Based on the majority opinion rather than clinical trial evidence, the following diagnostic criteria were put forth: clinical or biochemical evidence of hyperandrogenism, chronic anovulation, and exclusion of other known disorders (1). These criteria were an important first step toward standardizing diagnosis and led to a number of landmark randomized multicenter clinical trials in PCOS (2, 3). Since that time and as outlined during a number of subsequent international conferences (4), there has been a gradually increasing awareness that the clinical expression of PCOS may be broader than that defined by the 1990 NIH criteria.

Rotterdam Consensus on Diagnostic Criteria for PCOS

PCOS is a syndrome of ovarian dysfunction. Its cardinal features are hyperandrogenism and polycystic ovary morphology (5). Its clinical manifestations may include menstrual irregularities, signs of androgen excess, and obesity.

PCOS is associated with an increased risk of type 2 diabetes (6, 7). Since the 1990 NIH-sponsored conference on PCOS, it has become appreciated that the syndrome encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria (Table 1). It is now recognized that women with regular cycles and hyperandrogenism and/or polycystic ovaries (PCO) may have the syndrome (8–10). It has also been recognized that some women with the syndrome will have PCO without clinical evidence of androgen excess but will display evidence of ovarian dysfunction.

PCOS remains a syndrome and as such no single diagnostic criterion (such as hyperandrogenism or PCO) is sufficient for clinical diagnosis. PCOS also remains a diagnosis of exclusion. Known disorders that mimic the PCOS phenotype should be excluded.

Diagnostic Criteria for Clinical Trials and Familial Studies

The above-mentioned diagnostic criteria may not be suitable for trials focusing on clinical outcomes in women with PCOS. For instance, trials focusing on pregnancy as an outcome may place greater emphasis on anovulation as the identifying symptom, rather

TABLE 1

Revised diagnostic criteria of polycystic ovary syndrome.

1990 Criteria (both 1 and 2)
1. Chronic anovulation and
2. Clinical and/or biochemical signs of hyperandrogenism and exclusion of other etiologies.
Revised 2003 criteria (2 out of 3)
1. Oligo- or anovulation,
2. Clinical and/or biochemical signs of hyperandrogenism,
3. Polycystic ovaries and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome)

Note: Thorough documentation of applied diagnostic criteria should be done (and described in research papers) for future evaluation.

2003 Rotterdam PCOS consensus. *Fertil Steril* 2004.

than the presence of PCO or clinical hyperandrogenism. Similarly, trials seeking an improvement in hirsutism may deemphasize baseline ovulatory function and require some pathological terminal hair growth for entry. Moreover, women with chronic anovulation and hyperandrogenism and/or PCO appear to be at substantially greater risk for insulin resistance than those with hyperandrogenism and regular cycles (11, 12). Accordingly, it is essential that studies of the metabolic features of PCOS stratify affected women according to ovulatory function (i.e., chronic oligo-/amenorrhea vs. regular cycles).

Family studies are critical for understanding the spectrum of phenotypes and for identifying susceptibility genes for PCOS. More narrow diagnostic criteria may be used in family studies to identify affected individuals, such as the presence of PCO alone (13) or hyperandrogenemia per se (14). A rigid definition of PCOS based on the present or past proposed diagnostic criteria may hamper our understanding of this heterogeneous disorder.

Exclusion of Related Disorders

To establish the diagnosis of PCOS, it is important to exclude other disorders with a similar clinical presentation, such as congenital adrenal hyperplasia, Cushing's syndrome, and androgen-secreting tumors. Exclusion of 21-hydroxylase deficient nonclassic adrenal hyperplasia (NCAH) can be performed using a basal morning 17-hydroxyprogesterone level, with cutoff values ranging between 2 and 3 ng/mL (15). Some participants felt that the routine screening of hyperandrogenic patients for NCAH should take into account the prevalence of this autosomal recessive disorder in the population under study.

The routine exclusion of thyroid dysfunction in patients deemed to be hyperandrogenic was felt to have limited value, as the incidence of this disorder among these patients is no higher than that in normal women of reproductive age. However, because screening for thyroid disorders may be advisable in all women of reproductive age, the routine

measurement of TSH in the hyperandrogenic patient need not be discouraged.

The initial workup in women presenting with oligo-anovulation may also include the assessment of serum FSH and E₂ levels to exclude hypogonadotropic hypogonadism (i.e., central origin of ovarian dysfunction) or premature ovarian failure characterized by low E₂ and high FSH concentrations, according to World Health Organization (WHO) classification (16, 17). PCOS is part of the spectrum of normogonadotropic normoestrogenic anovulation (WHO 2) (5, 18). It should be emphasized, however, that serum LH concentrations are frequently elevated in these patients, as will be discussed later.

Most participants felt that the routine measurement of PRL in the evaluation of hyperandrogenic patients should be performed to exclude hyperprolactinemia, with a caveat that many hyperandrogenic patients may have PRL levels in the upper normal limit or slightly above normal.

Finally, syndromes of severe insulin resistance (e.g., for the diagnosis of the hyperandrogenic-insulin resistant-acanthosis nigricans, or HAIRAN, syndrome) (19), Cushing's syndrome (20), androgen-secreting neoplasms (20, 21), or high-dose exogenous androgens (22) should be excluded if clinically suspected.

Hyperandrogenism

Clinical phenotyping of PCOS involves determining the presence of clinical and/or biochemical androgen excess (hyperandrogenism), while excluding related disorders.

Clinical Hyperandrogenism: Most participants felt that the primary clinical indicator of androgen excess is the presence of hirsutism (23). However, the following issues should be emphasized:

- Normative data in large populations are still lacking.
- The assessment of hirsutism is relatively subjective.
- Few physicians in clinical practice actually use standardized scoring methods.
- Hirsutism is often treated well before the patient is ever evaluated endocrinologically.
- Hirsutism may be significantly less prevalent in hyperandrogenic women of East Asian origin (24) or in adolescence (25).

The sole presence of acne was also felt to be a potential marker for hyperandrogenism, although studies are somewhat conflicting regarding the exact prevalence of androgen excess in these patients (26). The sole presence of androgenic alopecia as an indicator of hyperandrogenism has been less well studied. However, it appears to be a relatively poor marker of androgen excess, unless present in the oligo-ovulatory patient (27). Overall, the clinical evidence of hyperandrogenism is an important feature of patients with PCOS, notwithstanding the above-mentioned limitations.

Biochemical Hyperandrogenism: Most patients with PCOS have evidence of hyperandrogenemia, and recent ob-

servations suggest that circulating androgen levels may also represent an inherited marker for androgen excess (14). However, it was clearly denoted that a proportion of patients with PCOS may not demonstrate an overt abnormality in circulating androgens (5, 28–31).

The limitations of defining androgen excess by the measurement of circulating androgen levels were felt to be due in part to the inaccuracy and variability of the laboratory methods of measurement that are often used (32–34):

- There are multiple androgens that may not be considered (35).
- There is wide variability in the normal population.
- Normative ranges have not been well-established using well-characterized control populations.
- Age and body mass index (BMI) have not been considered when establishing normative values for androgen levels (36, 37).
- Little normative data are present on adolescent and older women.
- Androgens are suppressed more rapidly by hormonal suppression than other clinical features and may remain suppressed even after discontinuation of hormonal treatment.

Notwithstanding these limitations, it was felt that the measurement of free T or the free T (free androgen) index (34) were the more sensitive methods of assessing hyperandrogenemia (38, 39). Recommended methods for the assessment of free T included equilibrium dialysis (33, 34), calculation of free T from the measurement of sex hormone-binding globulin and total T, or ammonium sulfate precipitation (40). It was the uniform impression that currently available direct assays for free T have limited value, particularly in the evaluation of the hyperandrogenic woman.

It was noted that measurement of total T only may not be a very sensitive marker of androgen excess. A small fraction of patients with PCOS may have isolated elevations in dehydroepiandrosteronesulphate (DHEAS) levels. Some felt that the measurement of total T and DHEAS had some value in detecting a patient with an androgen-secreting tumor (41), although more recent data suggest that the best predictor of these neoplasms is the clinical presentation (42).

Finally, little data are available on the value of routinely measuring androstenedione in hyperandrogenic patients (5), although it was noted that it might be somewhat more elevated in patients with 21-hydroxylase-deficient nonclassic adrenal hyperplasia than in patients with PCOS. Nonetheless, the paucity of normative and clinical data with androstenedione precluded its recommendation for the routine assessment of hyperandrogenemia.

Polycystic Ovaries (PCO)

Workshop participants felt that PCO should now be considered as one of the possible criteria for PCOS (see Table 1). According to the available literature (18, 43, 44), the criteria having sufficient specificity and sensitivity to define

PCO are the following: “Presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume (>10 mL)” (for a review, see 45). The subjective appearance of PCO should not be substituted for this definition. The follicle distribution should be omitted as well as the increase in stromal echogenicity and volume. Although increased stromal volume is a feature of PCO (46), it has been shown that the measurement of the ovarian volume is a good surrogate for the quantification of stromal volume in clinical practice (47). This definition does not apply to women taking the oral contraceptive pill, since its use modifies ovarian morphology in normal women and putatively in women with PCO (48). Only one ovary fitting this definition is sufficient to define PCO. If there is evidence of a dominant follicle (>10 mm) or a corpus luteum, the scan should be repeated during the next cycle. The presence of an abnormal cyst or ovarian asymmetry (which may suggest a homogeneous cyst) necessitates further investigation.

A woman having PCO in the absence of an ovulatory disorder or hyperandrogenism (“asymptomatic” PCO) should not be considered as having PCOS until more is known regarding the clinical presentation (49). In addition to its role in the definition of PCOS, ultrasound is helpful to predict fertility outcome of clomiphene citrate (50) and the risk of ovarian hyperstimulation syndrome (OHSS) and to assist in deciding whether the in vitro maturation of oocytes is desirable (51).

It is recognized that the appearance of PCO may be seen in women before undergoing ovarian stimulation for IVF in the absence of overt signs of the PCOS. These ovaries, when stimulated, behave like the ovaries of women with PCOS and are at increased risk for hyperstimulation and OHSS (52).

In addition, ultrasound provides the opportunity to screen for endometrial hyperplasia in these patients. The following technical recommendations should be highlighted:

- State-of-the-art equipment is required and should be operated by appropriately trained personnel.
- Whenever possible, the transvaginal approach should be used, particularly in obese patients.
- Regularly menstruating women should be scanned in the early follicular phase (cycle days 3–5). Oligo-/amenorrhoeic women should be scanned either at random or between days 3 and 5 after a progestin-induced withdrawal bleeding.
- Calculation of ovarian volume is performed using the simplified formula for a prolate ellipsoid ($0.5 \times \text{length} \times \text{width} \times \text{thickness}$) (53).
- Follicle number should be estimated both in longitudinal and antero-posterior cross-sections of the ovaries. The size of follicles <10 mm should be expressed as the mean of the diameters measured on the two sections.

TABLE 2

Summary of 2003 polycystic ovary syndrome (PCOS) consensus regarding screening for metabolic disorders.

Summary of consensus

- No tests of insulin resistance are necessary to make the diagnosis of PCOS, nor are they needed to select treatments.
- Obese women with PCOS should be screened for the metabolic syndrome, including glucose intolerance with an oral glucose tolerance test.
- Further studies are necessary in nonobese women with PCOS to determine the utility of these tests, although they may be considered if additional risk factors for insulin resistance, such as a family history of diabetes, are present.

2003 Rotterdam PCOS consensus. *Fertil Steril* 2004.

TABLE 3

Criteria for the metabolic syndrome in women with polycystic ovary syndrome. (Three of five qualify for the syndrome.)

Risk factor	Cutoff
1. Abdominal obesity (waist circumference)	>88 cm (>35 inch)
2. Triglycerides	≥150 mg/dL
3. HDL-C	<50 mg/dL
4. Blood pressure	≥130/≥85
5. Fasting and 2-h glucose from oral glucose tolerance test	110–126 mg/dL and/or 2-h glucose 140–199 mg/dL

2003 Rotterdam PCOS consensus. *Fertil Steril* 2004.

Insulin Resistance

Insulin resistance is associated with reproductive abnormalities in women with PCOS (see also Table 2). Improving insulin sensitivity through both lifestyle and pharmacological intervention can ameliorate these abnormalities. Insulin resistance, defined as decreased insulin-mediated glucose utilization, is commonly found in the larger population (10%–25%) when sophisticated dynamic studies of insulin action are performed (54). However, the criteria for selecting an abnormal cutoff point vary. Insulin resistance in women with PCOS appears even more common (up to 50%), both in obese and nonobese women (55). Reports of the prevalence on insulin resistance in women with PCOS vary depending on the sensitivity and specificity of the tests employed and the heterogeneity of PCOS.

There is currently no validated clinical test for detecting insulin resistance in the general population. Dynamic invasive tests such as the euglycemic clamp and frequently sampled glucose tolerance test are research procedures because of their intensive use of time and resources. Calculated indices based on fasting levels of insulin and glucose correlate well with dynamic tests of insulin action. However, there are multiple flaws that limit their widespread clinical use, including changes in beta-cell function with the development of diabetes (which alters the sensitivity of the tests), normal physiologic fluctuation in insulin levels, and the lack of a standardized universal insulin assay.

Other consensus conferences also recommended against screening for insulin resistance in both the general population and in high-risk populations because of these concerns and concerns regarding the value of these tests to predict clinical events (56). Instead, criteria have been developed for defining a metabolic syndrome, which includes components associated with the insulin resistance syndrome, including centripetal obesity, hypertension, fasting hyperglycemia, and dyslipidemia (Table 3) (57).

Other groups have recommended adding an oral glucose tolerance test (OGTT) to these fasting blood tests to evaluate

the 2-hour glucose level after a 75-g oral glucose challenge for glucose intolerance (WHO criteria, impaired glucose tolerance [IGT] >140 mg/dL to 199 mg/dL) (58, 59). IGT has long been recognized as a major risk factor for diabetes (60), and recent studies have shown that progression to diabetes in individuals with IGT can be delayed by lifestyle changes and pharmacological intervention (61, 62). Additionally, IGT identifies individuals at risk for excess mortality, especially women (63, 64). Given the high prevalence of IGT and type 2 diabetes as diagnosed by the OGTT among obese women with PCOS, it is prudent to screen obese women ($BMI >27 \text{ kg/m}^2$) with PCOS with an OGTT (6, 65). Further studies of the prevalence of features of the metabolic syndrome are necessary in both lean and obese women with PCOS.

Currently, there are scant data to indicate that markers of insulin resistance predict responses to treatment (3, 39, 66). Therefore, the role of these markers in the diagnosis of PCOS, as well as in selecting specific treatments, is uncertain. Tests of insulin sensitivity are of greatest interest in research studies of [1] the pathophysiology of PCOS, [2] young adolescents with a combined history of low birth weight and excessive postnatal catch-up, [3] mechanisms of response to therapy, and [4] family phenotypes. Further studies to identify predictive factors or early response factors to treatments of PCOS are needed.

Luteinizing Hormone

Both the absolute level of circulating LH as well as its relation to FSH levels are significantly elevated in women with PCOS as compared with controls (67, 68). This is due to an increased amplitude and frequency of LH pulses (69). Elevated LH concentrations (above the 95th percentile of normal) can be observed in approximately 60% of women with PCOS (5, 18), whereas the LH/FSH ratio may be elevated in up to 95% of subjects (68) if women who have recently ovulated are excluded. LH levels may be influenced by the temporal relation to ovulation, which transiently nor-

malizes LH, by BMI (being higher in lean women with PCOS), as well as by the assay system used.

The potential negative actions of LH on human reproduction are highly controversial. Some investigators have suggested that high LH levels could have detrimental effects on oocyte maturity and fertilization (70), as well as result in lower pregnancy and higher miscarriage rates (71). However, other studies have shown no untoward actions of LH on oocyte and embryo quality or on fertilization, implantation, and pregnancy rates (72, 73). Reduction of endogenous LH levels with GnRH agonists also provided conflicting results as some studies have suggested that this maneuver could reduce miscarriage rates (74), while others have questioned this therapeutic effect (75, 76). LH levels or the administration of exogenous LH activity were not found to affect the chances of ovulation or achievement of pregnancy using clomiphene citrate (39, 49) or exogenous gonadotropins (77, 78).

Based on the aforementioned data, the panel felt that measurement of serum LH levels should not be considered necessary for the clinical diagnosis of PCOS. LH levels could be useful as a secondary parameter (especially in lean women with amenorrhea or in research). Additional research is needed to further clarify the clinical relevance of LH in PCOS and the potential effects of LH suppression with GnRH analogs or its enhancement through LH activity administration at different stages of follicular maturation.

Long-Term Health Risks

Women with PCOS have multiple risk factors for diabetes including obesity, a family history of type 2 diabetes, and abnormalities in insulin action (both insulin resistance and beta-cell dysfunction). There is now clear evidence that women with PCOS are at increased (3–7 times) risk of developing type 2 diabetes (6, 7, 11, 79, 80). There are several lines of evidence suggesting that women with PCOS are also at increased risk of cardiovascular disease (81). Insulin-resistant states are associated with greater than normal susceptibility to coronary heart disease, and women with PCOS have evidence of dyslipidemia (82–85) and markers of abnormal vascular function (86–88). However, limited epidemiological studies have shown no direct evidence of an increased incidence of coronary heart disease in middle-aged women with a history of PCOS (although the incidence of stroke is slightly increased) (89).

Women with PCOS are also thought to be at increased risk for endometrial cancer through chronic anovulation with unopposed estrogen exposure of the endometrium. However, epidemiological evidence to support this hypothesis is limited (90).

Currently, no firm conclusions can be drawn, but the following statements represent the consensus view that PCOS is associated with an increased risk of type 2 diabetes:

- The risk is greater in anovulatory women with PCO, in obese subjects, and in those with a family history of type 2 diabetes.
- The risk of cardiovascular disease is uncertain at present (89, 91). Limited epidemiological data have shown no increase in cardiovascular events, but two factors need to be borne in mind: The young age of the cohorts studied so far (around 55 years) and the possibility that unknown factor(s) may be present in PCOS that protect the heart in the face of other risk factors.

More research is required to [1] assess the level of risk, [2] enable identification of patients at risk, [3] provide longitudinal follow-up of PCOS cohorts into their sixties and beyond, and [4] determine the place, timing, and efficacy of interventional measures.

Although many questions remain to be answered, lifestyle changes (diet and exercise) should be strongly encouraged to reduce the risk of both type 2 diabetes and cardiovascular disease (37, 92–95).

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The Role of Life style Modification in Management of Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome is a common endocrine disorder affecting women of reproductive age group characterized by various metabolic and reproductive dysfunctions. There are evidences that environmental toxins play a potential role in disrupting reproductive health. In this review we summarized existing research on a variety of environmental factors involved in the etiology, prevalence and management of polycystic ovary syndrome. Pubmed, PsycINFO and Google Scholar were searched for the reviews and studies from last five years included in this study. All searches were limited to human studies. We concluded that symptoms of polycystic ovary syndrome are reduced with certain dietary supplement, restricted diet and exercise. Health related quality of life along with weight, body hair, infertility, acne score improves well with an intervention of about 24-weeks of lifestyle modification. That is why a healthy lifestyle is usually recommended to improve overall health and fertility.

Key words: Polycystic ovary syndrome, dietary habits and exercise

Introduction

Polycystic ovary syndrome is most common endocrine-metabolic disorders affecting 8% to 13% women of reproductive age group and is associated with ovulatory dysfunction, hyperandrogenism and cardiometabolic risk. Due to sedentary lifestyle and stress incidence of metabolic disorders like PCOS are increasing day by day. Polycystic ovary syndrome is characterized by insulin resistance, elevated circulating leukocytes, and hypothesized to have higher adipose tissue inflammation. The condition is marked by presence of cysts on the ovaries leading to their obstructed functioning. Amenorrhea, infrequent menstruation & anovulation, imbalanced hormonal levels, chronic pelvic pain and irregular bleeding are the common symptoms of Polycystic Ovary Syndrome. Women with polycystic ovary syndrome have higher prevalence of infertility compared with women without PCOS. ‘The overweight-obese women having PCOS appears to have exacerbated reproductive dysfunction and cardio metabolic risk.¹ Early diagnosis and treatment may reduce the risk of long-term complications such as metabolic disorders,

obesity, diabetes, and coronary disease, and malignancies such as breast and endometrial cancer. Obesity worsens the presentation of PCOS and weight management is supposed to be an initial treatment strategy. Khademi 2010 et.al found that ‘Obese PCOS women show more difficulty in losing weight by exercise than lean women with PCOS’.¹ Though this target can be achieved through lifestyle modifications, by incorporating restricted diet, exercise and behavioral interventions. That is why a healthy lifestyle is usually recommended to improve overall health and fertility.

The actual cause of PCOS is unknown but environmental factors such as dietary habits play an important role in prevention and treatment of this syndrome. ‘Weight reduction even of about 5% can improve problems such as insulin resistance, high level of androgens, reproductive system dysfunctions in women with PCOS. Thus, lifestyle modification can be used as therapeutic strategies in these patients’.² Lifestyle intervention may improves secondary reproductive outcome, free androgen index, may reduce weight and BMI. Women inducing lifestyle intervention shows

significant improvement in cardio respiratory fitness and reduces resting heart rate. It may also be used for improvement of health related quality of life and other psychological complications in women with PCOS. This can make enormous difference and relieve symptoms like eating habits, participating in regular physical activity, maintaining healthy weight, reducing androgen level, reducing risk of DM and CVD. ‘Lifestyle intervention helps improving body composition parameters including BMI, waist circumference, waist hip ratio, body fat, total cholesterol, C-reactive protein and peak VO₂ MD’.³ Knowledge about these interventions increases healthy eating, active living, health care satisfaction, feelings and experiences about intervention and health concerns.⁴ Losing just 5-10% of your body weight helps regulating menstrual cycle and improving symptoms of polycystic ovary syndrome. Thirty minutes of moderate to vigorous intensity exercise at least 4 days a week along with healthy diet can help women with PCOS lose weight.

Effect of Exercise on Polycystic Ovary Syndrome

Healthy lifestyle including nutritious and balanced diet, yoga & exercise are found effective in management of polycystic ovary syndrome. Weight loss programs hold promise and efficient hospital or community-based programs may prove beneficial in women with PCOS. Regular exercise also increases quality of life in these women. In overweight and obese women with or without PCOS exercise contributes to lower insulin and free androgen levels which helps restoring hypothalamic-pituitary-gonadal axis regulation of ovulation. The mechanism by which exercise affects ovulation is probably via modulation of hypothalamic-pituitary-gonadal axis. ‘Despite various researches supporting weight loss as primary measure for PCOS management there is lack of studies comparing types of physical activity, intensity and settings. These gaps may be responsible for delaying an efficient and effective use of exercise as a therapeutic modality to treat anovulatory infertility including PCOS. Exercise with or without diet can lead to resumption of ovulation. Regular exercise for 30-60 min is associated with reduced risk of anovulatory infertility’.⁵ Moderate aerobic exercise intervention for more than or equals to a period of three months have favorable effects on various cardio-metabolic risk factors in women with polycystic ovary syndrome.

Some of these factors include total cholesterol level, fasting glucose, waist circumference and waist to-hip ratio, testosterone, sex hormone, C-reactive protein and systolic blood pressure.⁶ Continuous aerobic training and intermittent aerobic training both helps in reduction of anxiety and depression. After approximately four months or sixteen weeks of aerobic training significant reduction in testosterone level are found. ‘CAT significantly increases the total score of Female Sexual Function Index, improves FSFI domains of satisfaction and pain and reduced WHR. Intermittent aerobic training increases total FSFI score and improves desires, excitation, lubrication, orgasm and satisfaction in women with polycystic ovary syndrome’.⁷ Beneficial effects of exercise are found for a range of metabolic, anthropometric and cardio respiratory fitness related outcomes. ‘Short duration and aerobic exercise significantly affects fasting insulin level, total cholesterol, low density cholesterol, and triglycerides. Exercise also improves VO₂ max, waist circumference and body fat percentage’.⁸ Moderate intensity exercise independent of substantial weight loss improves endothelial function in women with PCOS by reducing circulating CD105+MP.⁹ Physical resistance exercise alone can improve hyperandrogenism, reproductive function, and body composition by decreasing visceral fat and increasing lean muscle mass. ‘PRT reduces plasma testosterone and fasting glucose, increased androstenedione concentration and sex hormone binding globulin concentration decreases in women with PCOS’.¹⁰ Regular physical activity is associated with better anthropometric and androgenic profile in women with PCOS. As compared to sedentary women with PCOS active women have lower waist circumference, lipid accumulation product and low androgen levels.¹¹

When compared to oral contraceptives which treat hyperandrogenism and menstrual disturbances structured exercise training program is helpful in effective management of anthropometric measures, insulin sensitivity indexes, lipid profile, cardiopulmonary function, inflammatory marker and frequency of menstrual cycle in women with PCOS.¹² ‘Obese adolescents having PCOS who have experienced childhood trauma can lose weight and acquire its health benefits when intervened with weight loss, mood, and sleep’.¹³ Weight loss, fertility hormones, FSH, prolectin, oestrogen, antral follicle count, baseline anti-mullerian

hormone and adiponectine are significantly correlated with reproductive function. Physical activity changes the level of anti-mullerian hormone and adiponectin. Moderate aerobic exercise for around twelve weeks had significant effect on reproductive functions by modulating adiposity, levels of adiponectine anti-mullerian hormones and fertility hormones. 'Participants who respond to aerobic exercise intervention show significant improvement in reproductive function, with lower baseline anti-mullerian hormone level, weight loss and increased adiponectine level. These women also shows significant improvement in ovarian process and a restoration of menstrual cycle'.¹⁴ Resistance training has beneficial effects on morphology of the ovaries and the glycemic index in women with PCOS. It has good effect on insulin resistance index, improves ovaries volume, body composition indices including weight, body mass index and body fat.¹⁵

Polycystic ovary syndrome is characterized by insulin resistance, elevated circulating leukocytes and more tissue inflammation. In obese individuals aerobic exercise reduces circulating leukocytes and improves insulin sensitivity. Women with polycystic ovary syndrome have higher circulating leukocytes. This condition can be reversed by aerobic exercise and is associated with improvement in insulin sensitivity. WBC is found higher and total adiponectin level is lower in PCOS women performing regular exercises. 'Regular aerobic exercise for four weeks reduces serum leptin; ratio of leptin to high molecular weight adiponectine after eight weeks and significantly increases serum dehydroepiandrosterone sulfate after sixteen weeks'.¹⁶ Exercise may normalize amino acid metabolite in women with PCOS. 'If regular exercise is performed, Leucine, glutamate, methionine, ornithine, phenylalanine, tyrosine and proline in women with PCOS may normalize and become equal to women without PCOS'.¹⁷

'Aerobic exercise increase vagal modulation, decrease sympathetic modulation and increases parasympathetic modulation, decrease resting heart rates and systolic blood pressure irrespective changes in BMI, fasting insulin and testosterone level'.¹⁸ Women with PCOS who meet department of health and human services guidelines for exercise have superior metabolic health parameters. Vigorous exercise is associated with reduced metabolic dysfunctions independent of age,

BMI and total energy expenditure. 'When compared with inactive women and moderate exercisers, it was found that vigorous exercisers had lower body mass index, higher level of HDL and sex hormone binding globulin and reduced prevalence of the metabolic syndrome'.¹⁹ Homeostatic assessment of insulin resistance improves after high intensity interval training, high density lipoprotein increases, endothelial function increases and body fat decrease.²⁰ Progressive aerobic exercise improves health related quality of life, cardio respiratory fitness and cardio metabolic profile of overweight/ obese women with polycystic ovary syndrome. While glancing psychological aspects 'exercise improves following domains of health related quality of life - physical functioning, general health and mental health'.²¹

Effect of Yoga on Polycystic Ovary Syndrome

Women with PCOS also suffer from emotional ill health, anxiety and depression. Medical yoga therapy is emerging as an effective modality in the management of much non-communicable disease. Yoga therapy also addresses psychological morbidity. Yoga has calming effect on the mind and body through balancing sympathetic and parasympathetic nervous system. Lifestyle modification including diet, exercise and weight loss is very important component of management of PCOS. 'Thus yoga results in multiple beneficial effects on neuroendocrine axis and facilitates adoption of healthier lifestyle addressing underlying hyperandrogenemia and insulin resistance in PCOS'.²² Due to disturbance in hypothalamo-pituitary-ovarian axis various symptoms like anxiety, depression, insomnia, loss of concentration, acne, infertility etc. appears in syndrome. It is a psychosomatic disorder too, so it is important to provide psychic and somatic treatment also. Yoga is the complete prescription for the healthy body and mind which deals with the root cause of this disorder i.e., obesity and stress. 'Daily yoga with for thirty minutes with four asans, four pranayam, meditation, and shavasan helps in weight reduction and stress management, thus normalizing hypothalamo-pituitary-ovarian axis and curing polycystic ovary syndrome. Asans like suryanamaskar, paschimottan asan, bhujangasan, shalabhasan etc. helps in weight reduction and toxin exertion from the body. Pranayam and relaxing yoga posture like Shavasana, makarasana etc. helps curing stress'.²³ Yoga and naturopathy therapy

for twelve weeks improves ovarian morphology and anthropometric measurements.²⁴ Regular mindful yoga practice can be used as complementary therapeutic option for women with PCOS. This lowers serum androgen (dehydroepiandrosterone) and free testosterone levels. Improvement occurs even in absence of weight loss and persists even if there is a lapse in practice.²⁵

Dietary Modification and PCOS

Overweight women with PCOS related infertility have eating behaviors inconsistent with achieving a healthy body weight. They have poor dietary intake, particularly related to whole grains, fiber and iron.²⁶ ‘PCOS women consume high glycemic index food items and lower legumes and vegetables’.²⁷ There is high prevalence of overweight status, obesity, and increased visceral fat in these women. Diet quality is negatively associated with obesity. Two of the primary ways diet affect PCOS are weight management and insulin production and resistance. ‘Diet therapy in these patients must reach specific goals such as improving insulin resistance, metabolic and reproductive function. Low-calorie diet can be used to achieve weight loss or maintaining a healthy weight. Diet must focus on limited intake of simple sugars, refined carbohydrates and intake food with low glycemic index, reduction of saturated and trans-fat. Attention must be paid to possible deficiencies of vitamin D, chromium and omega-3 fatty acid’.² Energy restriction and weight loss in PCOS improves ovulation rates, conception, hyperandrogenemia, glucose and insulin level, insulin resistance, and satiety hormones. Diet low in carbohydrate as compared to standard diet has 1-5% significant additional effect to caloric restriction in terms of weight loss.²⁸ Carbohydrates are the main stimulators of insulin release. Dairy products and starches elicit great postprandial insulin secretion than non-starchy vegetables and fruits. ‘Eight week dietary intervention using a low starch/low dairy diet in women with PCOS is effective in reducing weight, BMI, waist circumference, waist to hip ratio, fasting insulin and homeostasis model assessment of Insulin Resistance (HOMA-IR), total testosterone, free testosterone, and ferriman-Gallwey score’.²⁹ High dietary GI and low fibre intake are associated with PCOS.³⁰ Low carbohydrate diet is more beneficial in weight loss, reducing insulin and serum testosterone. ‘This diet when combined with exercise results in weight loss, decreased body fat,

increased insulin sensitivity, improved estradiol and LH: FSH ratio and other reproductive measures’.³¹ Dietary weight loss in adolescent women with polycystic ovary syndrome resulted in significant improvement in menstrual regularity, BMI, waist circumference, and hirsutism score.³² When these women are subjected to an anti-inflammatory hypocaloric diet with physical activity they show significant improvements in body composition, hormones, menstrual cycle, blood pressure, glucose homeostasis, dyslipidemia, C-reactive protein and serum amyloid acid and improved fertility with 12% spontaneous pregnancy rate.³³ A proper low-calorie diet with low glycemic index should be recommended along with PA to improve psychological, reproductive, and cardiovascular parameters for women with polycystic ovary syndrome.

There is currently no standard diet for PCOS. However, a widespread agreement about food which seems to be beneficial for these women are: A) A low glycemic such as whole grains, legumes, nuts, seeds, fruits, starchy vegetables, unprocessed and low carbohydrate good. B) An anti-inflammatory diet such as berries, fish, green leafy vegetables, extra virgin oil etc. C) DASH (dietary approaches to stop hypertension) diet which includes poultry, fruits, vegetables, whole grain, and low fat dairy products. DASH diet reduces hypertension and risk of heart disease. Other foods that can be included in diet are: natural unprocessed food, high fiber food, fatty fish, salmon, spinach, dark red fruit, blue& blackberries cherries, broccoli and cauliflower, dried beans, lentil; healthy fats such as olive oil, avocados, coconut; nuts like walnut, almonds, pistachios; spices like turmeric and cinnamon; and dark chocolate. Food to be avoided is: sugary beverages such as sodas and energy drinks; refined carbohydrates such as pastries, cakes, white processed bread; processed meat etc.

Other beneficial dietary habits are including small frequent meals, consumption at regular times, majority of carbohydrates consumption at lunch time or equally distributed through out the day and drinking plenty of water.

Conclusion

Due to sedentary lifestyle and stress incidence of metabolic disorders like PCOS are increasing

day by day. Early diagnosis and treatment including lifestyle modification may reduce the risk of long-term complications such as metabolic disorders, obesity, diabetes, and coronary disease, and malignancies such as breast and endometrial cancer. Losing just 5-10% of your body weight helps regulating menstrual cycle and improving symptoms of polycystic ovary syndrome. Moderate to vigorous regular physical exercise along with healthy and restricted diet helps these women achieving healthy body weight, normalizing hormonal profile and improving metabolic and reproductive functioning. Including yoga in daily life routine helps in both mental and physical health maintenance. Lifestyle modification is thus an effective measure in improving mental and physical health of women with PCOS.

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RESEARCH ARTICLE

Screening of potential biomarkers for polycystic ovary syndrome and identification of expression and immune characteristics

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Abstract

Background

Polycystic ovary syndrome (PCOS) seriously affects the fertility and health of women of childbearing age. We look forward to finding potential biomarkers for PCOS that can aid clinical diagnosis.

Methods

We acquired PCOS and normal granulosa cell (GC) expression profiles from the Gene Expression Omnibus (GEO) database. After data preprocessing, differentially expressed genes (DEGs) were screened by limma package, and Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis and Gene Set Enrichment Analysis (GSEA) were performed. Recursive feature elimination (RFE) algorithm and the least absolute shrinkage and selection operator (LASSO) Cox regression analysis were used to acquire feature genes as potential biomarkers. Time-dependent receiver operator characteristic curve (ROC curve) and Confusion matrix were used to verify the classification performance of biomarkers. Then, the expression characteristics of biomarkers in PCOS and normal cells were analyzed, and the insulin resistance (IR) score of samples was computed by ssGSEA. Immune characterization of biomarkers was evaluated using MCP counter and single sample gene set enrichment analysis (ssGSEA). Finally, the correlation between biomarkers and the scores of each pathway was assessed.

Results

We acquired 93 DEGs, and the enrichment results indicated that most of DEGs in PCOS group were significantly enriched in immune-related biological pathways. Further screening results indicated that JDP2 and HMOX1 were potential biomarkers. The area under ROC curve (AUC) value and Confusion matrix of the two biomarkers were ideal when separated and combined. In the combination, the training set AUC = 0.929 and the test set AUC = 0.917 indicated good diagnostic performance of the two biomarkers. Both biomarkers were highly expressed in the PCOS group, and both biomarkers, which should be suppressed in

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Abbreviations: BP, biological process; CC, cellular component; DEGs, Differential Expressed Genes; GC, granulosa cell; GEO, Gene Expression Omnibus; GO, Gene Ontology; GSEA, Gene Set Enrichment Analysis; HMOX1, Heme Oxygenase-1; IR, insulin resistance; JDP2, Jun Dimerization Protein 2; KEGG, Kyoto Encyclopedia of Genes and Genomes; MF, molecular function; PCOS, polycystic ovary syndrome; RFE, Recursive feature elimination; ROC, Receiver Operating Characteristic; ssGSEA, Single sample gene set enrichment analysis.

the preovulation phase, were elevated in PCOS tissues. The IR score of PCOS group was higher, and the expression of JDP2 and HMOX1 showed a significant positive correlation with IR score. Most immune cell scores and immune infiltration results were significantly higher in PCOS. Comprehensive analysis indicated that the two biomarkers had strong correlation with immune-related pathways.

Conclusion

We acquired two potential biomarkers, JDP2 and HMOX1. We found that they were highly expressed in the PCOS and had a strong positive correlation with immune-related pathways.

1 Introduction

Polycystic ovary syndrome (PCOS) is a widespread disorder of endocrine and metabolic abnormalities that affects up to 15% of women of adolescent and gestational age [1]. PCOS can lead to abnormalities in the female reproductive system and immune system, and the clinical manifestations are generally irregular menstruation and even amenorrhea, excessive male hormones, polycystic ovary morphology [2]. Severe PCOS can lead to insulin resistance (IR), female anovulatory infertility, pathological obesity, autoimmune diseases, local or whole body inflammation and many other diseases [3, 4]. The specific causes of PCOS are complex and multi-systemic, lack of targeted treatment, different diagnostic criteria and methods, and need to be adjusted according to different clinical symptoms [5]. In addition, it has been shown that follicular excess and increased size of the ovaries in PCOS are associated with insulin resistance (IR) and that the number of follicles may also be a predictor of IR [6]. However, the pathogenesis of PCOS is not yet perfect, and there are many hypotheses about different pathogenesis factors, such as chronic low-grade inflammation, genetic factors, lifestyle, post-translational modification mechanism of PCOS, and ovarian autophagy mechanism [7–9].

Ovarian granulosa cells (GC) are the main constituent cells of follicles, which can divide and differentiate in different degrees with the growth of follicles, and also play an important role in hormone secretion [10]. Abnormalities in GC can lead to ovary-related diseases, such as a deficiency of Rpg5 (an autophagy protein) in GC that can lead to premature ovarian failure [11]. Inflammation caused by high levels of male hormones can also lead to GC pyroptosis, causing ovarian function decline and tissue fibrosis [12]. The abnormal communication of oocyte and follicular cells and the damage of GC may be the key to PCOS, such as the damage of transregional projection in communication [13]. Therefore, understanding the abnormal mechanism of GC is very important for the study of PCOS.

The purpose of this study was to search for potential biomarkers of PCOS and explore the association between biomarkers and immune status in PCOS. In this research, Recursive Feature Elimination (RFE) algorithm was used for selection of feature gene. The prediction strength and practicability of this algorithm are relatively good, and it has been used many times in the screening of biomarkers for different diseases, such as chronic obstructive pulmonary disease, keloid disorder, and triple negative breast cancer [14–16].

2 Material and methods

2.1 Data sources and preprocessing

(1) Data sources. Granulosa cell expression profiles of PCOS were acquired from Gene Expression Omnibus (GEO) database: GSE137684, GSE34526, GSE138518, GSE168404,

Table 1. Information of datasets.

dataset	Platforms	PCOS	Control	Experiment type
GSE137684	GPL17077	8	4	array
GSE34526	GPL570	7	3	array
GSE138518	GPL11154	3	3	high throughput sequencing
GSE168404	GPL16791	5	5	high throughput sequencing
GSE155489	GPL20795	4	4	high throughput sequencing

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GSE155489 (Table 1) [17]. RNA-Seq expression profiles (GSE107746) of granulosa cells at five follicular development stages were acquired from GEO database.

(2) Data preprocessing. GSE137684 and GSE34526 (microarray) were combined as a training set. GSE138518, GSE168404, and GSE155489 (RNA-Seq) were combined as a test set, and the batch effect was removed using the ComBat function of the sva package (Figure S1) [18]. RNA-Seq expression profiles were converted into TPM format data.

2.2 Identification and enrichment of differentially expressed genes (DEGs)

We used limma package to identify DEGs, and the threshold was set to $p < 0.05$ and $|\log_{2}FC| > \log_{2}(1.5)$ [19]. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed on all upregulated DEGs in PCOS using the R software clusterProfiler package to assess their pathway processes [20], biological processes (BP), cellular components (CC), and molecular functions (MF). Gene set enrichment analysis (GSEA) was performed to further assess the enrichment of relevant functional pathways between different groups [21].

2.3 Selection and verification of biomarkers

The recursive feature elimination (RFE) algorithm of the caret package is used for characteristic gene selection and 10x cross-validation [22]. The key parameters we chose are: functions = "rfFuncs", method = "cv", number = 10. We then used LASSO regression of the glmnet package for characteristic gene screening [23]. The parameters chosen for the LASSO regression analysis were: nfolds = 5, family = 'binomial', type. Measure = 'deviance'. The potential biomarkers were acquired by comprehensive analysis of the two algorithms. To further assess the diagnostic performance of candidate biomarkers, the receiver operating characteristic (ROC) curve and its area under the curve (AUC), accuracy, sensitivity, and specificity were computed using the R software timeROC package and confusion matrix [24]. The gene of Insulin secretion pathway was downloaded from KEGG, and the IR score of each sample was computed by ssGSEA method [25].

2.4 Analysis of immune infiltration and biological pathways

The MCP counter algorithm was used to estimate the relative proportion of 10 kinds of immune cells [26]. MCP counter is an algorithm that allows stable quantification of the absolute abundance of 2 stromal and 8 immune cell populations in heterogeneous tissues from transcriptomic data [27]. The infiltration of 28 immune cells was represented by an enrichment score, which was computed using a single sample gene set enrichment analysis (ssGSEA) of the GSVA package [21]. We acquired the ssGSEA scores of each sample in the HALLMARK Pathway, and computed the correlation between the biomarkers and the scores of each pathway. In addition, we obtained 103 immunomodulation-related genes based on previous

studies and evaluated the relationship between PCOS-related genes and these genes using the spearman method [28].

2.5 Statistical analysis

The difference between the two groups was tested by Wilcoxon rank sum test [29]. Kruskal-Wallis test was used for the difference between the three groups and more [30]. Correlation analysis was computed using pearson method [31]. The P less than 0.05 is defined as a significant difference. Notably, * means p-value less than 0.05; ** means p-value less than 0.01; *** means p-value less than 0.001, and **** means p-value less than 0.0001. ns means there is no significant difference between two groups.

3 Results

3.1 Acquisition and enrichment analysis of DEGs

DEGs in PCOS group and normal control group were identified in microarray cohort and RNA-Seq cohort. A total of 1044 up-regulated genes and 695 and down-regulated genes were acquired in the microarray cohort (Fig 1A). A total of 464 up-regulated genes and 103 down-regulated genes were acquired in the RNA-Seq cohort (Fig 1B). Cross analysis between the two cohorts revealed 93 common DEGs (Fig 1C).

By KEGG enrichment analysis, Tuberculosis, Epstein-Barr virus infection, Phagosome and other pathway processes were found to be significant. Neutrophil activation, neutrophil activation involved in immune response, neutrophil degranulation, neutrophil mediated immunity is a process with significant enrichment in BP. Secretory granule membrane was the most significantly enriched component in CC. Actin binding and GTPase binding were the two most enriched functions in MF. (Fig 1D). These results suggest that PCOS is primarily associated with immune-related pathways and biological functions in patients. In addition, GSEA analysis indicated that the enriched gene set was closely related to antigen processing and presentation, B cell receptor signaling pathway, and neutrophil-mediated immunity in the PCOS group (Fig 2A and 2C). Metabolism-related pathway activity was significantly higher in the normal control group (Fig 2B).

3.2 Screening and validation of biomarkers

RFE and LASSO regression were used to screen 93 differential genes. Three genes were acquired by RFE algorithm: JDP2, HMOX1 and BNIP3 (Fig 3A). Nine genes were acquired by LASSO regression: TP53I11, MXRA8, JDP2, CDH3, STC1, HMOX1, COLQ, LTBP1 and LGMN (Fig 3B and 3C). JDP2 and HMOX1 are the common genes acquired by the two algorithms.

ROC analysis indicated that JDP2 and HMOX1 were of high value in distinguishing PCOS from normal samples, and the AUC values of the training set and the test set were ideal (Fig 3D and 3G). The ROC curve after the combination of the two genes still had a high AUC value, with the training set AUC = 0.929 and the test set AUC = 0.917 (Fig 3E and 3H). Confusion matrix results showed that the Sensitivity of the training set and the test set were both greater than 0.8, and the Accuracy was greater than 0.9. In addition, we demonstrated using PCA analysis that JDP2 and HMOX1 were able to distinguish between PCOS samples and normal samples (S1 Fig). These results indicating that the two biomarkers identified had good classification performance (Fig 3F and 3I).

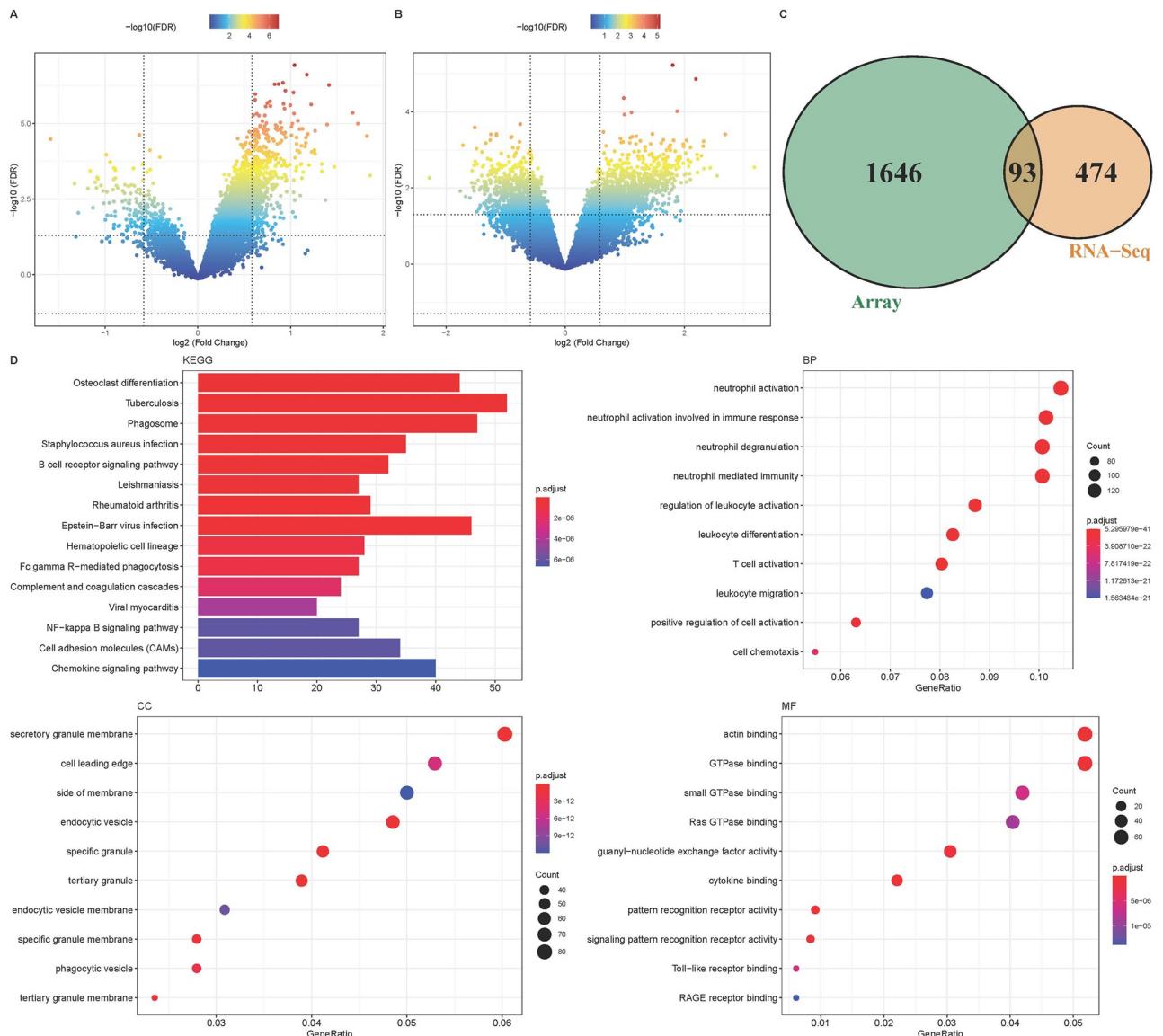


Fig 1. Acquisition and enrichment analysis of DEGs. A: PCOS data of microarray and DEGs volcano map of control group; B: PCOS data of the RNA-Seq cohort and DEGs volcano map of the control group; C: 93 common differential genes in the two datasets; D: GO and KEGG enrichment analysis of up-regulated genes in all PCOS data.

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3.3 Analysis of expression of two biomarkers

Next, we explored the differences in the expression of two genes in PCOS and normal controls. In both the training set and the test set, JDP2 and HMOX1 showed high expression in the PCOS group, $P < 0.001$ (Fig 4A and 4B). At the same time, the specific expression of markers at different developmental stages was explored. Here, their expression in granulosa cells at different follicular development stages was compared by dataset GSE107746. The results indicated that JDP2 and HMOX1, which should be inhibited during the pre-ovulation phase, were elevated in PCOS tissues, suggesting that high levels of JDP2 and HMOX1 expression in granulosa cells may also play an important role in follicular development in PCOS (Fig 4C).

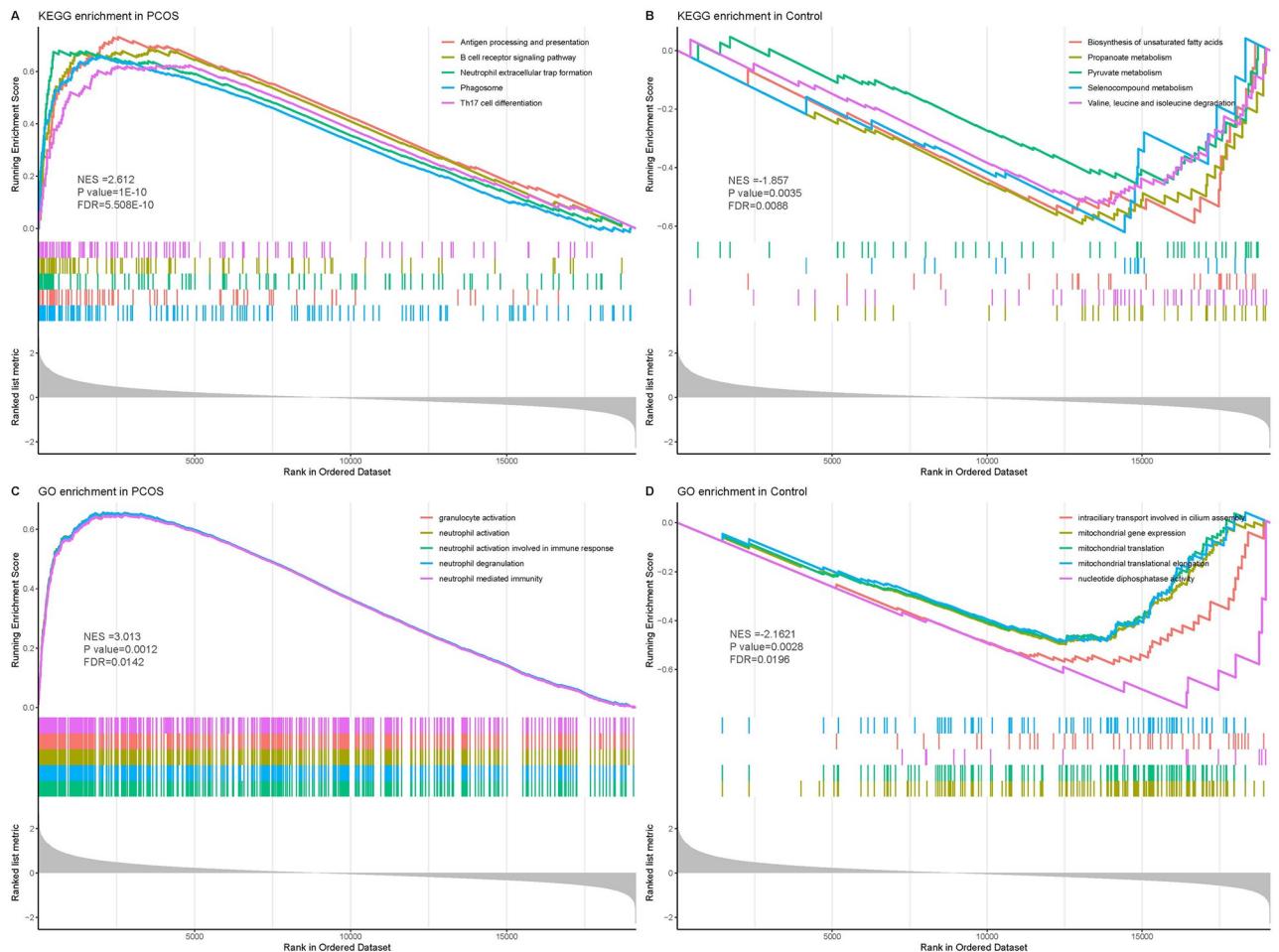


Fig 2. GSEA analysis in PCOS group and control group. A, C: GSEA showed immune signaling pathways and biological processes in the PCOS group; B, D: The 5 pathways most associated with the control group.

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Insulin resistance (IR) plays an important role in the development of PCOS, and the IR score for each sample was computed using the ssGSEA method. The results indicated that PCOS had a higher IR score (Fig 4D). The expressions of JDP2 and HMOX1 showed a significant positive correlation with IR score, and the correlation of HMOX1 was stronger, $P = 0.00076$ (Fig 4E). These results demonstrate the presence of higher levels of insulin resistance in PCOS patients and that patients with higher IR scores will have high expression of JDP2 and HMOX1.

3.4 Relationship of biomarkers to immune infiltration and biological pathways

We compared 28 kinds of immune cell scores between PCOS and normal control samples, and the results indicated that 21 kinds of immune cell scores were significantly higher in PCOS (Fig 5A, S1 Table). The immune infiltration results acquired by MCP Counter algorithm are consistent with the above, and the scores of B lineage, Monocytic lineage, and Neutrophils are higher than those of PCOS (Fig 5B). Correlation analysis was performed to assess the relationship between biomarkers and infiltrating immune cells. JDP2 showed significant positive

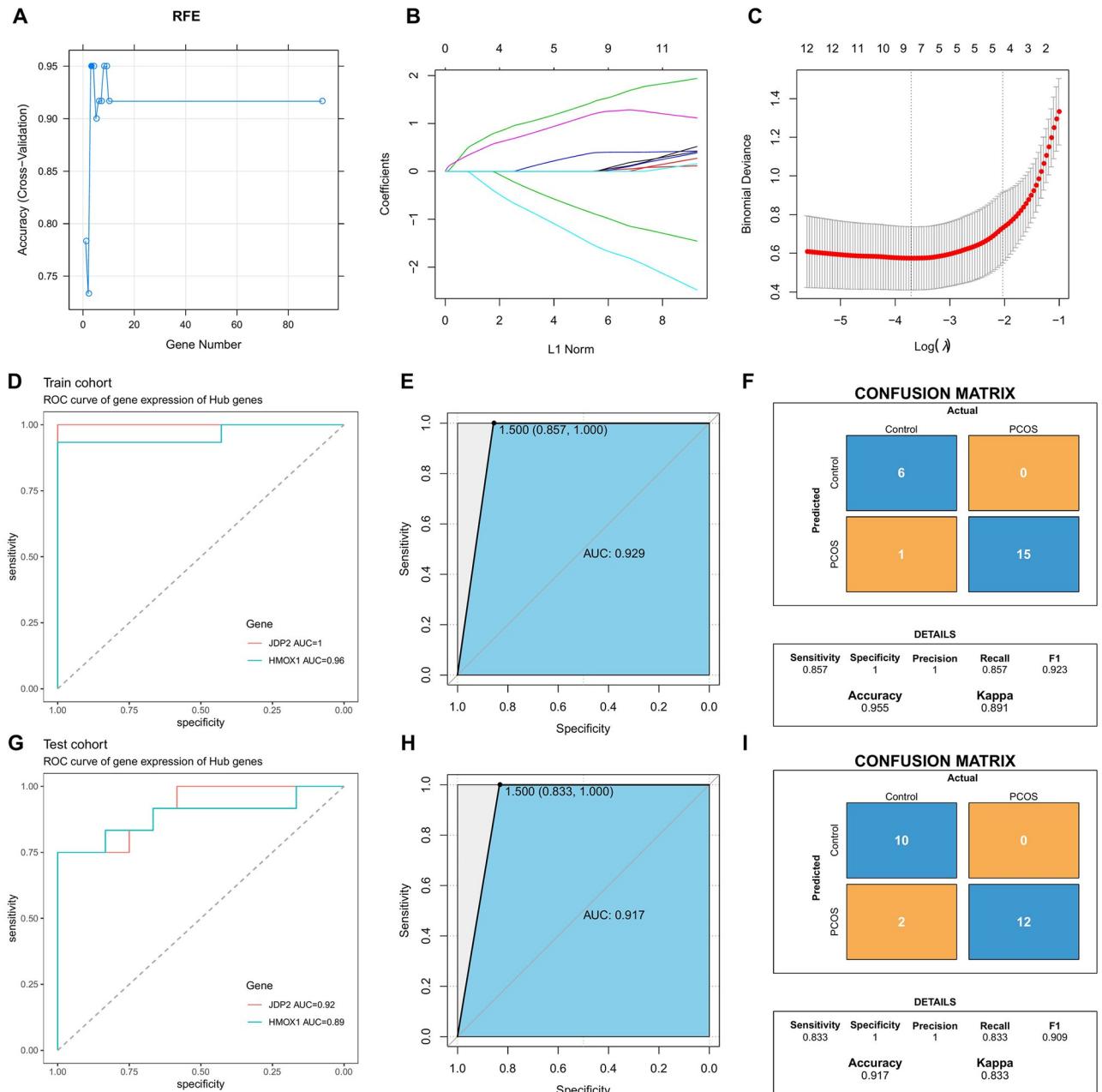


Fig 3. Screening and validation of biomarkers. A: Screening biomarkers based on RFE algorithm; B, C: Characteristic gene selection by LASSO regression; D: ROC curve of JDP2 and HMOX1 in training set; E: ROC curve of the training set combination JDP2 and HMOX1; F: Training set model performance evaluation; G: ROC curve of JDP2 and HMOX1 in test set; H: ROC curve of the test set combination JDP2 and HMOX1; I: Test set model performance evaluation.

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correlation with T cells and cytotoxic lymphocytes, with P values less than 0.05 (Fig 5C). HMOX1 showed significant positive correlation with monocytes and myeloid dendritic cells. The maximum value of P is 0.036 (Fig 5D). In addition, we further explored the relationship of PCOS-related genes with chemokine-related genes, immunoinhibitor-related genes, immunostimulator-related genes, MHC-related genes and receptor-related genes. As shown in S2

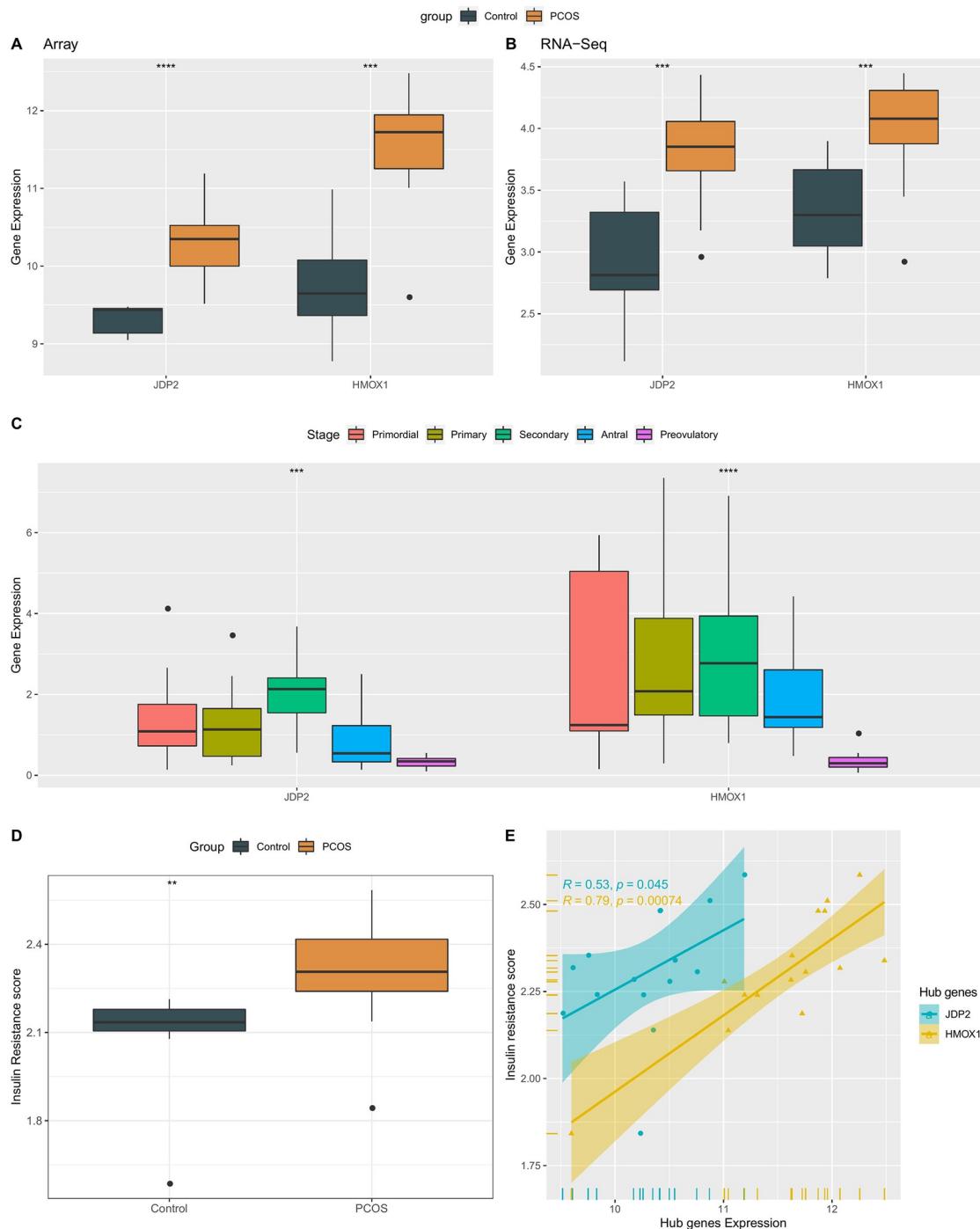


Fig 4. Analysis of expression of two biomarkers. A: The expression of JDP2 and HMOX1 in the training set; B: The expression of JDP2 and HMOX1 in the test set; C: Expression of JDP2 and HMOX1 in granulosa cells at different follicular development stages; D: The difference of IR score between PCOS and normal control group; E: JDP2 and HMOX1 were correlated with IR scores.

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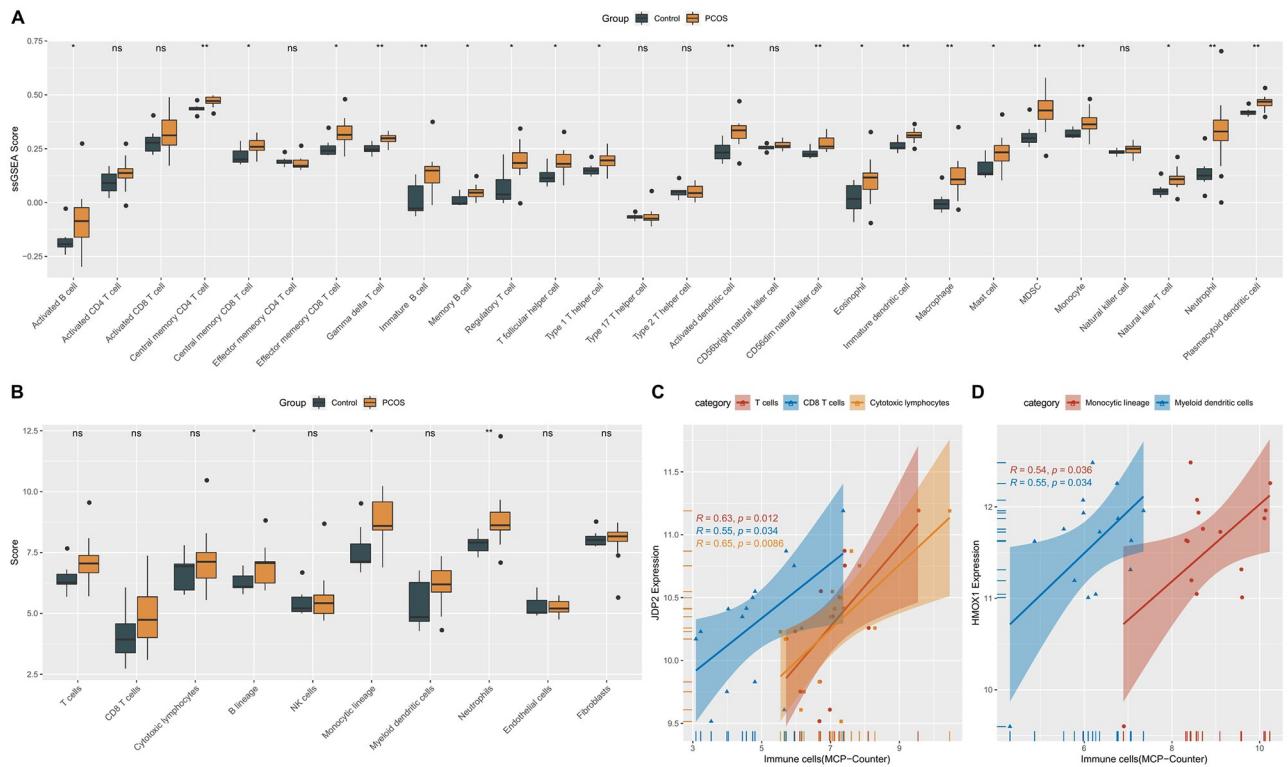


Fig 5. Association of biomarkers with immune infiltration. A: The immune scores between PCOS and control group were compared by ssGSEA method. B: MCP Counter method was used to compare the immune scores between PCOS and control group. C: The correlation between JDP2 and immune cells; D: Correlation between HMOX1 and immune cells.

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Fig, we found that PCOS-associated genes were significantly associated with most of the immunomodulatory genes, such as CCL4, CXCL17, CSF1R, CD48, IL6R, HLA, CCR1 and CCR5.

We computed the ssGSEA score of each sample in the HALLMARK Pathway, and computed the correlation between JDP2 and HMOX1 and the score of each pathway, respectively. In JDP2, INTERFERON ALPHA RESPONSE, INTERFERON GAMMA RESPONSE, ALLOGRAFT REJECTION and COMPLEMENT are four pathways with significant positive correlation (Fig 6A). In HMOX1, REACTIVE OXYGEN SPECIES PATHWAY, IL2 STAT5 SIGNALING, PI3K AKT MTOR SIGNALING, and IL6 JAK STAT3 SIGNALING and COMPLEMENT are the four pathways with significant positive correlation (Fig 6B). Comprehensive analysis indicated that the two gene organisms had strong correlation with immune-related pathways.

4 Discussion

PCOS is a common endocrine disorder in women [32]. Women with PCOS are often associated with a range of metabolic dysfunctions, including insulin resistance and obesity [33, 34]. Currently, more and more studies have demonstrated the identification of genes that characterize the pathogenesis of PCOS and help in the clinical diagnosis and treatment of PCOS. He et al. screened a total of seven important PCOS target genes based on the GEO database and weighted gene co-expression network analysis, including APOC3, ADCY2, C3AR1, HRH2,

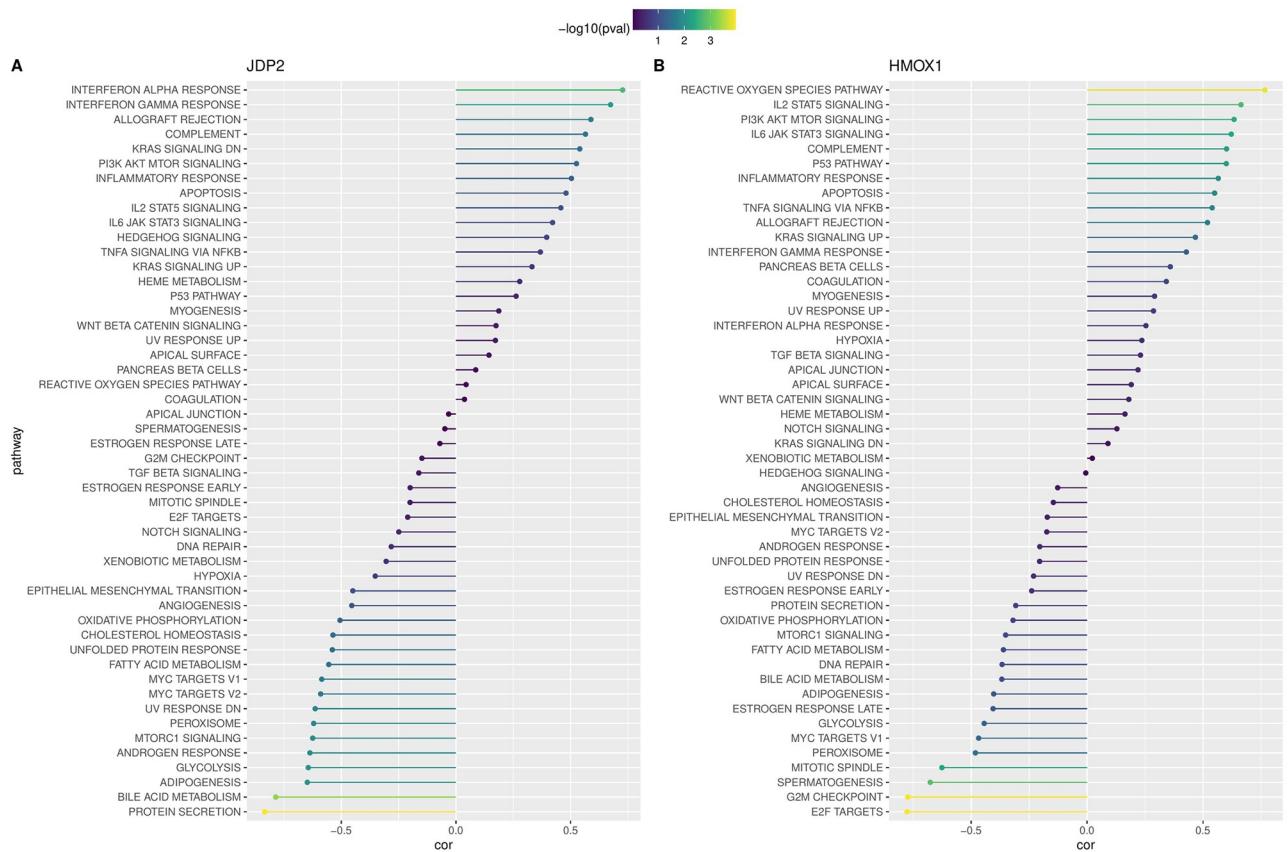


Fig 6. The association of biomarkers with biological pathways. A: The correlation between JDP2 and pathway score; B: The correlation between HMOX1 and pathway score.

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TAAR2, GRIA1, and MLNR [35]. The central gene OGN between PCOS and ovarian cancer was identified by bioinformatics by Zou et al. They showed that OGN regulates hormonal responses in PCOS and ovarian cancer, and found that OGN is strongly associated with desiccated iron anemia [36]. In this study, after multiple screening, we acquired two promising biomarkers JDP2 and HMOX1.Jun Dimerization Protein 2 (JDP2) is a member of the basic leucine zipper transcription factor family, and has diversified functions. It can be used as a cAMP response element and a histone chaperone to participate in and regulate important life processes. Such as cell cycle regulation, cell proliferation, cell apoptosis, can also be used as an oncogene to participate in the control of cell canceration [37]. Shimrit Avraham et al. found that JDP2 may also be involved in the regulation of SDF-1 expression in fibroblasts, a process that occurs frequently in tumor tissues and may inhibit the proliferation of cancer cells [38]. It has been found that CPG16 (a serine/threonine kinase) in pancreatic cells phosphorylates JDP2 by binding to it, reducing the activity of insulin promoters [39]. Notably, Jonak et al. showed that functional disruption of JDP2 can lead to early cessation of reproductive function and that this is associated with elevated follicle-stimulating hormone in women [40].

Heme Oxygenase-1 (HMOX1) can catalyze the degradation of heme, which produces carbon monoxide, iron bivalent ion and biliverdin to prevent ischemic injury and other diseases [41]. Overexpression of HMOX1 may increase the content of iron ions, resulting in ferroptosis of cardiomyocytes, and eventually induce cardiomyopathy [42]. HMOX1, found in another

infertility disorder, endometriosis, may play a key role in embryonic ferroptosis, including stabilizing mitochondria to function properly to stop ferroptosis [43, 44]. Maowei Ni et al. found in ovarian cancer that co-treatment with Shikonin and cisplatin may increase HMOX1 expression levels and help induce ferroptosis in cancer cells [45]. It has also been found that high HMOX1 expression levels are associated with higher macrophage infiltration and lower mitochondrial complex levels [46].

PCOS can lead to complex immune system disorders characterized by chronic low-grade inflammation [47]. According to the results of GO and KEGG enrichment analysis and GSEA enrichment analysis of DEGs, we found that the enrichment degree of immune-related genes and pathways was high in PCOS. The scores of most immune cells and the degree of immune infiltration were significantly higher in the PCOS group. This can lead to severe immune and inflammatory reactions in patients. Inflammatory factors such as interleukin-1 β released by relevant cells may play a pathological role in PCOS [48]. The biomarkers we screened, JDP2 and HMOX1, were highly correlated with immune-related pathways. JDP2 has been shown to be associated with the immune system in several studies. Pan et al. screened nine key genes (including JDP2) most associated with chronic lymphocytic leukemia by ferroptosis-based screening and constructed a risk model. They showed that the immune cell type and immune-related pathways of these patients were correlated with the risk score obtained from this model [49].

In this project, we screened potential biomarkers of PCOS, and identified the expression characteristics and immune characteristics of the biomarkers. The diagnostic ability and accuracy of biomarkers were verified by ROC curve and confusion matrix. We expect that our study will inform the development of clinical diagnosis and treatment strategies for PCOS.

There are still some limitations in this study. First of all, the pathological study on PCOS is still unclear, and we only chose GC expression profile data for analysis. However, the tissues and cells involved in PCOS are diversified, so comprehensive studies on the tissues involved in PCOS are still needed. Secondly, the experimental data came from the GEO database, and the sample size was insufficient. In the future, it is necessary to validate the role of our screened genes, including HMOX1 and JDP2, by performing further in vivo or in vitro validation experiments.

5 Conclusion

93 DEGs were identified in PCOS, and enrichment analysis revealed that the set of immune-related genes was differentially activated in PCOS. Recursive feature elimination (RFE) and LASSO regression were used for further feature selection of these genes, and finally JDP2 and HMOX1 were acquired as candidate biomarkers for PCOS.

Supporting information

S1 Fig. PCA analysis of JDP2 and HMOX1 distinguishing between PCOS and normal samples. JDP2 and HMOX1 could distinguish between PCOS (A) and normal (B) samples in both the training and validation cohorts.

(PDF)

S2 Fig. Relationship between PCOS-related genes and immunomodulation-related genes. Relationship of PCOS-related genes to chemokine (A), immunoinhibitory (B), immunostimulatory (C), MHC (D) and receptor-related genes (E).

(PDF)

S1 Table. Gene set of 28 immune cells.
(CSV)

Author Contributions

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Methodology: Xuanpeng Zhao.

Software: Xuanpeng Zhao.

Visualization: Qingyan Meng.

Writing – original draft: Baoshan Li.

Writing – review & editing: Baoshan Li.

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ORIGINAL ARTICLE

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Self-Administered Questionnaire to Screen for Polycystic Ovarian Syndrome

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a common yet underdiagnosed endocrinopathy with potentially serious sequelae. A screening questionnaire for PCOS can improve early identification and diagnosis.

Objective: The purpose of this study was to test the utility of a self-administered questionnaire to help identify women at risk for PCOS.

Study Design: We recruited women ages 18–50 with and without PCOS as defined by modified Rotterdam criteria to complete a self-administered survey of common PCOS signs and symptoms. The survey included questions regarding menstrual cycle characteristics and hyperandrogenism as measured by images from the Ferriman-Gallwey (FG) scoring system, and by report of depilatory practices.

Results: Fifty-one women with PCOS and 50 women without PCOS participated in this study. Many study participants were current users of hormonal contraceptives making it difficult to discern menstrual cycle characteristics. Hirsutism, defined by a modification of the FG score of ≥ 3 from the upper lip and abdomen based on self-assessments, provided a sensitivity of 76% and specificity of 70%, whereas report of any depilatory practices provided a sensitivity of 71% and specificity of 74%. The combined sensitivity of these measures was 93% with a specificity of 52%. In multivariate logistic regression, women who used depilatory techniques had an adjusted odds ratio (aOR) of PCOS of 6.6 (95% confidence interval [CI] 2.5–17.3, $p=0.0002$). Those with obesity had similar aOR of PCOS (aOR 6.7, 95% CI 2.5–17.9, $p=0.0001$). Addition of other variables did not improve model fit and the net sensitivity and specificity of these two variables did not improve those of depilatory practices and hirsutism.

Conclusions: Self-report of depilatory practices or hirsutism is sensitive for identifying women with PCOS. Given the prevalence of PCOS in reproductive-age women and the potentially serious health sequelae, it would be worthwhile to include questions about terminal hair growth and depilatory practices when providing general medical care to reproductive-age women to determine if further testing and screening for PCOS are indicated. This tool may also be helpful in populations where complete diagnostic evaluation may not be feasible.

Keywords: depilatory; hyperandrogenism; polycystic ovary syndrome

Introduction

Polycystic Ovarian Syndrome (PCOS) is the most common endocrinopathy affecting reproductive-age women, with a prevalence ranging from 6% to 20%.^{1,2} PCOS is likely underdiagnosed, due, in part, to nonuni-

form diagnostic criteria, health care provider unfamiliarity, and diversity of PCOS phenotypes.^{3–5} In addition, many women may not recognize that they have the condition and not seek appropriate evaluation and treatment. Moreover, all current diagnostic criteria require

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extensive diagnostic evaluation to exclude multiple conditions with overlapping presentation complicating both clinical diagnosis and identification of cases in large population-based research studies in which ruling out exclusion diagnoses may not be feasible.

Between 30% and 70% of women with PCOS are obese,^{6,7} and PCOS has been associated with type 2 diabetes,^{8,9} hypertension,¹⁰ cardiovascular disease,^{9–11} anxiety,^{12,13} depression,^{13–15} infertility,¹⁶ and endometrial cancer.¹⁷ PCOS is associated with obstetrical risks, including gestational diabetes and preeclampsia.^{18–20}

Studies have also demonstrated increased risk for children born to mothers with PCOS, including prematurity,^{18–20} neonatal intensive care unit admissions,¹⁹ attention-deficit hyperactivity disorder, and autism spectrum disorder.¹³ However, a study by Dokras et al. showed that physicians are often unaware of these health risks and cannot identify the appropriate diagnostic criteria for PCOS. This is more prevalent for general gynecologists and those with fewer patients with PCOS.²¹ Indeed, a large retrospective study found that there was a lower prevalence of PCOS in primary care clinics than in community samples, suggesting underdiagnosis despite suggestive symptoms.²² Given the long-term sequelae associated with PCOS, it is important to optimize the accuracy and frequency of diagnosis through screening and referral to appropriate specialists.

To simplify clinical definitions of hirsutism, previous studies have examined the utility of using only specific portions of Ferriman-Gallwey (FG) index as predictors of hirsutism. In 2000, Knochenhauer et al. examined 695 hyperandrogenic women and found that a hair growth score ≥ 2 on the chin and lower abdomen was a highly sensitive predictor for hirsutism.²³ Examining almost 2000 women, Cook et al. found that a hair growth score of the chin, lower abdomen, and upper abdomen ≥ 3 was able to accurately discriminate between hirsute and non-hirsute women at the same level as a modified FG score of >7 .²⁴ These simplifications of the FG index would render clinical evaluations less invasive. However, they also would allow for easier self-evaluation.

In addition, a questionnaire that identifies women who should undergo diagnostic workup for PCOS could reduce the number of women who go undiagnosed and untreated. Furthermore, a questionnaire for identifying PCOS would be useful in epidemiological studies of female reproductive health as such a questionnaire could be administered to large popula-

tions of women without requiring expensive visits and blood work to diagnose the condition.

The goal of this study is to utilize simplifications of the FG index to evaluate the efficacy of a self-administered questionnaire in distinguishing women at risk of PCOS.

Methods

Participants subjects

One hundred and one women 18–50 years of age were enrolled in St. Louis, MO, based on PCOS status. Fifty participants were recruited from the PCOS clinic at Washington University School of Medicine and had been previously diagnosed with PCOS, as defined by the modified Rotterdam criteria, including two of the following three features: clinical or biochemical signs of hyperandrogenism, polycystic appearing ovaries on ultrasound, and/or oligo-ovulation or anovulation.²⁵ The remaining 51 participants were women who had never been diagnosed with PCOS and were recruited from the Washington University School of Medicine infertility clinic, local gynecology offices, and the community through a research registry.

For inclusion, confirmation of PCOS diagnosis was made through medical chart review. At the time of enrollment, women were informed that the purpose of the study was to help develop a screening questionnaire for PCOS. Exclusion criteria included inability to provide informed consent and non-English speakers. This study was approved by the Washington University Human Research Protection Office (IRB no. 201510026).

Survey

Participants meeting study inclusion requirements were asked to complete a survey, which contained questions pertaining to the most common symptoms of PCOS. In addition, they were asked information about age, race, ethnicity, height, and weight if a current body mass index (BMI) was not available in the medical record.^{10,26} Survey responses were entered and stored on REDCap.²⁷

Menstrual cycle characteristics. Women were asked to characterize their menstrual cycle length and regularity and use of contraceptive methods, including all forms of hormonal contraception or long-acting reversible contraceptives. Women using these forms of contraception ($n=53$) and women who had been pregnant in the previous 6 months ($n=4$) were excluded from analyses of cycle pattern.



Symptoms of hyperandrogenism. Women were asked about the presence of acne in the last 3 months. They were able to choose “no acne,” “1–4 pimples,” and “5 or more pimples” on cheeks, chin, and forehead. Acne severity was defined as “no acne,” “physiological acne,” or “clinical acne,” respectively, based on modified definitions from Poli et al.²⁸

Women were asked whether they had ever used laser hair removal “in body parts other than bikini line, legs, or underarms.” They were also asked whether they had ever shaved, waxed, or bleached hair outside the previously mentioned areas. In addition, they were presented with images from the FG index to rate terminal hair growth in different body regions. Each region contained five images, the four original FG images as well as an FG image modified terminal hair to signify “no hair growth” (Fig. 1). Women selected the image corresponding to the extent of their terminal hair growth in the six body regions from the nine regions in the modified FG scale that are easiest to self-assess and most strongly associated with hirsutism: upper lip, chin, chest, upper and lower abdomen, and thighs.^{23,29} Hirsutism was defined by the simplified FG (sFG) score, or the sum of individual scores of the upper lip, lower abdomen, and upper abdomen. If the total sFG score was greater or equal to 3, the woman was considered to have hirsutism.²⁴

Statistical analysis

Chi-square, Fisher's exact, and Wilcoxon rank-sum tests were used to compare cases and controls, when appropriate. The sensitivity and specificity for sFG, individual body regions,²³ and depilatory practices in identifying PCOS were calculated. To evaluate the use of multiple screening questions concurrently, net sensitivity and specificity were calculated for hirsutism and use of depilatory practices. Net sensitivity and specificity were calculated for the combined body regions of the lower abdomen and chin as described in Knochenhauer et al.²³ To calculate the positive and negative predictive values of questions in the questionnaire, prevalence of hirsutism in PCOS was defined as 70%³⁰ and prevalence of PCOS in the population was defined as 5%–15%.⁵

To evaluate the merit of including multiple variables in screening, we performed a stepwise multiple logistic regression, including the following characteristics: obesity, as defined by BMI $\geq 30 \text{ kg/m}^2$, use of depilatory practices, hirsutism as defined by sFG, and presence of clinical acne.

For all analyses, $p < 0.05$ was considered statistically significant. SAS Version 9.4 (SAS Institute, Inc., Cary, NC) was used for all analyses.

Results

Fifty-one women with PCOS and 50 women without PCOS were enrolled in the study. There were no significant differences in age or contraceptive use between groups (Table 1). The majority of women with PCOS identified as white, whereas women without PCOS were more heterogeneous; however, this difference was not statistically significant. Women with PCOS had a median BMI of 32 kg/m^2 , and 67% were obese. The median average BMI for women without PCOS was significantly lower at 25 kg/m^2 ($p < 0.0001$), and only 22% were obese.

Women with PCOS were more likely to have clinical acne than women without PCOS and were more likely to use depilatory techniques to remove terminal hair growth. When examining only women who were not using hormonal contraception ($n = 24$ PCOS and 24 non-PCOS women), women with PCOS were more likely to have menstrual irregularity (55% vs. 10%; $p = 0.003$). The majority (73%) of women with PCOS met criteria for hirsutism by sFG ≥ 3 . For women with PCOS, 89% of those using combined oral contraceptives (COCs) and 63% not using oral contraceptives (OCPs) met criteria for hirsutism, but this difference was not statistically significant.

While a high percentage (28%) of non-PCOS women met criteria for hirsutism, the average total sFG was significantly higher in women with PCOS than in controls ($p < 0.0001$). Women with PCOS had significantly higher FG scores for terminal hair growth based on the modified FG images than non-PCOS women for all regions, except chest and upper abdomen. However, the median score for these regions for both cases and controls was low (Table 1).

The sensitivity and specificity of using sFG ≥ 3 for identifying PCOS were 76% and 70%, respectively (Table 2). Participating in any depilatory practice had similar sensitivities and specificities. When these two screening questions were combined, the net sensitivity was high at 93%, but specificity decreased to 52%. For regional terminal hair score of ≥ 1 , sensitivities ranged from 47% to 92% and specificities from 36% to 68% (Table 2). As expected, as score cutoffs increased, sensitivities decreased and specificities increased (≥ 3 and ≥ 4 , not shown). Net sensitivity and specificity for the lower abdomen and chin scores of ≥ 1 were 98% and



Upper lip		Chin			
No Hair	A few hairs at outer lip margin	A small mustache at outer lip margin	A mustache extending halfway from the outer margin	No Hair	A few scattered hairs
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chest		Upper abdomen			
No hair	Hair around the nipples	Hair around the nipples and in the middle of the chest	Complete cover	No hair	A few hairs in the middle
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lower abdomen		Thighs			
No hair	A few hairs in the middle	Streak of hair in the middle	Band of hair in the middle	Inverted V-shape growth of hair over the pubic area	No hair
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

FIG. 1. Ferriman-Gallwey images³⁹ used for participant selection.



Table 1. Demographic and clinical characteristics by polycystic ovary syndrome diagnosis

Characteristic	PCOS (51)	No PCOS (50)	Unadjusted p-value
Age	28 (25–33)	28.5 (23–35)	0.83
BMI	32 (28–39)	25 (22–30)	<0.0001
Race			
White	50 (98)	40 (87) ^a	0.08
African American	1 (2)	4 (9)	
Other	0 (0)	2 (4)	
Menstrual pattern irregularity ^b	11 (55)	2 (10)	0.003
Contraception	26 (50)	26 (50)	0.92
COC	19 (37)	12 (24)	0.15
Depilatory practice			
Electrolysis	8 (16)	5 (10)	0.37
Shave, wax, bleach	38 (75)	14 (28)	<0.0001
Clinical acne ^c	19 (37)	10 (20)	0.06
Hair			
Total sFG	4 (3–6)	1 (0–3)	<0.0001
Hirsutism by sFG	37 (76)	14 (28)	<0.0001
Locations			
Chin	1 (1–2)	0 (0–1)	<0.0001
Upper lip	2 (1–3)	1 (0–1)	<0.0001
Chest	0 (0–1)	0 (0–1)	0.12
Upper abdomen	0 (0–1)	0 (0–1)	0.16
Lower abdomen	1 (2–3)	1 (0–1)	<0.0001
Thigh	2 (1–3)	1 (0–2)	0.009

^aFour participants had unknown race.

^bFor patients not using hormonal contraception or intrauterine devices.

^cClinical acne defined as 5+ pustules on chin, cheeks, and forehead within previous 3 months.

BMI, body mass index; COCs, combined oral contraceptive pills; PCOS, polycystic ovary syndrome; sFG, simplified Ferriman-Gallwey Categorical data represented as n (%), and continuous and integer variables represented as median (interquartile range).

24%, respectively. However, increasing the score to ≥ 2 increased specificity to 74%, whereas sensitivity only decreased to 79%.

Positive predictive value (PPV) for identifying PCOS using sFG ≥ 3 ranged from 0.11 to 0.31 (Table 3). PPV ranges were similar for depilatory practices. The PPV for parallel use of both questions was higher at 0.14–0.36. Negative predictive values for these metrics were significantly higher.

Together, obesity and using depilatory practices were significant predictors for PCOS diagnosis (Table 4). Inclusion of additional variables, such as hirsutism, presence of clinical acne, or menstrual irregularity in those not on contraceptives, did not improve the fit of the model significantly. R^2 of the model was 0.41 and c-statistic was 0.81. Given that over 50% of women in our cohort were using contraception, analyses examining menstrual irregularity were not performed. Given the significance of these two predictors to the model,

Table 2. Sensitivity and specificity for polycystic ovary syndrome diagnosis based on regional terminal hair growth and depilatory practices

	Sensitivity (%)	Specificity (%)
Hirsutism ^a	76	70
Depilatory practices ^b	71	74
Hirsutism and depilatory practices combined ^c	93	52
Obesity	76	70
Obesity and depilatory practices combined ^d	93	52
Chin		
≥ 1	78	58
≥ 2	47	92
Lower abdomen		
≥ 1	92	41
≥ 2	61	80
Combined regions ^e		
≥ 1	98	24
≥ 2	79	74
Upper lip		
≥ 1	88	36
≥ 2	53	78
Upper abdomen		
≥ 1	47	69
≥ 2	22	83
Chest		
≥ 1	48	64
≥ 2	18	94
Thighs		
≥ 1	88	36
≥ 2	53	66

^aHirsutism is defined as sFG ≥ 3 .

^bDepilatory practices include shaving, waxing, or bleaching hair, or use of electrolysis on the face, chest, or abdomen.

^cNet sensitivity and specificity for hirsutism or depilatory practices.

^dNet sensitivity and specificity for obesity and depilatory practices.

^eNet sensitivity and specificity for combined body regions lower abdomen and chin.

sFG, simplified Ferriman-Gallwey index.

we also calculated the net sensitivity (93%) and specificity (52%) of obesity and the use of depilatory practices—the same as for depilatory practices and hirsutism by sFG. Therefore, the combinations of these questions did not improve upon the PPV and negative predictive value for hirsutism and depilatory practices.

Discussion

Principle findings

We found that asking women about their male-patterned hair growth and depilation practices through a self-administered questionnaire has high sensitivity and moderate specificity in predicting PCOS diagnosis, making questions regarding these practices ideal for PCOS screening.



Table 3. Positive and negative predictive values for hirsutism, depilatory practices, and combined lower abdomen and chin regions by varying polycystic ovary syndrome prevalence

Screening	Prevalence (%)	PPV	NPV
Hirsutism ^a	5	0.12	0.98
	10	0.22	0.96
	15	0.31	0.94
Depilatory practices ^b	5	0.11	0.98
	10	0.21	0.96
	15	0.29	0.94
Combined questions ^c	5	0.14	0.99
	10	0.26	0.99
	15	0.35	0.98
Lower abdomen and chin $\geq 1^d$	5	0.15	0.996
	10	0.27	0.99
	15	0.37	0.99
Lower abdomen and chin $\geq 2^e$	5	0.12	0.99
	10	0.23	0.97
	15	0.32	0.95

^aHirsutism as defined by sFG.

^bDepilatory practices include shaving, waxing, or bleaching hair, or use of electrolysis on the face, chest, or abdomen.

^cFor net sensitivity and specificity of hirsutism or depilatory practices.

^dFor net sensitivity and specificity of lower abdomen and chin each ≥ 1 .

^eFor net sensitivity and specificity of lower abdomen and chin each ≥ 2 . NPV, negative predictive value; PPV, positive predictive value.

Results

Consistent with previous work, the prevalence of hirsutism in our cohort of women with PCOS was 73%,³⁰ and obesity was a strong predictor of PCOS.^{31,32} Positive responses for hirsutism as defined by sFG or for depilatory practice had sensitivity and specificity of over 70%. Positive responses to both of these screening questions gave a high sensitivity of 93%, but lower specificity at 52%.

Clinical implications

PCOS is associated with a myriad of poor health outcomes for women,^{8–20} as well as their offspring.^{13,18–20} In addition to poor health outcomes, women with PCOS have lower markers of quality of life, both physically and psychologically when compared to age-matched controls.³³ It is estimated that PCOS costs the United States health care system \$4.4 billion dollars throughout a woman's reproductive lifespan. However,

only 2% of this cost is spent on initial evaluation.³⁴ Furthermore, the diagnostic process for many women with PCOS is inefficient and unsatisfactory. Gibson-Helm et al. found that more than 2 years and two health professionals were needed for accurate diagnosis of PCOS in >33% of cases.³⁵ In a large Australian cohort of women with PCOS, quality of life was associated with perceived quality of information given about their diagnosis.³³ Gaps in physician knowledge about the risks of PCOS and delays in diagnosis result in missed recommended screenings, such as blood pressure, cholesterol, and hemoglobin A1C.³⁶ Given the significant delay in diagnosis and impact on quality of life and long-term health, identification of women at risk of PCOS is vital.

The FG scoring system for hirsutism currently relies on physician evaluation. However, these examinations are cumbersome and frequently prohibitive in epidemiological studies. In addition, when women use depilatory techniques to remove hair, accurate evaluation by a physician may not be possible. Compared to more objective measurements of hirsutism, such as photographic scoring or hair measurements, scoring by the FG method is more subjective and has been shown to have high interobserver and intraobserver reliability.^{37,38}

In 2005, Wild et al. asked 21 women with PCOS to score themselves and be scored by three trained professionals. They found considerable variability in scoring and concluded that self-scoring was not clinically useful. However, all scores were significantly higher than 6, indicating that all observers were in agreement that the women met criteria for hirsutism.³⁷

More recently, Pedersen et al. sought to validate a questionnaire for use in the diagnosis of PCOS and noted that a history of infrequent menses, hirsutism, obesity, and acne was strongly predictive of a diagnosis of PCOS and developed a four-item questionnaire that yielded a sensitivity of 77% and specificity of 94%. However, in contrast to our study presented here, they recruited women with menstrual irregularity, hirsutism, and infertility, which limit generalizability. They also used the National Institutes of Health (NIH) diagnostic criteria for PCOS, which requires oligo-ovulation or anovulation and clinical or biochemical hyperandrogenism for diagnosis, which differs from our study.³⁹

While self-evaluation may be less accurate than evaluation by a trained professional, this study demonstrates that women can accurately determine whether they have hirsutism. As a solution for high variability in scoring, Cook et al. introduced the simplified FG method, which reduces the number of body regions evaluated,

Table 4. Multivariate logistic model for polycystic ovary syndrome prediction

Variable	aOR	95% CI	p
Obesity	6.7	2.5–17.9	0.0001
Depilatory practices	6.6	2.5–17.3	0.0002

aOR, adjusted odds ratio; CI, confidence interval.

while still accurately diagnosing hirsutism.²⁴ In our study, we used the sFG to designate hirsutism; however, we asked patients to evaluate themselves. Given that 37% of generalists are unaware of the diagnostic criteria for PCOS,²¹ self-screening questionnaires may be able to improve targeted referrals to specialists.

Research implications

Simple, self-administered questionnaires improve the ability to conduct large epidemiological studies, as they do not rely on expert evaluation. Implementation of a questionnaire to screen for PCOS, which includes questions about depilatory practices and hirsutism, may help in epidemiologic studies of PCOS.

Strengths and limitations

We note three key strengths of this study. This adds to the extremely limited literature that has examined the utility of a screening questionnaire to identify women at risk for PCOS. As a chronic disease with significant long-term sequelae and lifestyle and medical interventions, PCOS is a prime disease for a screening questionnaire. This screening test is both sensitive and specific and has a high negative predictive value. While the PPV was relatively low, this reflects the overall prevalence of PCOS. Finally, the questions do not rely on menstrual irregularity. Given the large proportion of reproductive-age women who use contraception and whose menstrual cycles may be normalized or affected by these methods, it is vital that a screening tool does not rely on menstrual regularity.

Several limitations of our study must be considered. First, as with all case-control studies, recall and selection bias are two major considerations. For example, women with PCOS who report to clinics may be more symptomatic than women with PCOS who do not present for evaluation. Therefore, the women with PCOS in our study may be more symptomatic than undiagnosed PCOS patients. In addition, as the participants were not blinded to the purpose of the study, their responses are subject to recall bias.

Second, our cohort predominantly identified as white, which limits its generalizability. Given that terminal hair growth can vary by race and ethnicity, it is important for future studies to include a more heterogeneous sample. Depilatory techniques are frequently employed for removal of eyebrow hair in women without hirsutism. Our questionnaire did not specifically ask women if their facial hair removal was in areas with male-patterned growth, which may have led to falsely elevated proportions of women answering yes to this question.

Third, for several participants, self-reported weight and height were used to calculate BMI. While self-reported weight and height are not as precise as measurements conducted in clinic, they have been shown to be accurate.²⁶

Fourth, given the large portion of women on OCPs, questions about menstrual cycle characteristics could not be used in the final model. Studies have remedied this problem by excluding women on COCs. However, exclusion of women on COCs biases results since symptomatic women are more likely to have been prescribed COCs. Also, given that ~40% of reproductive-age women use some form of hormonal contraception or long-acting reversible contraceptive,⁴⁰ it is important for a screening tool to identify individuals at risk of PCOS without relying on questions about menstrual regularity. Furthermore, asking women to recall their menstrual cycle characteristics before initiating hormonal contraception is not without limitations, including recall bias, which will increase the longer a woman is on contraception. Furthermore, cycle characteristics several years prior are not necessarily a good predictor of current cycle characteristics. Therefore, while it would be ideal to know current cycle characteristics of all women, this has limited utility in a general population.

Conclusions

Straightforward self-screening questions on obesity, depilatory practices, and male-patterned terminal hair growth can aid in identifying women at risk for PCOS. This has significant implications for helping women and physicians correctly identify who should be further worked up for this endocrinopathy.

Condensation

A questionnaire capturing self-report of depilatory practices and/or hirsutism is sensitive for identifying women with PCOS.

Author Disclosure Statement

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Abbreviations Used

- aOR = adjusted odds ratio
BMI = body mass index
CI = confidence interval
COC = combined oral contraceptive pill
NIH = National Institutes of Health
NPV = negative predictive value
OCP = oral contraceptive
PCOS = polycystic ovary syndrome
PPV = positive predictive value
sFG = simplified Ferriman-Gallwey



A Study of Psychological Distress Among Women with Polycystic Ovarian Syndrome in Kashmir

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ABSTRACT

Background: Polycystic Ovarian Syndrome, was previously thought to be an endocrine condition. Research has now demonstrated that polycystic ovarian syndrome affects a patient's quality of life and is a metabolic, hormonal and psychosocial condition. Women's joys are disrupted by PCOS because the stigma attached to hyperandrogenism is strongly felt and may harm women's psychological development.

Methods: The aim of the study was to comprehend the psychosocial problems experienced by women in Kashmir and to obtain a thorough understanding of the coping mechanisms employed by women with PCOS. The research design was both qualitative and quantitative in nature. Thematic analysis was used to derive themes from the data. Sampling was purposeful in nature.

Results: The study underscores that women with PCOS encounter numerous difficulties encompassing social and psychological aspects. Psychological issues like mood swings, stress, anxiety and sleeping disorders are prevalent among women with PCOS. Furthermore, the research has revealed that menstrual disorders significantly contribute to depression in women. The study also highlights a connection between infertility and psychological problems.

Conclusion: In conclusion, the research underscores the multifaceted challenges faced by individuals with PCOS. Therefore, understanding these issues is crucial for developing effective coping mechanisms and improving the quality of life for women dealing with PCOS.

Key Words: PCOS, Stress, Kashmiri Women, Coping Strategies

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INTRODUCTION

The female body has the potential to give birth to a child and procreate a family. Childbirth usually requires various different body parts of women to function normally. However, due to certain factors, the ovaries may experience certain problems and may not perform the desired function. Such a problem associated with women has been called PCOS. 5 to 20 percent of women suffer from PCOS.¹ World Health Organization reveals that 116 million women globally suffer from PCOS.² The primary cause of anovulation-induced female infertility is PCOS. As per the Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004)³, it is delineated by these criteria. Once other causes of cycle disorders or hyperandrogenism have been ruled out, the diagnosis is established when at least two of the following three criteria are met: polycystic ovary aspect on ultrasound, clinical and/or biological hyperandrogenism and cycle abnormalities.⁴

This research on mental distress among women with Polycystic Ovary Syndrome in Kashmir holds significant importance in understanding and addressing the unique challenges faced by this specific population. In the context of Kashmir, where cultural and social factors may influence health outcomes, this qualitative and quantitative inquiry sheds light on the lived experiences of women dealing with both PCOS and mental distress. The findings can provide valuable insights into the factors contributing to mental health challenges among these women, offering a culturally sensitive perspective.

The study was conducted to examine the psychological problems of women suffering from PCOS and to explore the coping strategies adopted by women with PCOS.

METHODOLOGY

Gaining a comprehensive understanding of the psychological issues faced by women with PCOS was the aim of the study. The study was primarily qualitative in nature but in order to collect more information, the data was collected from 50 women. Furthermore, qualitative research was carried out with 15 participants in order to fully comprehend the research problem and to delve deeply into the unique experiences and feelings of 15 women affected by PCOS. By integrating the two methods, the research aimed to improve the knowledge of the psychological effects of PCOS. Structured questionnaire was used to collect quantitative data from the participants. Semi-structured questions were asked during in-depth individual interviews with 15 PCOS-afflicted women, aged 18 to 35. Further, Purposive sampling was used, and it persisted until data saturation was achieved. Thematic analysis was used to analyze the data. The research was conducted at the tertiary care hospital of Srinagar. The hospital is located in the Union Ter-

ritory of Jammu and Kashmir, India. Interviews were conducted in-depth with each individual, using semi-structured questions such as "*How far has this disorder affected your mental state?*" and "*What are your experiences with this disorder at this stage of life?*" as well as "*How are you dealing with this problem?*" In-depth data was also gathered from the participants using a tape recorder. The duration of each interviews lasted 30 to 55 minutes. Interviews were recorded with prior permission from the participants. Data was collected by two female research assistants.

Data Analysis: In this study, thematic analysis was used. In qualitative studies, thematic analysis is a flexible and foundational method. At the initial stage, to immerse themselves in the data, the research team transcribed the recorded audio interviews and the members read the transcripts meticulously. In order to produce the initial codes, the research team members extracted the semantic units. After that, the codes were collated into possible themes. The whole research team reviewed the themes for generating a thematic map. Lastly, the themes were well defined and given names and the final report was prepared. The approaches used in this study to confirm the accuracy of the data included the selection of participants with a diversity of experiences, member checking, use of a coding outline, lengthy engagement with the data, and team consensus on themes. The data gathered was time and again cross-checked in order to minimize the errors in the data. The four standards put forward by Guba and Lincoln⁵ were applied to guarantee the accuracy of the findings. Reliability, credibility, transferability, and confirmability were the requirements. To enhance credibility, a range of data gathering techniques, including focus group discussions (FGDs), field notes and participant selection based on the greatest diversity of demographic attributes, were employed in conjunction with in-depth interviews. Quantitative data was analyzed in a percentage manner.

RESULTS

Table 1 stated highlights the socio-demographic profile of the participants and highlights the age, marital status, occupation and educational status of the participants.

Psychological issues of the Participants: The table 2 illustrates the variety of psychological problems that participants are facing. The fact that 8 percent of the participant's experience mood swings. Similarly, worry and stress are indicated by 6 percent and 14 percent of participants. 22 percent underscoring the detrimental effects on sleep patterns. 6 percent of participants are feeling irritated, 12 percent feel low in self-esteem and 4 percent are feeling frustrated. In addition, 6 percent of participant's feel overwhelmed. 8 percent of participants are feeling uninterested in life's pursuits. In addition, 14% of participant's express dissatisfaction with their bodies.

Table 1: Socio-demographic Profile of the Participants (N =50)

Variable	Participants (%)
Age	
18-20	13 (26)
21-30	23 (46)
31-35	14 (28)
Family Type	
Nuclear	37 (74)
Joint	13 (26)
Educational Attainment	
10th to 12th	11 (22)
Graduation	32 (64)
Masters and above	7 (14)
Occupation Type	
Employed	17 (34)
Unemployed	33 (66)
Marital Status	
Married	10 (20)
Unmarried	40 (80)

Table 2: The effect Polycystic Ovary Syndrome on mental health of the participants.

Effect of PCOS on Mental Health	Participants (%)
Mood swings	4 (8)
Worried	3 (6)
Stress	7 (14)
Sleep disturbances	11 (22)
Irritated	3 (6)
Low self esteem	6 (12)
Frustration	2 (4)
Overwhelmed	3 (6)
Lack of interest	4 (8)
Dissatisfaction with body image	7 (14)

Table 3 and figure 1 highlights codes, sub-themes and themes which were describe in detail below:

Theme 1. Disturbed Mental Health

Anxiety, despair and negative body image are among the typical and severe mental health issues that women with PCOS commonly experience.

Sub-theme 1.1: Impact of Stress on Mental Well-being

The participants reported that due to menstrual disorders, they remain in a bad mood and feel very anxious because of menstrual disorders. This disorder reminds them that they are suffering from a health problem. They feel mentally stressed and irritated as well.

"With each passing day, we feel that this problem will come to an end and we will start living a normal life again. To get rid of this problem, we are taking all medicines prescribed by the doctor on time. We are worried about our future. Negative thoughts disturb mind" (R, 1, 5 and 7).

"In order to ease our mental stress, we are taking antidepressants as well, that makes us feel comfortable for some time, but as medicine becomes less effective, we again start thinking about our problem. We want to forget this problem forever" (R, 6 and 8).

Theme 2. Dissatisfied with Body Image

It is argued by many researchers that women with PCOS often report low satisfaction with their body image, as growth of hair and neck contribute to this dissatisfaction.

Sub-theme 2.1: Effects of Societal Influence on Body Image Perception

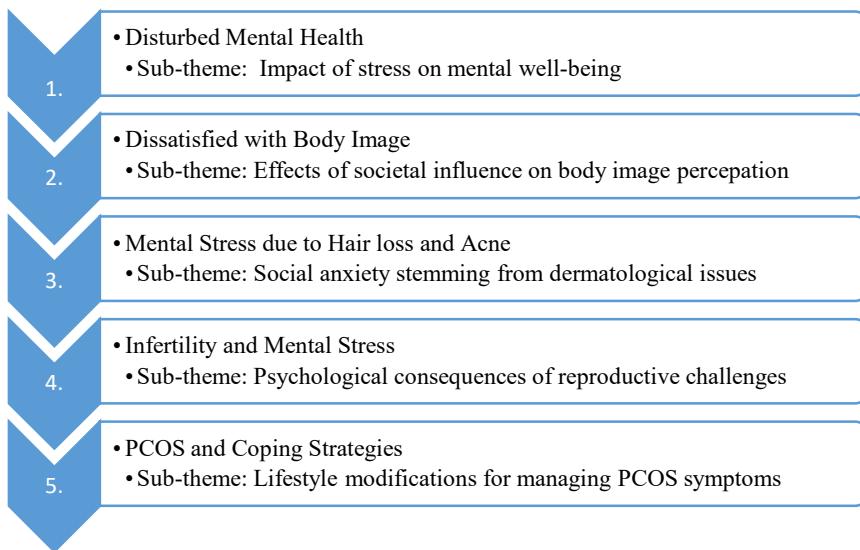
Because of obesity, participants are facing many social and psychological problems. Women with obesity are prone to many health problems like heart disease, diabetes, kidney disease, etc.

"Participants stated that earlier, we used to wear medium-size clothes, but now, due to an increase in weight, we have to wear large-size clothes. We cannot wear the clothes we used to. This PCOS has increased our weight. Taking medicine is a hope that our problem will come to an end" (R, 2, 4 and 9).

"Because of PCOS, our obesity has increased so much that sometimes we prefer not to attend marriage ceremonies and other functions. It takes too much time to motivate ourselves to attend social gatherings" (R, 7, 13 and 14).

Table 3: Codes, Sub-themes and Themes

Codes	Sub-themes	Themes
Constant overwhelms	Impact of chronic stress on mental well-being	Disturbed mental health
Persistent anxiety		
Lack of escape		
Inadequacy	Effects of societal influence on body image perception	Dissatisfied with body image
Comparison to ideal bodies		
Societal influence		
Avoidance of social events	Social anxiety stemming from dermatological issues	Mental stress due to hair loss and acne
Embarrassment		
Skin and hair concerns		
Immense pressure	Psychological consequences of reproductive challenges	Infertility and mental stress
Mental health toll		
Reproductive struggles		
Pushing negative thoughts out	Lifestyle modifications for managing PCOS symptoms	PCOS and coping strategies
Spending time with friends		
Symptom management		

**Figure 1: Themes and Sub-themes**

We are women and having hair on their faces is not pleasant for them. We want this problem should come to end.

"The growth of hair on face, chest and around neck because of PCOS has made our lives stressful. The problem is more serious for women who are unmarried. We are not getting how to express our feelings" (R, 3, 8 and 14).

Theme 3. Mental Stress due to Hair loss and Acne

Polycystic ovary syndrome can cause hair loss in women. Inflammation, insulin resistance and hormonal imbalance are few of the factors that contribute to hair loss in PCOS.

Sub-theme 3.1: Social Anxiety Stemming from Dermatological Issues

Hair loss and acne are the main causes of people losing their physical attractiveness. As per the participants, these visible problems are the main causes of stress and even of low self-esteem as well.

"We are feeling depressed because of acne and hair loss. We always pray that their problem should come to an end. Our faces do not look good because of acne and hair loss" (R, 12 and 14).

"The participants reported that sometimes they think it is a manageable problem and with the passage of time, their problem will come to an end. Their families are spending a lot of money on their treatment" (R, 4 and 8).

Theme 4. Infertility and Mental Stress

The most typical cause of infertility in women is PCOS. Infertile women experience internal as well external social pressures.

Sub-theme 4.1: Psychological Consequences of Reproductive Challenges

The participants reported that they have not received adequate information about PCOS. The participants revealed that the stigma attached to infertility is another stressful problem.

"Some Participants were found married while differing in years of marriage mentioned that they are not able to conceive because of PCOS. They think that they have become infertile and cannot conceive now" (R, 6 and 11).

"We are taking medicine regularly, but still, nothing good is happening. We are feeling stressed all the time" (R, 03 and 15).

Theme 5. PCOS and Coping Strategies

Coping is essential for managing a variety of issues, such as PCOS, which has a significant impact on women's mental and physical health.

Sub-theme 5.1: Lifestyle Modifications for Managing PCOS Symptoms

Participants try to cope with this problem by not disclosing their problem to anyone, so as to reduce their psychological challenges.

"The participants revealed that in order to cope with this problem, they always try to push the negative thoughts out of their minds" (R, 05 and 08).

"We are students and because of PCOS, we are not able to concentrate on our studies. In order to reduce the level of stress, we prefer to utilize most of our free time in watching comedy movies and serials" (R, 1, 9 and 11).

We do not have time to think about this problem and keep ourselves busy with friends and family mem-

bers. If we keep on thinking about this problem, then we cannot do anything in our life.

"I am not upset because doctor said that this problem is very common and could happen to anyone, and this problem is not so serious. This feeling reduces my mental stress" (R, 10).

"Participants narrated that though they are trying their level best to come out of this problem and are adopting various coping methods, but fear of this problem is not ready to leave us" (R, 2, 4, 6 and 15).

DISCUSSION

According to the national task force of the Indian Council of Medical Research (ICMR), over 30 percent of Kashmiri women meet the Rotterdam Criteria for PCOS prevalence, potentially representing the highest percentage globally (ICMR, 2023).⁶ It is noteworthy that PCOS is not solely an endocrine disorder but a combination of metabolic and psychosocial challenges. Patients who are diagnosed with PCOS have been reported to experience severe psychological effects from a number of variables, including difficulties finding a PCOS specialist, a lack of knowledge at the time, delays and a diagnosis related to pathology.⁷ Anxiety and depression disorders are much more common in PCOS patients.⁸ In fact, compared to non-PCOS individuals, these patients have five times more anxiety problems and three times more depressive symptoms.⁹ Emotional distress in women with PCOS may be pathophysiological, psychological or both.¹⁰ Many women view physical characteristics like acne and hirsutism or prospective outcomes like obesity and infertility, as stigmatizing and potentially distressing.¹¹

Case-control research by Sulaman¹² et al. has revealed that PCOS patients were far more likely to experience anxiety and anxiety disorders. As per the views of Glowinska, Duleba, Zielona-Jenek¹³, et al. (2020), PCOS patients also frequently exhibit negative body image dissatisfaction. Researchers like Deeks, Gibson-Helm, Paul¹⁴, et al. (2011) and Kitzinger, Willmott¹⁵ (2002) have also narrated that individuals with PCOS may have negative body image due to feelings of dissatisfaction with their appearance.¹⁶ The study underscores that women with PCOS encounter numerous difficulties encompassing social and psychological aspects. Psychological issues like mood swings, stress, anxiety, sleeping disorders and dissatisfaction with body image are prevalent among women with PCOS. Furthermore, the research has revealed that menstrual disorders significantly contribute to depression in women. The study also highlights a connection between infertility and psychological problems such as depression and anxiety in women with PCOS. Social stigma compounds their psychological challenges, particularly among unmarried participants who harbor fears of infertility due to this condition. There is a dire need of professional

psychological interventions to help them cope with and normalize their psychological distress.

The study has certain limitations. The sample size was relatively small, which may limit the generalizability of the findings to a larger population.

CONCLUSION

The views shared by individuals grappling with Polycystic Ovary Syndrome reveal a profound impact on their physical and mental well-being. Many express the emotional toll of menstrual disorders, anxiety and the burden of PCOS, creating a persistent negative mind-set. The coping mechanisms employed by some, such as engaging in enjoyable activities and maintaining a busy lifestyle, reflect an attempt to navigate the challenges posed by PCOS. However, the pervasive nature of negative thoughts indicates the need for more comprehensive support and awareness.

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Socio-Cultural Perspective On Polycystic Ovary Syndrome Patients: From Lived Experience To Treatment

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Abstract

This study aims to narrate the socio-cultural factors surrounding Polycystic Ovary Syndrome (PCOS) among both unmarried and married women of reproductive age group. The study intends to explore personal, familial and societal trends related to PCOS patients. For the present study 20 In-depth interviews (10 from each married and unmarried women group), 06 case studies, and 03 patient's life histories were used to cover the qualitative part of the study to analyze detailed information on recurrent themes pertaining to the respondents' experiences with PCOS while the quantitative aspects of the study were covered by the socio-economic profiles of the patients. The data was collected from two public hospitals of Rawalpindi. Thematic analysis of the data showed a strong association with PCOS. A significant correlation was also found between PCOS ¹and lifestyle of the patients furthermore, the study presents shows that a low socio-economic and lower position of the women is deeply connected with prevalence, effects and treatment of PCOS suggesting that financial difficulties make the problem worse. Majority of the PCOS patients mentioned that their marriages were strained, likewise unmarried women also faced challenges, discrimination and prejudice emphasizing the syndrome's wider social, economic and emotional ramifications. Additionally, married women's PCOS related health issues were made more difficult by the stress and social pressure they faced from their husbands, in-laws, and society at large, which increased their emotional burden. This study also only reveals the distressing experiences of the women with PCOS but it also demonstrates how the condition is intricately linked to general culture at the household and social levels. The study suggests future qualitative research to cover the mental health and wellbeing issues of women. Moreover, education and public awareness campaigns are direly needed at all levels to connect the home, community, and healthcare facility to lessen the problem of PCOS and its sensitization.

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Introduction

The term 'socio-cultural' refers to the combined influence of social and cultural elements on individuals, groups, communities, and societies. It explains that human behavior, beliefs, norms, values, and practices are shaped not only by individual psychology but also by broader social structures and cultural contexts (Cherry, 2022). The theoretical concept of term socio-cultural is 'The mental abilities of the people in a society are shaped by their social interaction with each other and by the culture in which they live'. The term 'socio-cultural' encompasses the combined social and cultural factors that influence the behavior, beliefs, norms, values, and practices of individuals, groups, communities, and societies. It represents a continuum of societal and cultural influences that affect thoughts, emotions, and, indirectly, the health of individuals within a society (Cooney et al., 2017). Individuals learn and develop psychologically through societal interactions. The socio-cultural theory posits that societal interactions play a crucial role in an individual's psychological development. Learning is inherently a social process, and an individual's cognitive functions are shaped by these societal interactions (Cherry, 2022). In an anthropological perspective, the socio-cultural anthropology present that human societies spread in time and space in a way by considering the commonalities across them. For the approach of understanding contemporary challenges, the study applied a holistic strategy of connecting local and global, past and present (Robbins, 2016). The term "socio-cultural" encompasses a broad array of factors that aid in understanding its influence on society. Society regulates behaviors and interactions through various socio-cultural elements, including institutions, organizations, and systems such as family, education, lifestyle, and social class. Societal and cultural expectations are shaped by these socio-cultural factors, which include cultural norms, beliefs, values, customs, traditions, and ideologies. Understanding socio-cultural factors is crucial due to their significant impact on society (Di Fede et al., 2009). In anthropology, "socio-cultural" refers to the study of how diverse individuals adapt within their societies by examining their aspirations, struggles, and cultural interactions. Socio-cultural anthropologists investigate how natural, biological, and technological aspects of a society's culture influence individual lives and social relationships (Doda, 2005). These factors influence the behavior, beliefs, and identities of both individuals and societies. They offer social support in addressing various social challenges, including healthcare issues (Citron, 2022). Socio-cultural factors play a crucial role in the development and functioning of individuals within a society. While they frequently impact societal roles, they also contribute significantly to addressing healthcare problems through socio-cultural support. Additionally, factors such as stressors can have both positive and negative effects on the identification and treatment of illnesses (Di Fede et al., 2009).

There are some diseases in life which symptoms are so embarrassing for a patient or for the survivor of that disease. These symptoms do not allow a patient to survive from a socio-cultural perspective in society. For this reason, social stigma was made about the disease and patient. 'These social stigma causes psychological, physical and social health consequences (Anagnostis et al., 2018), like exclusion, discrimination and loss of opportunity in social health, shame, blame and humiliation in mental health and refraining from treatment all this can to a stressful life for a patient which causes disease aggravation (Akbari et al., 2023). The personality of women who have PCOS, get disturbed due to these socio-cultural factors. 'Through examination it is come to know that 16% of PCOS have major depression and 2%

have bipolar disorders. Depression and anxiety, found more in the PCOS women than that of general population (Basirat & Kheirkhan, 2020).

Living in a society with such disease like PCOS may depress the self-consciousness and lower self-esteem of patient. 'The cultural perception about the women role in a society is highly valued. As the reproductive inability, of women or infertility due to PCOS lead to feeling inadequacy and failure in society in which motherhood is highly valued (Dewailly et al., 2010). A PCOS patient also faces social stigma that had a great effect on the personality of patient in socio-cultural perspective. 'Some symptoms of PCOS like infertility, obesity, unwanted hair growth causes social stigma in patients and causes anxiety, depression, and a negative image of body (Cooney et al., 2017).

This all impart a negative effect between socio-cultural factors such family relationships, work, employment, and the patient (Hudson, 2008; Joham et al., 2022; Kaur et al., 2021). Socio-cultural factors, combined with socio-economic status, significantly impact individuals' lives. For example, a PCOS patient with a low socio-economic status may be unable to afford treatments for symptoms such as hirsutism, obesity, and infertility. These symptoms, exacerbated by social stigmas and cultural norms, can lead to body image issues and diminished self-esteem. Consequently, these factors indirectly affect women's ability to pursue higher education, secure high-paying jobs, and access other career opportunities (Di Fede et al., 2009). When managing a chronic disease, patients strive to improve their lifestyle and live contentedly with their condition. To achieve this, they employ various coping mechanisms to address social stigmas, cultural norms, and other social and medical challenges. These coping strategies include maintaining a healthy diet (Shahid et al., 2022), engaging in regular exercise and physical activities, practicing stress-relief meditation, minimizing unnecessary obligations, fostering positive social connections, seeking peer support, and avoiding negative coping methods such as alcohol and substance use (Wilder & Pype, 2021).

The symptoms of PCOS are conspicuous and often conflict with societal cultural norms for women. Exploring the socio-cultural perspective on the personality of individuals living with PCOS involves understanding the intricate interplay between cultural norms, societal expectations, and individual experiences (Pathak & Nichter, 2015). In various cultural contexts, femininity and womanhood are frequently associated with fertility, physical appearance, and overall health. For women with PCOS, symptoms such as irregular menstruation, hirsutism, and infertility can challenge these traditional ideals of femininity, potentially impacting their self-concept and social identity (Becker & Nachtigal, 2019).

These socio-cultural factors have contributed to the formation of social stigmas surrounding PCOS. The stigma associated with PCOS related symptoms, such as weight gain and acne, can lead to feelings of shame and social isolation, adversely affecting the psychosocial well-being of affected individuals. Additionally, cultural beliefs and gendered expectations shape the experiences of women with PCOS, influencing their self-esteem, body image, and interpersonal relationships (Simbar, 2014).

Within the context of socio-cultural factors, socio-economic status also influences the lives of PCOS patients. Socio-economic status encompasses factors such as income, education, occupation, and access to resources, all of which significantly impact the experiences and outcomes of individuals living with PCOS. Number of researches indicate that lower socio-economic status is associated with a higher prevalence and severity of PCOS. Individuals from

disadvantaged socio-economic backgrounds may encounter barriers to accessing healthcare services, diagnostic testing, and treatment options (Anagnostis et al., 2018; Sirmans, 2019).

Patients with low socio-economic status also experience significant stress due to the high costs associated with medication and treatment, particularly for infertility. This financial strain can exacerbate depression, anxiety, and mood swings. The total additional healthcare-related economic burden of PCOS, including pregnancy-related and long-term morbidities in the United States, was estimated to be \$4.3 billion annually in 2020 USD. Combined with previous analyses, the total economic burden of PCOS is estimated at \$8 billion annually in 2020 USD (Riestenberg & Jagasia, 2022).

Every society has its own culture and corresponding cultural norms. The symptoms of PCOS often conflict with these norms of beauty, fertility, and femininity, leading to stress and low self-esteem in affected individuals. Cultural norms surrounding femininity, fertility, and health intersect with the manifestations of PCOS, shaping the lived experiences and identities of those affected. Symptoms such as irregular menstruation, hirsutism, and infertility deviate from culturally idealized standards of womanhood, leading to feelings of shame, stigma, and social isolation among individuals with PCOS (Rashid & Kareem, 2022).

There is no specific treatment for PCOS, but it can be managed with certain medications and ethno-medicines. Due to societal pressures, patients may feel ashamed to consult a physician, and in some cultures, norms restrict patients from seeking medical treatment, leading to delayed consultations and increased complications. Research has shown that many chronic diseases cannot be permanently cured; however, their symptoms can be managed, and patients can improve their quality of life through healthy lifestyle changes. PCOS, being a lifelong disorder, can be managed with proper medical care. This includes symptom management through healthy lifestyle changes, cultural practices, and medications (Pal, 2014).

Many patients initially try to avoid medications and instead focus on healthy lifestyle changes as the first step in managing PCOS. To improve their lifestyle, PCOS patients are advised to increase daily physical activities, engage in regular moderate exercise, and prevent insulin resistance. An active routine can help maintain a healthy weight and reduce the risk of diabetes. This routine might include a daily 20–30-minute walk after meals (Shahid et al., 2022). PCOS is a hormonal disorder (Azziz, 2011). To regulate hormone levels and address related issues, some Ayurvedic treatments are also utilized. These treatments include herbal therapies and lifestyle changes. Ayurvedic herbs used for PCOS include Ashwagandha (also known as winter cherry), which helps regulate cortisol levels to reduce stress; Cinnamon, which aids in managing insulin resistance; and Turmeric, which acts as an anti-inflammatory agent. Ayurvedic therapies also incorporate yoga to alleviate anxiety. Recommended yoga poses, known as asanas, include Supta Baddha Konasana (butterfly pose), Bharadvajasana (twist), Chalanasana (mill churning pose), and Shavasana (corpse pose) (Forthingham, 2020).

In certain cultures, religious treatments are also employed to manage PCOS. Patients may visit Darbars, recite verses from the Quran, or seek the assistance of practitioners who provide taweez (amulets). Taweez, often inscribed with Quranic verses or prayers, is a cultural practice among some Muslims believed to offer protection or healing. However, Islamic scholars advise against relying exclusively on these practices and emphasize that they should complement, not replace, professional medical treatment. Consulting unqualified practitioners or quacks is generally discouraged, as it can lead to misinformation and potential harm (Kaur et al., 2021).

In medical anthropology, some biomedicines are also considered traditional medicines, as they are commonly used as initial treatments by physicians within a given society. For PCOS, traditional treatments include medications such as Metformin and oral contraceptive pills (birth control), as well as natural supplements like Berberine, Chromium, and Inositol, which aid in managing PCOS symptoms. Additionally, significant lifestyle changes, including weight loss and regular exercise, are crucial for symptom management and overall recovery (Andonian, 2023).

Theoretical Framework

The present study aligns with various theories in anthropology and medical anthropology. From a socio-cultural perspective on PCOS, it relates to the theory of cultural relativism, proposed by Franz Boas the theory posits that cultural beliefs and practices should be understood within the context of the specific culture in which they occur, rather than through the lens of external absolutes (Kendra, 2023). The theory of cultural relativism can be applied to the socio-cultural context surrounding PCOS by examining how cultural beliefs, values, and practices shape the perception, experience, and management of the condition. For instance, in cultures where fertility is highly valued, symptoms of PCOS such as irregular menstrual cycles or infertility may have profound social and emotional consequences (Tzuriel & Tzuriel, 2021). Additionally, cultural attitudes toward body image, gender roles, and healthcare-seeking behaviors influence how individuals with PCOS are perceived and supported within their communities. Adopting a cultural relativist perspective allows researchers to understand the diverse global interpretations and responses to PCOS, leading to more culturally sensitive approaches in diagnosis, treatment, and support for affected individuals (Forthingham, 2020; Rashid et al., 2019).

The perspective discussed previously is rooted in anthropological theory; however, given that PCOS is a medical condition, it is also relevant to theories in medical anthropology. PCOS can be analyzed through both epidemiological and ecological approaches. These approaches examine the interplay between biological and cultural factors in health and disease. They focus on understanding how certain factors can influence the likelihood of developing a disease, including cultural practices that may either contribute to illness or compel individuals to adopt a sick role (Robbins, 2016).

For instance, studies on PCOS using these approaches explore how factors such as genetics, lifestyle, and environmental influences contribute to the condition's development and manifestation across different demographic groups. They also investigate how cultural beliefs, social norms, healthcare systems, and environmental conditions affect the prevalence, diagnosis, and management of PCOS (Sheehan, 2004). By integrating epidemiological and ecological perspectives, medical anthropologists can achieve a comprehensive understanding of PCOS, considering both individual and broader societal factors. This approach aids in developing more effective interventions and healthcare policies tailored to diverse populations (Rashid et al., 2019; Robbins, 2016; Scott & Palincsar, 2013).

Review of Literature

Medical anthropology as a sub field of applied anthropology has interrelated the biological and cultural aspects of human health to explain the impact of culture on health and diseases. "Medical anthropology deals with the collective study of biological and cultural aspects about humans to explain the influence of culture on human health and disease. Cultural factors engage

symbols with biology in a minds-body dynamics manifested in traditional healing practices, psychosomatic illness and many other ways by which beliefs effect the health" (Winkelman, 2009).

The study of human beings first clicks to the study of health of human being. There are many aspects other than medicine to study humans. When culture and health behavior and social programs related to public health are involved with medicine then a new field evolves belongs to applied anthropology called medical anthropology. "Medical anthropology is the primary discipline addressing the interfaces of medicine, culture and health behavior and incorporating cultural perspectives into clinical settings and public health programs" (Doda, 2005).

The topic of the study is "Polycystic Ovary Syndrome (PCOS): An Anthropo-medical study of women's reproductive health narratives in selected public hospitals of Rawalpindi". The topic briefly discusses the cause and effects of PCOS, it highlights the socio-cultural impact on PCOS patient and how they cope from these social stigmas, and it discusses about knowledge and treatment strategies adopted by women having PCOS. PCOS is an endocrine disorder. It can affect individual's assigned female at birth, typically during their reproductive years. It is characterized by a combination of symptoms, including irregular menstrual cycles, excess androgen levels (male hormones), and the presence of multiple cysts on the ovaries. This hormone release in females when females do not ovulate due to insufficient number of ovulatory hormones. Because of these ovaries develop small cysts. These cysts then secrete the androgen hormone. PCOS patients have high level of androgen hormone which create complication in menstrual cycle, and other symptoms of PCOS (Altman, 2023).

A follicle is a sac in which egg development occurs, 'PCOS ovary contains large number of follicles, and they are up to 8mm (approx. 0.3) in size. In PCOS follicles are unable to release egg that is why no ovulation take place. This is very common disease affecting 1 in 10 women in UK. PCOS often manifests with a range of symptoms, such as acne, excessive hair growth (hirsutism), weight gain, and infertility. The exact cause of PCOS is not fully understood, but it is believed to involve a combination of genetic, hormonal, and environmental factors. Insulin resistance, where the body's cells do not respond effectively to insulin, is also commonly associated with PCOS. This hormonal imbalance can disrupt the normal functioning of the reproductive system, leading to difficulties with ovulation and fertility (Altomara, 2021). PCOS patients suffer a lot psychologically and socially as well. PCOS not only affects physical health but can also have significant psychological, socio-cultural and emotional impacts, including depression, anxiety, social stigmas and body image concerns. Management of PCOS typically involves a combination of lifestyle modifications, such as dietary changes and exercise, along with medications to regulate menstrual cycles, manage symptoms like acne and excess hair growth, and improve fertility outcomes. Early diagnosis and comprehensive management are crucial in minimizing the long-term health risks associated with PCOS, including type 2 diabetes, cardiovascular disease, and endometrial cancer (Deanna & Sachdev 2023).

The term socio-cultural can be better explained by socio-cultural theory. 'Socio-cultural theory has both sociological and psychological dimensions and both of these dimensions deal with the importance of culture and society in the development and shaping of an individual in a society. It elaborates that how friends, parents and the society interact in the development of an individual's cognitive, learning and socio-cultural abilities'(Main, 2023).

Socio-cultural theory under the umbrella of anthropology underpins that “socio-cultural anthropology studies the social, symbolic, or nonmaterial and material lives of contemporary and historically recent human societies, taking the concept of culture central to its goal. It discusses the social and cultural aspect of an individual of a society, by describing and analyzing the lives of people and their traditions” (Doda, 2005). While discussing the socio-cultural perspective about the PCOS patient, it has been seen that ‘women that suffering from PCOS have high level of anxiety and depression, which impart a great effect on patient’s identity, mental health and quality of life. The disorders related to anxiety and depression in PCOS patients ranges from 28% to 39% for anxiety and 11% to 25% for depression (Dewani, 2023).

A patient with PCOS often faces additional challenges due to societal expectations. The societal and cultural pressures can exacerbate feelings of depression and frustration. Symptoms such as hirsutism, menstrual irregularities, and obesity can contribute to mental health issues. Of particular concern is infertility, especially in cultures where fertility is closely tied to notions of femininity. This can place significant emotional strain on married women, adversely affecting their quality of life and marital relationships (Arlt, 2022).

Research indicates that there is no definitive or permanent cure for PCOS in women. However, the symptoms can be managed through a combination of medical or ethno-medical treatments and lifestyle modifications. Studies have shown that lifestyle changes, including a healthy diet, regular exercise, and weight management, are prioritized in the treatment of PCOS (Dunne, 2006). These modifications help regulate hormone levels in both married and unmarried women. Additionally, medical practitioners typically initiate treatment with birth control pills to normalize menstrual cycles and may also prescribe medications for insulin resistance, such as those used to manage diabetes (Lucidi, 2023).

Traditional treatments for PCOS vary widely across cultures and regions of the world. These treatments often draw upon traditional medicine systems that have been practiced for centuries and are deeply rooted in local beliefs and customs. ‘Many traditional medicine systems, such as Traditional Chinese Medicine (TCM), Ayurveda, and Indigenous healing practices, utilize herbal remedies to address symptoms associated with PCOS. These herbs may include Fenugreek, Cinnamon, Licorice root, Saw Palmetto, Chaste Berry, and others, believed to regulate menstrual cycles, balance hormones, and improve fertility (Forthingham, 2020).

When seeking treatment, patients should consider the symptoms of irregular menstrual cycles, acne, hirsutism, weight gain, and, for married women, infertility. Addressing these symptoms often involves managing insulin resistance and regulating hormones. Initial steps should include dietary changes: avoiding processed or preserved foods, incorporating whole foods, and balancing carbohydrates and proteins. Additionally, the diet should include sources of healthy fats such as olive oil, fatty fish, and tree nuts. Ensuring adequate intake of iron, magnesium, and fiber is also crucial (Watson, 2023).

Besides all this there are some religious practices that are done for the treatment of some symptoms of PCOS. ‘It is guided by some religious Islamic scholars that recitation of Surah Al- Fatiha helps in the cure of menstrual cycle irregularity. Fasting in the month of Ramadan also lesson the stress and help in weight balance. The verses for the cure of infertility due to PCOS are the verses of Surah Al- Bakarah, the translation of that surah is in surah 21: 89–90, Allah says: “And (remember) Zakaria, when he cried to his Lord: “O my Lord! Leave me not without offspring, though Thou are the best of inheritors.” So we listened to him and granted

him Yahya (John). We cured his wife (barrenness) for him.” Similarly, the Prophet PBUH says: “Marry the kind and fertile women who will give birth to many children for I shall take pride in the great numbers of my ummah” (Nation) (Al-Bar et al., 2015; Altman, 2023; Deanna & Sachdev 2023; Forthingham, 2020; Society, 2008).

Materials and Methods

The researcher utilized anthropological research methods, specifically employing a descriptive approach covering Case Studies, In-depth interviews, and life histories. The study has provided detailed descriptions of these tools to explore the research questions (Singh, 2023). Case studies and life histories made it possible to gather thorough and specific information from a variety of sources, including observations, interviews, and documents, to have a deeper comprehension of the instances that were being investigated (Shahzad et al., 2017). Furthermore, the case study method was especially helpful for examining complicated or unusual phenomena in the real-world settings surrounding PCOS, providing insights into behaviors, processes, and outcomes that might not be captured through other research methods and offering workable solutions to particular problems or challenges faced by women with PCOS (Rashid et al., 2019).

Materials and Methods

For the present research, the research made use of purposeful sampling based on understanding of the study’s objectives. Firstly, female obstetric patients within a larger group of gynecology patients were identified. The focus was then narrowed to those diagnosed with Polycystic Ovary Syndrome (PCOS), as determined by their Luteinizing Hormone (LH) test and abdominal ultrasound results, reviewed by physicians. The study specifically targeted married women experiencing infertility who were in their reproductive age and unmarried women who had reached puberty and were 14 years old and above. Given the qualitative nature of the study, a large sample size was not required. A total of 20 in-depth interviews, 06 case studies & 03 life histories were conducted.

Results and Discussion

Relationship between Occupation and Household Income

The correlation analysis revealed a significant relationship between the two variables in the socio-economic survey: occupation and household income, as shown in Table 1. Socio-economic status has been linked to Polycystic Ovary Syndrome (PCOS). Specifically, women from lower socio-economic backgrounds were found at a higher risk of developing PCOS, which is often exacerbated by financial stress. Additionally, women who experienced low socio-economic status during childhood were also at increased risk (Azziz, 2011).

Table 1: Table showing Relationship between Occupation and Household Income

Correlations

	Occupation	Household Income
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Occupation	Pearson Correlation	1	.203*.015
	Sig. (2-tailed)		
	N	143	143
Household Income	Pearson Correlation	.203*	1
	Sig. (2-tailed)	.015	
	N	143	143

*. Correlation is significant at the 0.05 level (2-tailed).

PCOS Patient's: Family type and their interpersonal relationships

The correlation analysis of the socio-economic survey indicated a significant relationship between the variables of household members and family structure, as presented in Table 2. The study found that common family types were joint, nuclear experiencing childlessness associated with Polycystic Ovary Syndrome (PCOS). The type of family structure can influence the management of PCOS symptoms, either positively or negatively, depending on the support network and coping mechanisms available to the patients (Stephens, 2006).

Table-2: Table showing Relationship between Members in Household and Family Type

Correlations

Members in Household	Pearson	Members in Family type	
		Household	
		1	-.223**
	Correlation		
	Sig. (2-tailed)		.007
	N	143	143
Family type	Pearson		
		-.223**	1
	Correlation		
	Sig. (2-tailed)		.007
	N	143	143

**. Correlation is significant at the 0.01 level (2-tailed).

Relationship between Marital Status of PCOS Patients and Family Type

The correlation analysis revealed a significant relationship between marital status and family type, as illustrated in Table 3. This analysis indicated that married patients, particularly those living in joint family structures, experience higher levels of stress related to infertility compared to their unmarried counterparts. In cultures where fertility is highly valued as a marker of femininity, married women with PCOS face greater stress due to societal pressure and cultural expectations than unmarried women (Mumtaz & Salway, 2007).

Table 3: Table showing Significant Relationship between Marital status and Family Type

Correlations

		Marital status	Family Type
Marital status	Pearson Correlation	1	.216**
	Sig. (2-tailed)		.010
	N	143	143
Family type	Pearson Correlation	.216**	1
	Sig. (2-tailed)	.010	
	N	143	143

**. Correlation is significant at the 0.01 level (2-tailed).

From a socio-cultural perspective, patients with PCOS, particularly those experiencing infertility, face significant challenges in societies where fertility is equated with femininity. PCOS patients encounter complex difficulties shaped by cultural attitudes, societal expectations, and gender norms. The condition often carries considerable stigma due to its association with infertility and irregular menstrual cycles. Women with PCOS may feel pressured to conform to traditional maternal roles, leading to feelings of inadequacy and social isolation. Additionally, cultural beliefs and misconceptions about PCOS can impact their willingness to seek treatment and adhere to medical recommendations. To enhance the well-being and quality of life for PCOS patients, it is essential to address these socio-cultural factors through education, awareness campaigns, and culturally sensitive healthcare practices (Dunaif, 2017).

Qualitative Findings

Thematic categories were extracted from qualitative in-depth interview, case studies and life histories. Thematic analysis is presented in subsequent headings surrounding women with PCOS. Qualitative analysis of the 20 respondents revealed 05 main themes : 1) “Link between PCOS and Stress”; 2) “Stress of PCOS Associated with Previous Medical History”; 3) “Stress

Linked with Symptoms of PCOS and Societal Response” ; 4) “Straining Marital Relationship: PCOS, Painful Sexual Experiences”; and 5) “Reliance on Ethno-Medicinal Treatment and Spiritual Engagement”. The study found that existing literature on PCOS is more generalized and needs to be contextualized to have local insights into the problem. This study’s findings not only resonate with existing literature but also attempts to bridge the gap in capturing experiences of women of reproductive age group in accessing care in localized context. Nearly all participants connected “stress” with PCOS. Women with PCOS experienced barriers to care, structural violence, stigma and mental health, meaninglessness in life, historical experiences or traumas and negative societal trends of husbands, in-laws and overall society. It draws our attention to the dominance of traditionality and lack of information at multiple ends. In this context, there is a continued need for awareness and access to information and health facility to be addressed in reproductive health policy to lessen the burden of PCOS and associated mental and wellbeing issues among women of reproductive age group. Some of the socio-cultural perceptions faced by PCOS patients are presented in the subsequent sections.

Link between PCOS and Stress

Stress prior to having PCOS

The theme brings together many challenging concerns related to PCOS among both married and unmarried women. Study found that excessive stress among such women led to significant hormonal disturbances. Studies found that chronic stress disrupts the delicate balance of hormones involved in ovarian function, such as cortisol and insulin, which are already dysregulated in PCOS. Stressors can range from psychological factors, such as work pressure or emotional strain, to physical factors, such as illness or inadequate sleep. These stressors can exacerbate insulin resistance a common characteristic of PCOS and further impair ovarian function, resulting in irregular menstrual cycles and ovarian cyst formation. Additionally, heightened stress may aggravate PCOS symptoms, including weight gain and acne (Chaudhuri, 2023; Dokras, 2011).

Majority of the participants reported experiencing considerable stress before the onset of PCOS symptoms. For instance, one respondent described significant familial stress, attributing it to difficulties in adjusting to her in-laws and mistreatment from the beginning of her marriage. Another respondent noted that a stressful home environment exacerbated her condition, stating that she only found relief when away from home. These observations suggest that individuals who face elevated stress levels or live in high-stress environments may be more prone to hormonal imbalances, which can contribute to chronic conditions such as PCOS.

Stress of PCOS Associated with Previous Medical History

Since many deliberations were about the relationship between the previous medical history of the respondents with PCOS. Many respondents reported an increase in negative mental health associated with their previous medical history that was perceived to have an impact on having PCOS, one respondent was of the view that stress of any previous chronic disease also cause hormonal imbalance. Similar findings were stated in a study that chronic diseases preceding PCOS can induce stress responses that exacerbate hormonal imbalances and contribute to the development or worsening of PCOS symptoms. The psychological burden of managing chronic diseases alongside PCOS can compound stress levels, impacting overall health and well-being (Huang, 2016). Related to PCOS, most of the participants spoke about it with the following expressions.

One of the respondents shared that,

"I was experiencing constipation over the past 3-4 years, accompanied by severe abdominal pain, a sensation of stretching during bowel movements, and the presence of blood in the stool due to having PCOS" (IDI-UM3).

A carrier of minor thalassemia, indicated her problem in the following manner,

"I was having persistent anxiety about her condition led to hormonal imbalances, which contributed to the development of PCOS" (IDI-UM7).

A 20-year-old respondent narrated that,

"I was suffering from H. pylori infection, noting that the heavy medications required for treatment caused hormonal disruptions, which also resulted in PCOS" (IDI-UM10).

Majority of the respondents of the study mentioned hormonal disturbances due to their pre-existing conditions, which ultimately contributed to the onset of PCOS. In summary, this discussion underscores those various diseases, whether chronic or not, can cause significant hormonal disturbances. Furthermore, treatments for certain conditions can exacerbate these hormonal imbalances, potentially leading to the development of PCOS.

Stress Linked with Symptoms of PCOS and Societal Response

The symptoms of PCOS such as obesity, hirsutism, hair loss, acne, irregular menstrual cycles, and infertility can significantly impact an individual's self-esteem and mental well-being. The societal pressures associated with beauty standards and fertility expectations can intensify these effects. As a result, PCOS patients often face heightened stress due to both the physical manifestations of the condition and the societal stigma and criticism they encounter. The societal expectations related to fertility and body image can further exacerbate feelings of inadequacy and isolation among affected individuals. The pressure to adhere to traditional feminine roles and the stigma surrounding reproductive health issues contribute to the emotional strain experienced by those with PCOS (Benson et al., 2009; Chaudhuri, 2023; Damone et al., 2019).

Body Image Distress due to PCOS

The symptoms of PCOS including hirsutism, hair loss, and acne, and obesity can contribute to a sense of inferiority among affected individuals, leading to increased stress. These visible symptoms frequently clash with societal beauty standards, resulting in feelings of inadequacy and reduced self-esteem. The pressure to conform to traditional beauty ideals can intensify the psychological burden experienced by women with PCOS, often resulting in elevated levels of anxiety and depression.

Patients, whether married or unmarried, commonly experienced stress related to these visible symptoms. For example, one patient noted that her obesity and facial hair led to the rejection of her initial marriage proposal, exacerbating her concerns about her appearance and deepening her sense of inferiority. In summary, the visible manifestations of PCOS, such as hirsutism,

obesity, acne, and hair loss, often draw societal criticism and stigma. This external scrutiny can contribute to a pronounced inferiority complex regarding personal appearance, significantly increasing the stress experienced by those affected.

PCOS, Infertility, and Irregularity of Menstrual Cycle

In cultures where fertility is highly valued as a marker of femininity, infertility becomes a significant issue, leading to the development of numerous social stigmas surrounding this condition. These stigmas contribute to the stress experienced by patients. The irregularity of menstrual cycles or severe menstrual cramps can heighten stress and anxiety related to the fear of infertility, often exacerbated by societal myths and expectations.

In such cultural contexts, the expectation for women to fulfill traditional maternal roles places additional pressure on those unable to conceive. This inability to achieve pregnancy can result in social stigma, criticism, and increased pressure from family and community members, further compounding the emotional distress experienced by women with PCOS. The societal demand for normative reproductive health intensifies stress related to irregular menstrual cycles and contributes to the overall negative impact on the mental health and well-being of affected individuals (Bai & Ding 2019).

The data gathered from the study reveals that nearly all married individuals with PCOS experience infertility, with only 1% reporting a diagnosis of PCOS after childbirth. Both married and unmarried patients frequently encounter challenges with irregular or painful menstrual cycles. For instance, one respondent, who had been married for six years, reported an inability to conceive due to PCOS, accompanied by painful periods and frequent watery discharge causing considerable discomfort. Another respondent experienced divorce after three years of marriage, attributing it to infertility. Additionally, a divorced respondent described a severe episode of menstrual pain following a four-month gap, which required an emergency hospital visit.

These observations indicate that irregular menstrual cycles, which can occur as often as twice a month or as infrequently as every four to six months, are a significant source of stress. Moreover, societal stigmas associated with infertility often lead to negative social consequences, such as divorce, which further exacerbates stress among affected women.

PCOS and Women Lifestyle

Unhealthy lifestyle and bad routine habits lead to adverse changes in the body metabolism, causes hormonal disturbance which can lead to chronic diseases like PCOS. ‘PCOS can be influenced by unhealthy lifestyle and routine habits, such as poor diet, lack of exercise, and irregular sleep patterns. These habits can contribute to obesity and insulin resistance, which are key factors in the development and exacerbation of PCOS symptoms. A diet high in processed foods and sugars can lead to weight gain and insulin spikes, aggravating hormonal imbalances. Sedentary lifestyles further worsen these effects, as physical inactivity is associated with higher insulin resistance. Irregular sleep patterns and chronic stress also disrupt hormonal regulation, exacerbating PCOS symptoms’(Marshall, 2020).

When discussing lifestyle changes appeared to be a relevant issue. When asked about its relevance some patients reported having PCOS due to their bad routine and bad eating habits, one respondent named Salma responded definitively, she said:

"I used to sleep at 4:00 am in the morning and wake up at 2:00 pm in the afternoon. In breakfast I use to have a cup of tea with some rusks and then I had meal at 9:00 pm at night. Later I was diagnosed with irregular periods and infertility" (IDI-UM2).

There was another respondent Misbah who described her PCOS issue in the following manner.

"I used to work online till late night for 10 hours with a habit of eating fast food. Later I was diagnosed with PCOS due to irregular periods and obesity" (IDI-UM6).

Likewise, there were many other patients from the study sample who were experiencing a disturbed routine coupled with bad eating habits ultimately leading to PCOS. Such findings endorsed that sedentary lifestyles, insomnia and bad food habits lead to worst metabolic and hormonal changes that causes PCOS.

Low Socio-economic Status and PCOS

PCOS patients with low Socio-economic status feel difficulty in getting treatment and having healthy diet due to financial crisis. Low socio-economic status (SES) is closely linked to the prevalence and severity of PCOS due to limited access to healthcare, nutritious food, and health education. Women from lower SES backgrounds often face barriers in obtaining timely and effective medical care, which can lead to delayed diagnosis and inadequate management of PCOS. Financial constraints may limit their ability to purchase healthy foods, leading to diets high in processed foods and low in essential nutrients, exacerbating insulin resistance and obesity associated with PCOS. Furthermore, stress related to financial instability and poor living conditions can worsen hormonal imbalances and PCOS symptoms (Marzullo, 2019).

There were approximately fifty to sixty percent patients from the sample who were from low socio-economic status making it very hard for them to get treatment, majority of them were married and had infertility issues.

One respondent named Sana 30 years of age reflected on the severity of the problem in the following way,

"My husband is the only one who makes money in our household, so it is very difficult for me to get treatment. Should we eat or should we get treatment in such inflation?" My in-laws "do not understand and always criticize me for infertility." (IDI-M13)

While another respondent Malika 32 years of age reported that,

"I had faced a low socio-economic position since childhood, and my family lived in constant stress owing to financial hardships. I also suffered from severe baldness and had last menstruation seven months ago" (IDI-UM5).

She claimed that it is very difficult for her to receive PCOS treatment owing to the financial crunch of the family and overall inflation. She was just receiving medication for PCOS related to hair loss since she was unmarried.

From these cases it can be safely concluded that low socio-economic status has a direct link with cure of PCOS. Having low status causes stress and it becomes difficult for the patients to get treatment, knowledge and healthy diet or supplements suggested by the physicians. Many participants spoke of having access to quality health and awareness surrounding the myths and stigma related to PCOS and increasing community-based knowledge around mental health and wellbeing issues is essentially important where women cannot openly talk about their health concern and do not have free access to health care facility. Medical facilitation needs to be provided at their doorsteps.

Straining Marital Relationship: PCOS, Painful Sexual Experiences

Straining Marital Relationship: PCOS, Painful Sexual Experiences is a theme that was developed to reflect the underlying stress connections of a married women with their partners. Researchers have shown that in married women who are diagnosed of PCOS had to face painful intercourse and the is more than normal which make them mentally disturbed that they were not mentally ready for that but if they refuse, they had to face strain in their relationship. 'PCOS patients often face criticism and strain in their marital relationships due to dyspareunia, or painful intercourse, which is a common symptom of the condition. This pain can be caused by hormonal imbalances, ovarian cysts, or vaginal dryness associated with PCOS. Such issues can lead to reduced sexual satisfaction and intimacy, causing frustration and misunderstanding between partners. Husbands may not fully understand the medical complexities of PCOS, leading to unwarranted criticism or feelings of rejection. This can exacerbate the emotional stress and mental health challenges faced by women with PCOS (Zhang, 2019).

There were some married women who participated in this study complained about having misunderstanding with their partner and mental disturbance due to painful sexual experiences.

One respondent Samra, 35 years of age reported that,

"My husband has threatened me of second marriage if I do not have a satisfying sex with him". She further said that "my husband works in a public hospital for night duty, we only had a met up at weekends so, my husband gets angry that after a week I came and you are not ready and refusing me, for this reason we were having complexities in our relationship" (IDI-M14)

Such cases signify that PCOS causes misunderstanding and complexities in marital relationships due to painful sexual relationships. The patients do not feel mentally satisfied because of pain and it causes emotional distress and strain in their relationship.

Case Study 1: Women with PCOS facing Societal Pressure

In this case, a 26-year-old patient Wajiha, who was married for six years, has struggled with infertility issues. Over a span of two to three years, she experienced a significant weight gain from 52-79 kgs, despite having a height of 5'6". Her infertility issues led to painful sexual experiences and considerable mental distress. Her husband threatened to give her divorce and going for a second marriage on this stance her in-laws offered no support. To manage her stress, she began working as a teacher at a school, with additional evening teaching at a coaching academy and taught Quran at a local center. Her busy schedule helped her to avoid dwelling on societal negativity. She acquired substantial information about PCOS through online

research, although she still experienced hidden stress related to infertility and obesity, she found ways to cope up.

This case underscores that PCOS not only leads to infertility but also significantly heightens stress due to societal pressures. The patient's experience illustrates how societal expectations surrounding fertility and parenting, which are often regarded as central to a woman's identity and social role, can intensify psychological distress. Such pressures from family, friends, and society can exacerbate the emotional difficulties associated with PCOS, affecting overall mental health and wellbeing (Helm, 2017).

Case Study 2: PCOS, Infertility, and Divorce

Another 25 years patient Noureen 5'4" tall women experienced considerable weight gain of 72 kgs was diagnosed with PCOS four years ago. She was still struggling with this condition since she was 19 years old. Despite having PCOS before marriage, she did not disclose it to her fiancé, nor did she seek any kind of treatment initially. After three years of marriage, her husband remarried, leading to their divorce, which was attributed to infertility aimed PCOS. The patient experienced significant emotional trauma following the separation but later engaged in a nursing course at a local hospital as a means of coping.

Her diet predominantly consisted of fast food and soft drinks, and she frequently ruminated on her situation. She received medical treatment, including injections, and was advised to follow an exercise regimen and a structured routine, which she found challenging. The patient reported mood swings and irregular menstrual cycles. Through her nursing course and social media research, she gained extensive knowledge about PCOS.

This case study underscores that overcoming excessive worry and adhering to medical advice are crucial for managing PCOS. Effective management of PCOS requires the patient's commitment to following physician recommendations and maintaining a healthy lifestyle, including a balanced diet. Women with PCOS may face significant marital strain due to infertility, which can lead to divorce in many cultural contexts. Fertility is often highly valued and considered essential for marital stability and fulfillment. Infertility related to PCOS can result in not only personal distress but also substantial societal and familial pressure, exacerbating tensions and potentially leading to marital dissolution (Alnaeem, 2019).

Case Study 3: Stressful Environment, low Socio-economic Status and treatment of PCOS

Another patient Amina, a 25-year-old woman was diagnosed with PCOS a year ago when she was preparing for marriage in a few months. She has faced significant socio-economic challenges throughout her life, which have contributed to her PCOS diagnosis. The stress associated with her financial difficulties and educational struggles has exacerbated her condition.

The patient reported an absence of menstruation from the previous eight months, with her periods now extending beyond two weeks. She also experienced severe hair loss and academic pressure, as she was currently pursuing a bachelor's degree. Additionally, she reported emotional distress related to her marriage and ongoing familial conflicts associated both with her studies and PCOS.

Despite applying various treatments, such as topical oils and natural remedies, her hair loss persisted. She has been prescribed supplements and medications to regulate her menstrual cycles but is facing financial strain in affording these treatments. The patient had adopted a healthier lifestyle, including improved dietary habits, and has sought information about PCOS from peers and social media.

This case highlights the impact of socio-economic status on the development and management of PCOS. Low socio-economic status (SES) is a significant stressor that can both contribute to and exacerbate PCOS. Women from lower SES backgrounds often experience chronic stress due to financial instability, limited healthcare access, inadequate nutrition, and poor living conditions. This case underscores the importance of addressing socio-economic factors and maintaining focus on personal health goals despite external challenges (Baghla, 2023).

Life History of A PCOS Patient

Areeba, was diagnosed with PCOS one year ago. Currently she was 22 years old. She was born in a low socio-economic household. Despite financial constraints, her parents ensured that she and her two brothers received education from a local school and later from a college located in the city. Areeba got married at the age of 19 while pursuing her graduation. Her father, who had worked in Saudi Arabia for many years, had returned permanently to Pakistan by the time she got married. During her marriage, Areeba encountered several challenges. Her in-laws mistreated her and tried to keep her from her husband by causing controversies. Her husband did not show any support either. This led to a fight between the couple. Areeba contracted an *H. pylori* infection, which worsened due to lack of treatment. She told her in-laws and husband about these problems, but they did not believe her. On the basis of misunderstanding and noncooperation she often returned to her parents' house where she also endured terrible mistreatment, including an attempted suicide by her mentally sick sister-in-law.

Areeba's marriage lasted only three months, and she suffered from serious emotional stress. She experienced irregular menstrual periods and obesity, which resulted in a combined diagnosis of PCOS and *H. pylori* infection. After having divorce, she sought help from a psychologist later she is working at a local hospital. Over time, she has made significant progress in managing her stress related to PCOS. This case underscores that low socio-economic status is closely linked to PCOS. Additionally, severe traumatic experiences can lead to hormonal imbalances that contribute to chronic conditions such as PCOS. Trauma-induced stress can disrupt the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol and androgen levels, which are associated with PCOS. Furthermore, stress from trauma may lead to unhealthy behaviors, such as overeating or physical inactivity, which exacerbate conditions like obesity and insulin resistance that are commonly linked to PCOS (Cooney 2017).

Reliance on Ethno-Medicinal Treatment and Spiritual Engagement

In anthropology ethno-medical treatment refers to treatments other than bio medical treatment. 'Ethno-medical treatments for PCOS encompass a range of traditional and cultural practices that communities utilize to manage symptoms and improve wellbeing. These practices often include herbal remedies, dietary modifications, and lifestyle adjustments that have been passed down through generations and rooted in cultural beliefs. For example, in some cultures, specific herbs or teas are believed to regulate menstrual cycles or alleviate symptoms like hirsutism.

Dietary changes may focus on avoiding certain foods or incorporating others believed to have therapeutic benefits' (Acharya, 2021),

The sample data indicates that many PCOS patients have utilized various home remedies in addition to conventional medical treatments. For instance, one respondent mentioned that her mother prepared fresh vegetable juices specifically for managing PCOS. Others reported using specialized herbal teas or drinking ample water, which they believe helps in reducing stress. Many patients have incorporated regular exercise and adopted healthier dietary practices to improve their condition. One participant noted using a mixture of besin (gram flour) and shahad (honey) as a topical treatment for acne.

Additionally, some patients integrate religious practices into their treatment regimen. For example, one individual recited Surah Al-Fatehah seven times over water and consumed it, believing it would aid in her recovery. Another patient mentioned reciting Surah Yaseen and Manzil, expressing her faith in Allah's ability to cure her. Delay in seeking treatment connects the patients with unqualified practitioners and Pirs (saints) who provide them amulets or special waters, often further complicating the management of PCOS.

These findings suggest that alongside medical treatments, ethno-medicinal approaches, including home remedies, exercise, balanced diet, and religious recitations, play a significant role in managing PCOS. Such integrative practices appear to complement conventional therapies and contribute positively to the overall treatment strategy for PCOS.

Conclusions

Socio-culture encompasses the interplay of social and cultural factors that shape human behavior, beliefs, and interactions within a community. Present research focused on how cultural, social, influence health, illness, and healthcare practices surround women with PCOS by specifically addressing social stigmas associated with PCOS. Societal criticism contributes to heightened stress among patients, exacerbating their condition. Particularly, individuals with low socio-economic status and low education were severely affected by the problem. Moreover, these condition presents numerous societal challenges that affect both personal identity and relationships of women and their experiences remain untapped. Married women often face societal judgment regarding infertility, while unmarried women grapple with fears of future infertility and concerns about beauty standards related to PCOS. Patients with PCOS frequently feel ashamed to discuss their condition openly which delays their consultation with healthcare professionals and leads to more severe complications. Cultural practices, including reliance on home remedies and treatments from unqualified practitioners, such as those providing amulets or special waters, often further complicate the management of PCOS. To reduce the burden of PCOS and its sensitization, education and public awareness programs are direly needed at all levels.

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Sleep disturbances in women with polycystic ovary syndrome: prevalence, pathophysiology, impact and management strategies

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Abstract: Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting the reproductive, metabolic and psychological health of women. Clinic-based studies indicate that sleep disturbances and disorders including obstructive sleep apnea and excessive daytime sleepiness occur more frequently among women with PCOS compared to comparison groups without the syndrome. Evidence from the few available population-based studies is supportive. Women with PCOS tend to be overweight/obese, but this only partly accounts for their sleep problems as associations are generally upheld after adjustment for body mass index; sleep problems also occur in women with PCOS of normal weight. There are several, possibly bidirectional, pathways through which PCOS is associated with sleep disturbances. The pathophysiology of PCOS involves hyperandrogenemia, a form of insulin resistance unique to affected women, and possible changes in cortisol and melatonin secretion, arguably reflecting altered hypothalamic–pituitary–adrenal function. Psychological and behavioral pathways are also likely to play a role, as anxiety and depression, smoking, alcohol use and lack of physical activity are also common among women with PCOS, partly in response to the distressing symptoms they experience. The specific impact of sleep disturbances on the health of women with PCOS is not yet clear; however, both PCOS and sleep disturbances are associated with deterioration in cardiometabolic health in the longer term and increased risk of type 2 diabetes. Both immediate quality of life and longer-term health of women with PCOS are likely to benefit from diagnosis and management of sleep disorders as part of interdisciplinary health care.

Keywords: polycystic ovary syndrome, sleep, sleep disturbance, hypothalamic-pituitary-adrenal, cardiometabolic health

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder with implications for reproductive, psychological and metabolic health. Despite first being identified in the 1930s, recognition of an association between PCOS and sleep disturbances is relatively recent. A search of the PubMed database indicates that the majority of research on this topic has been published after 2005 and the body of work remains quite small (Figure 1).

In this review, we first provide an overview of PCOS and summarize the clinical and epidemiological literature pertaining to sleep disturbances and disorders among women with the condition. The pathways through which PCOS may influence sleep are then described in detail, focusing on the endocrine, psychosocial and behavioral characteristics that are often present among women with PCOS, drawing attention to probable bidirectional relationships (Figure 2). Current knowledge about the long-term

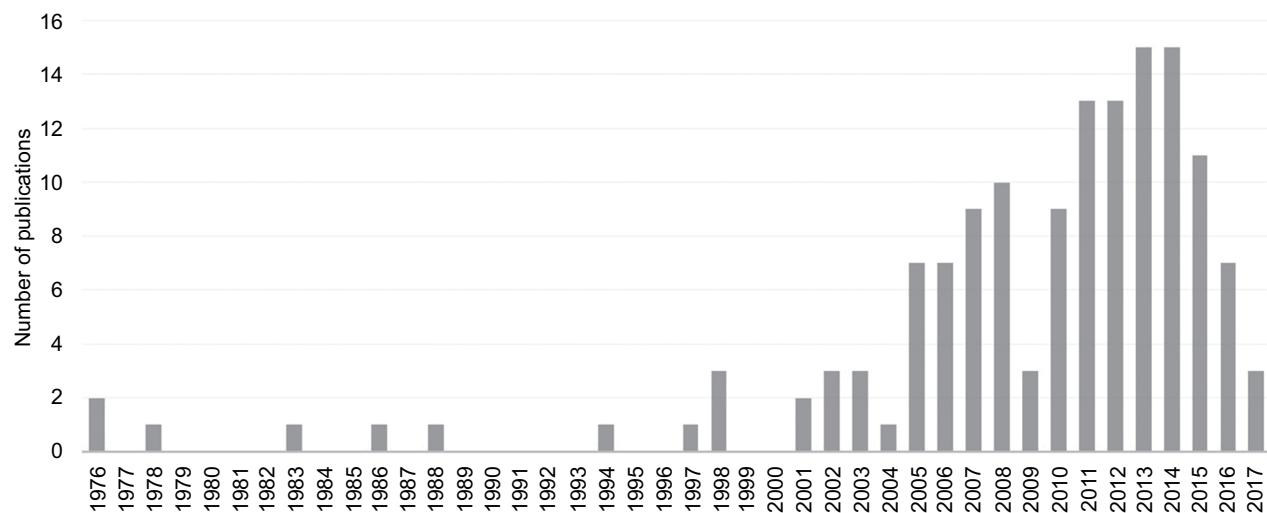


Figure 1 The number of articles published in PubMed per year on the topic of PCOS and sleep.

Abbreviation: PCOS, polycystic ovary syndrome.

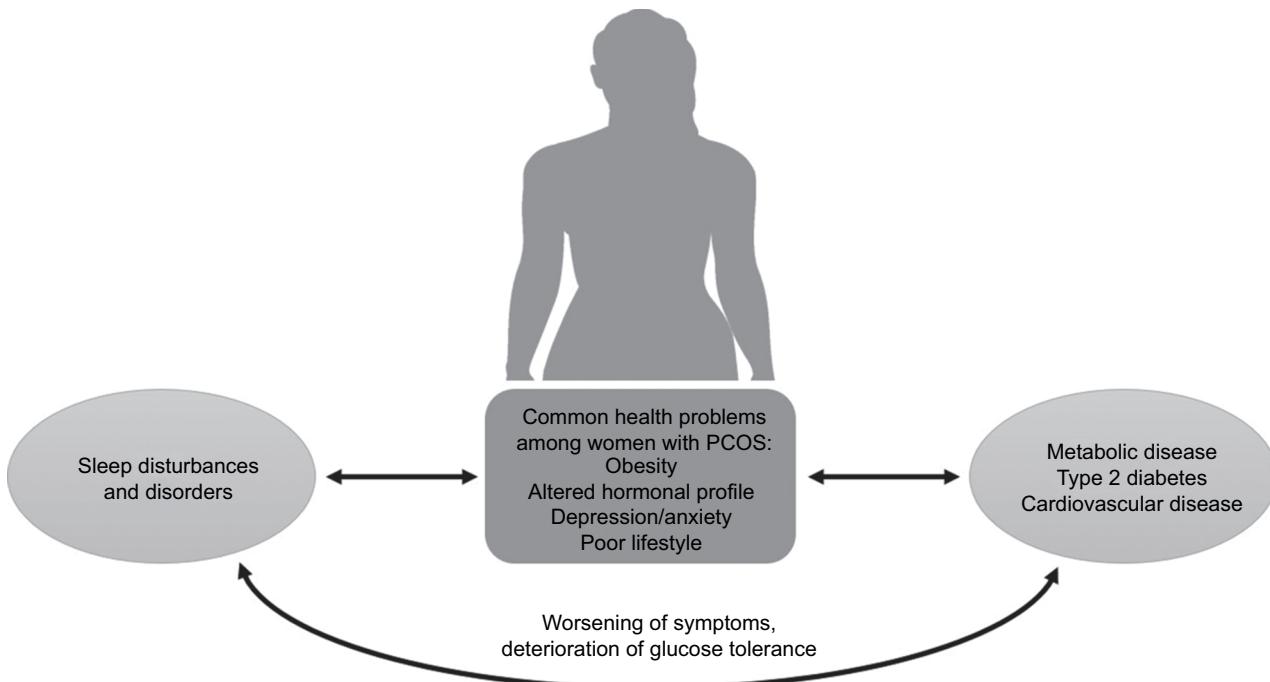


Figure 2 Summary of the bidirectional pathways through which PCOS interacts with sleep disturbances, with potentially detrimental effects on long-term cardiometabolic health.

Abbreviation: PCOS, polycystic ovary syndrome.

consequences of PCOS for cardiometabolic health is outlined as well as the potential contribution of impaired sleep to deterioration of health profiles.

Polycystic ovary syndrome

PCOS is an endocrine disorder that manifests in an array of symptoms that varies from one woman to another.¹ This

heterogeneity has hampered the definition of the syndrome, etiological research, recognition in clinical practice and appropriate treatment and support for women.

PCOS was first recognized as a clinical entity in the 1930s. At that time it was named Stein–Leventhal syndrome, after the two clinicians who first reported the disorder in seven women who presented with hirsutism, amenorrhea and

enlarged bilateral polycystic ovaries, along with obesity.^{2,3} Once considered a reproductive disorder acquired by adult women, it is now widely accepted that PCOS is a lifelong metabolic condition.⁴

Features of the syndrome classically emerge during puberty, but diagnosis can be difficult because irregular menstruation is common in normal development.^{1,5} Excess body hair accumulates gradually, reflecting increasing duration of androgen exposure. Some girls (and women) with PCOS have severe acne vulgaris (predominantly on the lower face, neck, chest and upper back).¹

Historically, recognition of PCOS by clinicians was erratic.^{6,7} In addition, reluctance to seek medical advice (e.g. due to embarrassment) meant that many women did not receive a diagnosis until they sought fertility treatment, or lifelong.⁸ Undiagnosed PCOS is still relatively common.⁹

Currently, there are three sets of criteria for diagnosing PCOS, summarized in Figure 3. Differences between the criteria reflect controversy about the pathogenesis of PCOS and the different forums in which experts' opinions were canvassed.³ In 1990, experts at a conference sponsored by the US National Institutes of Health (NIH) produced the first attempt at defining PCOS clinically. The NIH criteria specify (in order of importance) that clinical and/or biochemical signs of hyperandrogenism should be present as well as oligo- or anovulation (i.e. irregular or no periods).¹⁰ In 2003, the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine produced a statement, known as the Rotterdam criteria, specifying that two out of the following three must

be met for a diagnosis of PCOS: clinical and/or biochemical hyperandrogenism, oligo- or anovulation and polycystic ovaries on ultrasound.¹¹ In 2006, the Androgen Excess Society (AES) Taskforce produced criteria specifying that hyperandrogenism must be present for diagnosis, in addition to either oligo- or anovulation or polycystic ovaries on ultrasound (or both).¹² There have been several attempts to subclassify the syndrome using clinical and metabolic criteria, without universal agreement.^{3,13}

All diagnostic criteria specify that diagnosis of PCOS should only be made after exclusion of other endocrine disorders including congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, thyroid dysfunction and hyperprolactinemia. Early studies of women with PCOS suggested they had elevated prolactin, and explored overlap in symptoms between hyperprolactinemia and PCOS, but these are now considered to be two distinct conditions.^{14–18}

Beyond the enlargement of ovaries originally noted by Stein and Leventhal,² ovaries with multiple cysts (follicles with arrested development) have other features, including a thickened covering capsule and greatly increased stromal tissue. The thecal and stromal layers produce excess androgen, and this led to the view that pathogenesis is primarily ovarian.¹⁹ While recognizing wider metabolic involvement, the AES takes the position that PCOS is primarily a disorder of hyperandrogenism.¹² Lack of consensus on this matter persists because hormone signaling has a major role in systems such as the hypothalamic–pituitary–adrenal (HPA) axis, so the disorder could have a central origin, and there are conflicting results from interventions in which androgens were

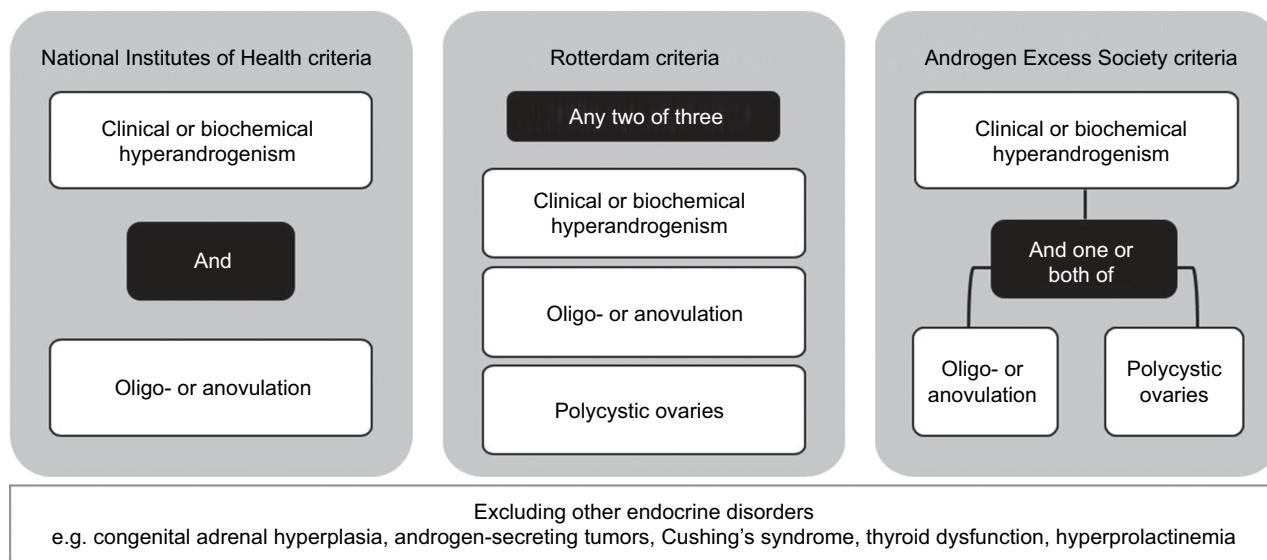


Figure 3 A summary of the three sets of criteria for the diagnosis of PCOS: the National Institutes of Health criteria (1990),¹⁰ the Rotterdam criteria (2003)¹¹ and the Androgen Excess Society criteria (2006).¹²

Abbreviation: PCOS, polycystic ovary syndrome.

reduced in women with PCOS.³ Additionally, constructive debate is impeded by lack of a reliable assay designed to measure androgens in the range relevant to women, approximately one-tenth that of men.^{20,21}

Research undertaken in the 1980s demonstrated insulin resistance in women with PCOS, underpinning the alternative view that this is the cardinal feature of the syndrome, with hyperinsulinemia causing hyperandrogenemia and anovulation.³ Even lean women with PCOS generally have insulin resistance of an intrinsic form,²² which appears to be the result of a defect in post-binding insulin signaling that disturbs metabolic but not mitogenic functions.²³ This abnormality appears unique to PCOS, as it has not been observed in other conditions of insulin resistance, including obesity and type 2 diabetes.²⁴ Thus, when women with PCOS have high body weight, they are affected by both intrinsic and extrinsic insulin resistance.³ PCOS has recently been conceptualized as a condition of severe metabolic stress,²⁵ a position that we support as it provides a way to account for the pervasive molecular and biochemical derangements that occur in PCOS and variation in symptom profiles.

Clustering of diagnosed PCOS and isolated hormonal and metabolic symptoms within families supports a genetic component to the etiology of PCOS;²⁶ however, phenotypic variation suggests that multiple genes are involved.²⁷ Familial and cohort studies have identified numerous gene loci as candidates for conferring susceptibility to PCOS. These include polymorphisms in loci associated with androgen receptors and with insulin signaling. For many of the candidate loci, it remains unclear as to how they relate to specific PCOS characteristics.²⁷

Support for fetal or early life origins of PCOS stems from animal models in which exposure to androgen excess, or growth restriction or acceleration, has produced symptoms of PCOS.^{3,28} It is unlikely that maternal androgens reach the fetus in human pregnancies, although fetal ovarian androgen production is possible.³ Birth phenotypes in humans have consistently been associated with insulin resistance, type 2 diabetes and the metabolic syndrome.^{29–32}

While we accept a genetic contribution, our research^{33,34} is premised on interactions with the fetal environment producing epigenetic changes that culminate in PCOS.³⁵ Hypothesized “programming” of metabolic function is not simply about growth of the fetus or size at birth, although these are overt signs of perturbed development in utero.³⁶ A range of conditions, including maternal under- and overnutrition and mental distress, can inhibit the activity of an enzyme in the placenta (11 beta-hydroxysteroid dehydrogenase) that is

critical to reducing fetal exposure to maternal glucocorticoids.³⁷ Through this process, it is proposed that overexposure of the fetus alters the set points and function of the HPA axis, with profound implications for metabolism.

Uncertainties about PCOS also persist because it is difficult to study in representative population-based samples of women. Obtaining self-reports of doctor-diagnosed PCOS will result in misclassification of a substantial proportion of women as unaffected. Some symptoms can be reported reliably but others require invasive tests, and the sensitive nature of symptoms may affect participation. Thus, few studies with community-based samples have been undertaken to date, although clinic-based samples have been reported on extensively.

We retrospectively established a birth cohort of Australian women using records from a large maternity hospital.⁹ We traced over 90% of 2199 female babies three decades after they were born. Around half of the young women who were eligible joined the study and completed an initial interview in which medical and reproductive history, including symptoms of PCOS, were reported. Women were asked to provide a blood sample for assessment of free testosterone. Those with evidence of both hyperandrogenism and oligo- or anovulation were classified as having PCOS as per the NIH criteria. Women with one or both of those two symptoms were referred to a clinic for ovarian ultrasound so that we could apply the Rotterdam criteria. The prevalence of PCOS was $8.7 \pm 2.0\%$ with NIH criteria, $11.9 \pm 2.4\%$ with Rotterdam criteria assuming those who did not consent to ultrasound did not have cystic ovaries and $17.8 \pm 2.8\%$ with Rotterdam criteria using multiple imputation for missing ultrasound data. Over two-thirds of those classified as having PCOS had not been diagnosed previously.

Sleep disturbances and disorders and PCOS

Sleep disturbances include altered sleep duration, delay of sleep onset, difficulty in maintaining sleep or awakening early.³⁸ Insomnia is defined as impairment in the ability to initiate or maintain sleep, including extended periods of wakefulness during the night. Chronic insomnia disorder is diagnosed when insomnia occurs at least three nights per week and for at least three months.³⁹ Obstructive sleep apnea (OSA) is characterized by frequent cessations of breathing during sleep and may occur along with other sleep disturbances.⁴⁰ Clinically, OSA is diagnosed by detecting the frequency of events that are apneic (no airflow for 10 seconds) and hypopneic (decreased airflow for 10 seconds

associated with either an oxyhemoglobin desaturation or an arousal detected by electroencephalography), as per the apnea–hypopnea index (AHI). A diagnosis of OSA is made when AHI is ≥ 15 or when AHI is ≥ 5 with symptoms such as daytime sleepiness, loud snoring and witnessed breathing interruptions.⁴¹

Sleep disturbances and disorders have repercussions for daytime mood, cognition and psychomotor functioning,⁴² which acutely affect well-being and daily activities, and can inhibit performance in roles such as that of parent or employee.^{43,44} Aspects of cognition that appear most affected are attention, executive function and working memory,^{42,45} with significant implications for productivity.⁴⁴ Fatigue, attention deficits and psychomotor impairment can affect safety, increasing the risk of workplace and motor vehicle accidents.⁴² Thus, poor sleep represents a serious health problem.

As mentioned, it is difficult to study PCOS in representative population-based samples; so evidence concerning the prevalence of sleep disturbances and disorders across the full spectrum of PCOS severity is limited. We identified only three such studies (Table 1), summarized here, each supporting an excess of sleep disturbances and disorders in women with PCOS that was not accounted for by obesity.

Two studies have drawn on the Taiwan National Health Insurance Research Database in which PCOS and sleep

disorders were recorded using International Classification of Diseases codes (and thus required recognition and formal diagnosis).⁴⁶ In a longitudinal design, data for women with PCOS ($n = 4595$) and a comparison group of women matched for age ($n = 4595$) were assembled over 2–8 years. Women with PCOS had greater incidence of OSA (1.71 vs 0.63 per 1000 person-years), a difference not due to obesity or demographic characteristics (adjusted hazard ratio [HR] = 2.6, 95% confidence interval [CI] 1.6–4.0). In the second study, sleep disorders excluding OSA were considered as part of an investigation of PCOS and psychiatric disorders.⁴⁷ Over a 10-year period, compared to an age-matched comparison group of women ($n = 21,724$), those with PCOS ($n = 5431$) were 50% more likely to be diagnosed with a sleep disorder (HR = 1.5, 95% CI 1.2–1.9).

In the community-based cohort of Australian women that we undertook, sleep disturbances were self-reported using a modified version of the Jenkins questionnaire,⁴⁸ by 87 women with PCOS (as per Rotterdam criteria) and 637 women of similar age.⁴⁸ Sleep disturbances, specifically difficulty falling asleep (odds ratio [OR] = 1.9, 95% CI 1.3–3.0) and difficulty maintaining sleep (OR = 1.9, 95% CI 1.1–3.3), were twice as common in women with PCOS compared to those without. The former association persisted after accounting for body mass index (BMI) and depressive symptoms, but

Table 1 Summary of population- and community-based studies of sleep disturbances and PCOS in women

Study, country	Study design	Study groups	Outcomes of interest	Key results
Hung et al, ⁴⁷ Taiwan	Retrospective cohort constructed from the National Health Insurance Database (98% coverage)	5431 with PCOS and 21,724 without PCOS matched for age	Diagnosis of new-onset sleep disorders: ICD-9 780.5 (insomnias) and 307.4 (difficulty initiating and maintaining sleep, excluding OSA)	<ul style="list-style-type: none"> Women with PCOS were more likely to be diagnosed with sleep disorders: HR = 1.495 (95% CI 1.176–1.899) Most developed in the first year since diagnosis of PCOS
Lin et al, ⁴⁶ Taiwan		4595 with PCOS and 4595 without PCOS matched for age and time of enrollment	Diagnosis of OSA during follow-up (2–13 years)	<ul style="list-style-type: none"> Women with PCOS had a greater incidence of OSA (1.71 vs 0.63 per 1000 person-years) HR = 2.63 (95% CI 1.57–4.04) adjusted for demographics (urbanization, income) and comorbidities (hypertension, dyslipidemia, diabetes, obesity)
Moran et al, ⁴⁸ Australia	Cross-sectional analysis of data from a cohort based on births (1973–1975) at a large maternity hospital	87 with PCOS and 637 without PCOS	Sleep disturbance assessed using modified Jenkins questionnaire	<ul style="list-style-type: none"> Any sleep disturbances two times higher in women with PCOS Difficulty falling asleep: OR = 1.94 (95% CI 1.28–2.95), attenuated but still significant after adjusting for BMI and depressive symptoms Difficulty maintaining sleep: OR = 1.92 (95% CI 1.12–3.31), mediated by BMI and depressive symptoms PCOS not associated with early awakening or daytime sleepiness

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICD-9, International Classification of Diseases, Ninth Revision; OR, odds ratio; OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome.

not the latter. PCOS was not observed to be associated with unintended early morning waking or daytime sleepiness.⁴⁸

Clinic-based studies of sleep disturbances in women with PCOS

Polysomnographic assessments of clinical samples of women with PCOS have been undertaken, with OSA the focus in the majority (summarized in Table 2). Interpretation of the findings of these studies should be tempered with understanding of the limitations of this literature: clinic-based samples of women with PCOS are likely to comprise women with the most severe symptoms;⁴⁹ comparison groups are often convenience samples of women attending clinics for reasons other than PCOS; and sample sizes are often modest.

OSA is common in clinical samples of women with PCOS, affecting 17–75%, substantially higher than in other women of similar age and BMI, and thus is not attributable to the tendency of women with PCOS to be obese.^{50–54} One study has shown that OSA is elevated in women who have BMI in the normal range along with PCOS.⁵⁴ Women with PCOS have consistently been shown to have elevated AHI,

regardless of OSA diagnosis.^{50,51,53–55} Few differences in other polysomnographic variables, such as sleep latency, sleep efficiency and waking after sleep onset, have been found.^{50,51,54,55}

We have not systematically attended to studies of adolescents, given the difficulty in diagnosing PCOS at that stage of development and the likelihood that selection procedures (including factors involved in seeking an early diagnosis) contribute to inconsistent findings in polysomnographic studies.^{56–58} Of interest, however, one study demonstrated higher AHI and more OSA among obese girls with PCOS ($n = 28$) referred to a sleep clinic compared with a control group of girls ($n = 28$) matched for age and BMI, but no differences from a control group of boys ($n = 28$).⁵⁹

Excessive daytime sleepiness (EDS) is a hallmark of sleep disturbance in men, but may not be as relevant to women⁶⁰ who are more likely to report low mood or irritability or morning headaches following poor sleep.^{48,61} Nevertheless, EDS in women with PCOS has been investigated,^{50,51,54,55} usually using the Epworth Sleepiness Scale.^{50,51,55} Predominantly, the clinical studies have shown PCOS to be associated with EDS, often in the absence of OSA. For example, in one study

Table 2 Summary of clinic-based studies of sleep disturbances and PCOS in women

Study, country	Study design	Study groups	Outcomes of interest	Key results
Fogel et al, ⁵⁰ USA	Cross-sectional, PCOS and comparison group	18 with PCOS, all obese; and 18 without PCOS matched for age and weight	AHI, AHI (REM sleep), OSA (AHI >5 with EDS), ESS, sleep onset latency, sleep efficiency, % stages 3 and 4 and % REM sleep	<ul style="list-style-type: none"> • AHI: PCOS 22.5 ± 6.0 vs controls 6.7 ± 1.0, $p = 0.008$ • AHI (REM sleep): PCOS 41.3 ± 7.5 vs controls 13.5 ± 3.3, $p < 0.01$ • OSA: PCOS 44.4% vs controls 5.5%, $p = 0.008$ • ESS: PCOS 9.5 ± 0.9 vs non-PCOS 5.8 ± 0.8, $p < 0.01$ • No significant differences in other PSG variables • Clinically significant insomnia was higher in PCOS <ul style="list-style-type: none"> o AIS – 12.6% vs 3.2%, $p = 0.01$ o ISI – 10.5% vs 1.1%, $p = 0.004$ • No significant difference in ESS or PSQI
Franik et al, ⁶² Poland	Cross-sectional, PCOS and comparison group	95 with PCOS and 95 without PCOS	AIS, ISI, ESS and PSQI	
Gopal et al, ⁸⁷ USA	Cross-sectional, PCOS and comparison group	23 with PCOS, all premenopausal and obese; and literature-based historical controls	Snoring, RDI, OSA (RDI ≥ 5) and other variables (e.g. arterial oxygen saturation)	<ul style="list-style-type: none"> • 16/23 (69.6%) met the criteria for OSA • 5/23 required CPAP • No correlation was found between degree of obesity and severity of OSA • No results reported for other variables
Mokhlesi et al, ⁸⁶ USA	Cross-sectional, PCOS and comparison group	17 with PCOS, all nonobese; 27 with PCOS, all obese; 26 without PCOS, all nonobese; and 8 without PCOS, all obese	Berlin questionnaire for assessment of OSA risk	<ul style="list-style-type: none"> • Women with PCOS had higher prevalence of high-risk OSA (47% vs 15%, $p < 0.01$) • None of the nonobese PCOS and nonobese control women screened positive for OSA • Obese PCOS vs obese controls had similar prevalence of OSA • BMI was only independent predictors of OSA

(Continued)

Table 2 (Continued)

Study, country	Study design	Study groups	Outcomes of interest	Key results
Suri et al, ⁵¹ India	Cross-sectional, PCOS and comparison group	50 with PCOS, all untreated; and 16 without PCOS, matched for age, who reported snoring	RDI, SDB (RDI ≥5 with symptoms, RDI >15 without symptoms), sleep onset, TST, WASO, REM sleep (minutes), NREM sleep (minutes), sleep efficiency, ESS and RERA	<ul style="list-style-type: none"> SDB: OR = 46.5 (95% CI 14.6–148.4), no longer significant after adjusting for BMI and WC Higher RDI in PCOS with SDB (22.5) compared to controls with SDB (9.0), $p = 0.01$ WASO: PCOS 55.4 ± 57.9 vs non-PCOS 30.5 ± 26.4, $p = 0.025$ ESS: PCOS 12.5 ± 3.2 vs non-PCOS 9.32 ± 1.7, $p < 0.001$ No other significant differences in PSG variables
Tasali et al, ⁵² USA	Cross-sectional, PCOS and comparison group	40 with PCOS, all nondiabetic, completed questionnaires 8 with PCOS, referred for PSG; and 8 without PCOS, matched for age, nonobese	ESS, PSQI and Berlin questionnaire Sleep efficiency, sleep latency, TST, TWT, REM sleep (minutes) and NREM sleep (minutes)	<p>Measures of sleep efficiency in PCOS vs controls</p> <ul style="list-style-type: none"> PCOS women had significantly lower sleep efficiency and REM and NREM sleep compared to controls PCOS women had significantly higher sleep latency, TWT and TST compared to controls <p>Measures of SDB severity in PCOS women</p> <ul style="list-style-type: none"> AHI total (mean ± SE) = 7.0 ± 1.2 MAI total (mean ± SE) = 17.6 ± 1.8 ODI total (mean ± SE) = 10.8 ± 2.2 Minimum oxygen saturation (%) = 80.6 ± 1.6 All values were higher during REM than NREM sleep OSA: adjusted OR = 7.1 (95% CI 1.7–45.7), adjusted for age, BMI and ethnicity Presence of OSA associated with significantly higher MAI and minimum oxygen saturation among PCOS group. Data not presented for four control women with OSA No significant difference in TST
Tasali et al, ⁵³ USA	Cross-sectional, PCOS and comparison group	52 with PCOS; and 21 without PCOS, matched for age and BMI	AHI, OSA (AHI >5), TST, MAI and minimum oxygen saturation	<p>Measures of SDB severity in PCOS women</p> <ul style="list-style-type: none"> AHI total (mean ± SE) = 7.0 ± 1.2 MAI total (mean ± SE) = 17.6 ± 1.8 ODI total (mean ± SE) = 10.8 ± 2.2 Minimum oxygen saturation (%) = 80.6 ± 1.6 All values were higher during REM than NREM sleep OSA: adjusted OR = 7.1 (95% CI 1.7–45.7), adjusted for age, BMI and ethnicity Presence of OSA associated with significantly higher MAI and minimum oxygen saturation among PCOS group. Data not presented for four control women with OSA No significant difference in TST
Vgontzas et al, ⁵⁴ USA	Cross-sectional, PCOS and comparison group	53 with PCOS, all premenopausal; and 452 without PCOS	Sleep apnea (AHI ≥10 with clinical symptoms), upper airway resistance syndrome, SDB, EDS, sleep latency (minutes), WASO, total wake time, % sleep time, % stage 1, % stage 2, % SWVS and % REM sleep	<ul style="list-style-type: none"> Sleep apnea: OR = 28.7 (95% CI 4.9–294.4) Upper airway resistance syndrome: OR = 27.6 (95% CI 2.1–1423.0) SDB (all): OR = 30.6 (95% CI 7.2–139.4) SDB (BMI ≥32.3): OR = 5.1 (95% CI 1.1–31.3) EDS (BMI <32.2): OR = 10.3 (95% CI 2.5–60.0) EDS (BMI ≥32.2): OR = 3.8 (95% CI 1.4–11.6) No significant differences in other PSG variables
Yang et al, ⁵⁵ Taiwan	Cross-sectional, PCOS and comparison group	18 with PCOS, all nonobese and untreated; 10 without PCOS, matched for age and BMI	AHI (total, NREM sleep, REM sleep), ARI (total, NREM sleep, REM sleep, spontaneous, PLM-related), PLM, ESS, sleep efficiency, sleep latency, % REM sleep and REM sleep latency	<ul style="list-style-type: none"> Mean total AHI: PCOS 0.79 ± 0.21 vs non-PCOS 0.29 ± 0.09, $p = 0.041$ Mean AHI (NREM sleep): PCOS 0.57 ± 0.19 vs non-PCOS 0.03 ± 0.03, $p = 0.014$ No significant differences in other PSG variables None of the women in the study had AHI >5

Note: Sleep efficiency = TST/TIB.

Abbreviations: AHI, apnea-hypopnea index; AIS, Athens Insomnia Scale; ARI, arousal index; BMI, body mass index; CI, confidence interval; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; MAI, microarousal index; NREM, non-rapid eye movement; ODI, oxygen desaturation index; OR, odds ratio; OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome; PLM, periodic limb movement; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; RDI, respiratory distress index; REM, rapid eye movement; RERA, respiratory effort-related arousal; SDB, sleep-disordered breathing; SE, standard error; SWVS, slow-wave sleep; TIB, time in bed (minutes); TST, total sleep time (minutes); TWT, total wake time (minutes); WASO, wake after sleep onset (minutes); WC, waist circumference.

80% of women with PCOS ($n = 53$) complained of EDS but only 17% were diagnosed with OSA.⁵⁴

Insomnia in women with PCOS has received very little attention. Among a clinical sample of Polish women with PCOS ($n = 95$), 13% had insomnia according to the Athens Insomnia Scale and 10% according to the Insomnia Severity Index (ISI), with corresponding proportions among controls ($n = 130$) of 3% and 1%, respectively.⁶²

How pathophysiology of PCOS is linked to sleep disturbances

Since PCOS is characterized by metabolic disturbances, and as the endocrine system has an important role in governing the sleep–wake cycle, it is likely that PCOS interferes with arousal and sleep or that there is a more complex interrelationship.

The sleep–wake cycle in humans is driven by the interaction between two processes, Process S, which is sleep promoting, and Process C, which promotes wakefulness.⁶³ Process S represents the homeostatic need for sleep and accumulates over the time spent awake. Process C is regulated by the circadian system and ensures that sleep and wakefulness coincide with environmental light–dark stimuli.⁶⁴ The circadian system is coordinated centrally by the suprachiasmatic nucleus in the hypothalamus and is synchronized with environmental stimuli.⁶⁵ The suprachiasmatic nucleus relays circadian information to other areas of the brain, such as the pituitary and pineal pineal glands, and to peripheral tissues via the regulation of clock-gene expression and neuroendocrine signaling.⁶⁶

Melatonin and cortisol play important roles in regulating sleep and wakefulness. Melatonin, secreted by the pineal gland, is increased at night and decreased during the day, thus communicating light–dark information.^{64,67} Cortisol, which is secreted from the adrenal cortex and regulated by the HPA axis, also follows a circadian pattern, steadily increasing during sleep and peaking in the morning.^{67,68}

As illustrated in Figure 2, there are several pathways through which PCOS and sleep disturbances may be associated. The pathways outlined here have been identified based on the endocrine profiles of women with PCOS, the unique stressors they experience, and related psychological and behavioral factors.

Obesity

Obesity is common in women with PCOS and exacerbates the metabolic stress that we and others view as central to pathogenesis of the syndrome.²⁵ In a meta-analysis of mainly clinic-based samples ($n = 35$ studies),⁶⁹ 49% of women with PCOS were classified as obese (95% CI 42–55%) and 54%

had central adiposity (95% CI 43–62%). The proportions were around twofold higher than among comparison groups (obesity: relative risk [RR] = 2.8, 95% CI 1.9–4.1; central adiposity: RR = 1.7, 95% CI 1.3–2.3). These proportions should not be interpreted as prevalence estimates for all women with PCOS because obesity has been shown to be more common (and more extreme) in clinical samples than in community-based studies.⁴⁹ For example, in the Australian Longitudinal Study on Women's Health (overall $n = 9145$), at wave 4, 478 women reported having received a diagnosis of PCOS and, on average, had moderately higher BMI (mean difference 2.5 kg/m^2 , 95% CI 1.9–3.1) and moderately greater longitudinal weight gain over a 10-year period (mean difference 2.6 kg kg/m^2 , 95% CI 1.2–4.0) compared to their peers.⁷⁰

Variation in BMI among women with PCOS appears to be related to factors such as age and ethnicity and possibly to severity of the syndrome.⁶⁹ It is not clear why women with PCOS are predisposed to obesity, nor whether it reflects physiology or psychology. Some literature suggests that appetite and satiety are altered in PCOS, with affected women reporting higher postprandial hunger and lower satiety after a test meal compared to other women.⁷¹ Underlying postprandial suppression of gut hormones such as ghrelin, cholecystokinin, glucagon-like peptide 1 and peptide YY may occur in PCOS.^{71–74} Alternatively or additionally, obesity may reflect abnormalities in energy expenditure as women with PCOS have been found to have reduced resting metabolic rate (1659 kJ/day)⁷⁵ and reduced thermic effect of food (42 kJ/meal, equivalent to weight gain of 1.9 kg/year).⁷⁶ Psychological factors are consistent correlates of poor weight management;⁷⁷ as will be described presently, women with PCOS have relatively more anxiety and depression, and relatively poor self-esteem, body image and quality of life (QoL), compared to their peers.⁷⁸

Obesity is one of the strongest risk factors for OSA,⁷⁹ attributable to anatomical changes of the upper airways and thoracic region.⁸⁰ Longitudinal studies of men and women demonstrate that a 10% increase in body weight predicts a sixfold increase in risk of developing moderate-to-severe sleep-disordered breathing.⁸¹ When obesity is severe ($\text{BMI} > 40 \text{ kg/m}^2$), the prevalence of OSA in men and women is as great as 92%.⁸²

There is evidence that obesity contributes to sleep disturbances beyond OSA.⁸³ Several studies have shown that obesity is associated with objectively assessed daytime sleepiness and subjective reports of fatigue, independently of OSA.^{84,85} Vgontzas et al⁸³ have proposed two possible mechanisms through which obesity produces these sleep disturbances. In one pathway, shorter sleep duration and subjective fatigue in obese

individuals is related to psychological distress and upregulation of the HPA axis. In the second pathway, in which sleep duration is not altered, metabolic parameters such as insulin resistance as well as lack of physical activity are invoked, with normal- or downregulation of the HPA axis. Both pathways are proposed to be associated with hypercytokinemia.⁸³

There is some evidence that obesity directly contributes to OSA among women with PCOS, although, as highlighted previously, it does not fully account for findings from community- and clinic-based studies. For example, high BMI in women with PCOS ($n = 53$) has been associated with elevated risk of OSA and daytime sleepiness.⁵⁴ In a study of women with ($n = 44$) and without ($n = 34$) PCOS, obesity was the strongest predictor of sleep apnea risk (as measured by the Berlin questionnaire),⁸⁶ in contrast to another study of obese women with PCOS ($n = 23$), among whom there was no relationship between the degree of obesity and sleep apnea severity (as per AHI).⁸⁷

On balance, the evidence supports contributions to sleep disorders both of PCOS and obesity. From the perspective of stress, the former is metabolic while the latter is oxidative, which might aggravate sleep harmonically,²⁵ but studies that examine this are lacking.

Hyperandrogenemia

The prevalence of OSA differs by sex, with obese women having lower risk compared to males of similar BMI.⁸⁸ Men and women often have different clinical presentations for OSA. For example, when matched for age, BMI, AHI and EDS score, women were less likely than men to present with witnessed apnea but more likely to report insomnia.⁸⁹ Differences between men and women may be due to differences in the anatomy of the upper airway, sex hormones and/or central adiposity.^{90,91}

Women with PCOS commonly have increased testosterone (free and bound) and androstenedione, and hyperandrogenemia is a diagnostic criterion. Excess androgen is known to induce changes in body composition, including increased central adiposity. In women with PCOS, serum androgen levels are positively correlated with waist–hip ratio, independent of obesity.⁹² Androgen-induced changes to central adiposity, rather than increased weight overall, may contribute to OSA in these women.

This proposition is supported by work showing that among obese women with PCOS ($n = 18$), the severity of OSA was correlated with both the degree of androgen excess and waist–hip ratio.⁵⁰ Similarly, among nonobese women with ($n = 18$) and without ($n = 10$) PCOS, who did not have

OSA, AHI during non-rapid eye movement (NREM) sleep was correlated with total testosterone.⁵⁵ An inconsistent finding has been reported for a group of women with PCOS ($n = 44$) in whom risk of OSA was determined by the Berlin questionnaire.⁸⁶

Few studies have investigated the potential role of hyperandrogenemia in other forms of sleep disturbance in women. Mixed findings about androgens and sleep architecture have been reported from polysomnographic studies of adolescent girls with PCOS.^{56,93}

Insulin resistance

There is considerable evidence for a relationship between sleep disturbances and insulin resistance, with numerous studies demonstrating that sleep restriction and/or sleep disorders can exacerbate insulin resistance.^{94–96} Insulin resistance may also have a role in the development of sleep disturbances. For example, in a cross-sectional study of risk factors for EDS ($n = 1741$) undertaken in the US, diabetes (fasting glucose >126 mg/dL) was strongly associated with EDS.⁸⁴ Similarly, in a small study of men with OSA, those with EDS ($n = 22$) had higher plasma insulin levels and insulin resistance compared with those without EDS ($n = 22$) when matched for age, BMI, and AHI.⁹⁷ A prospective study of incident OSA in a population-based sample of French men and women ($n = 3565$) also demonstrated that fasting hyperinsulinemia predicted development of OSA, independently of BMI.⁹⁸

The mechanisms by which insulin resistance may lead to OSA or EDS are unknown. Evidence from animal and human studies has demonstrated that insulin increases sympathetic outflow,^{99,100} which may in turn affect sleep architecture and the risk of sleep-disordered breathing and daytime sleepiness.

In a polysomnographic study of women with ($n = 53$) and without ($n = 452$) PCOS, Vgontzas et al found that insulin resistance was the strongest risk factor for sleep apnea, before and after controlling for age, BMI, and free and total testosterone levels.⁵⁴ Similar findings were reported in another study of women with PCOS ($n = 40$), with higher fasting insulin levels observed among those with elevated risk of OSA (as per Berlin questionnaire).⁵²

If insulin resistance causes sleep disturbances, then treatment with insulin sensitizers should be mitigating. Adolescent girls with PCOS who received metformin treatment reported reduced sleep disturbances and daytime sleepiness, but it is not possible to distinguish between effects of improved insulin resistance and the concomitant reductions in BMI and hyperandrogenemia.¹⁰¹ In a recent pilot for a

randomized placebo-controlled trial, nondiabetic individuals with insulin resistance and OSA ($n = 45$) were allocated to receive either pioglitazone or placebo. Pioglitazone produced no improvement in OSA symptoms or other measures of sleep quality, despite significant improvements in insulin sensitivity.¹⁰² Thus, there is insufficient evidence to draw conclusions about this matter, and we recommend further research.

Cortisol

In a recent longitudinal study of obese girls aged 13–16 years with ($n = 20$) and without PCOS ($n = 20$), the role of the steroid metabolome was investigated. No difference in morning cortisol concentration was found between the two groups, although levels were twice as high as those reported in studies of girls of normal weight.¹⁰³ Furthermore, weight loss was associated with a decrease in cortisol whether or not the girls had PCOS. Together, this suggests that the adrenal stimulation was attributable to obesity rather than to PCOS.

Findings concerning women with PCOS are somewhat contradictory. In one study ($n = 21$ with PCOS, 11 overweight/obese; $n = 10$ without PCOS, none overweight/obese), 24-hour cortisol profiles were obtained. While there was no difference in mean 24-hour cortisol levels overall, women with PCOS had lower night-time cortisol levels compared to controls, and this was most pronounced for the women with PCOS who were not overweight/obese.¹⁰⁴ In another study, evening, but not morning, plasma cortisol levels were higher in women with PCOS ($n = 40$) compared to women of similar age and BMI without PCOS ($n = 55$).¹⁰⁵ It is possible that elevated cortisol levels among women with PCOS reflect high BMI, as one study showed that concentration and profiles of cortisol excretion were similar for obese women with ($n = 15$) and without ($n = 15$) PCOS.¹⁰⁶

Complete HPA function in women with PCOS has not been described. Any changes – whether due to PCOS or associated obesity – are relevant, as dysfunction of the HPA axis at any level impacts on sleep, including increased sleep fragmentation, decreased slow wave sleep, and shortened sleep time.¹⁰⁷

There is evidence that women with PCOS have a heightened physiological response to emotional stress. When exposed to an experimental stressor, women with PCOS ($n = 32$) had higher levels of adrenocorticotropic hormone immediately and 15 minutes post-stress, and higher serum cortisol level 15 minutes post-stress, compared to women without PCOS ($n = 32$), matched for age and BMI. This was despite the emotional response (state anxiety) reported by the two groups being similar.¹⁰⁸

Sleep deprivation is itself a stressor and is associated with elevated cortisol levels.¹⁰⁹ It is therefore possible that a bidirectional relationship exists between stress-related hyperactivity of the HPA axis and sleep disturbances in women with PCOS.¹¹⁰

Melatonin

A study of melatonin secretion over 24 hours in women with PCOS has not been undertaken. Melatonin from a single blood sample taken between midnight and 4 am was higher among women with PCOS ($n = 50$) compared to controls ($n = 50$).¹¹¹ Two studies have demonstrated elevated 24-hour urinary 6-sulphatoxymelatonin (the primary metabolite of melatonin) in women with PCOS ($n = 22$ in the first and $n = 24$ in the second study) compared to controls ($n = 35$ and $n = 26$, respectively).^{112,113}

However, the changes in melatonin described in women with PCOS are unlikely to result in the profound sleep disturbances that have been reported in this subpopulation, particularly given 6-sulphatoxymelatonin was not found to be correlated with sleep efficiency.¹¹³ A strong correlation between melatonin obtained from a single blood sample (as above) and testosterone was found in women with PCOS,¹¹¹ and melatonin was reduced after hyperandrogenemia was attenuated by cyproterone acetate-ethynodiol treatment.¹¹⁴ This suggests that elevated melatonin levels described in women with PCOS may be a result of androgen excess. Conversely, chronic administration of melatonin to women with PCOS (2 mg per day for six months) significantly decreased testosterone levels and reduced menstrual irregularities,¹¹⁵ suggesting that supraphysiological levels of melatonin can reduce androgen levels.

Psychosocial aspects of PCOS and association with sleep

A number of psychosocial aspects of PCOS are likely to contribute to sleep disorders and disturbances in affected women. These are summarized in Figure 4.

Mental health profiles of women with PCOS

Anxiety and depression are well recognized to be associated with sleep disorders.^{116–118} A systematic review of nine longitudinal studies found suggestive, though not definitive, evidence of a bidirectional relationship.¹¹⁹ A recent study of young women ($n = 171$) followed over two weeks found reciprocal dynamics between anhedonic depression and disrupted sleep to be especially potent.¹²⁰

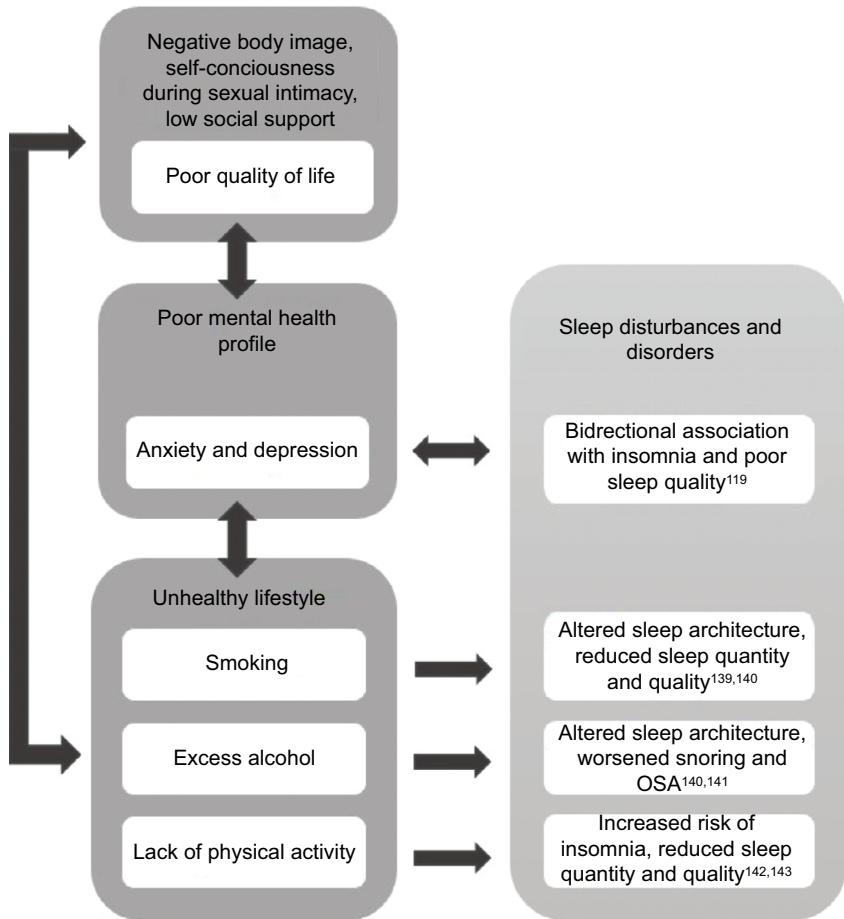


Figure 4 Summary of psychosocial and behavioral factors that are common among women with PCOS and their potential contribution to sleep disturbances and disorders.
Abbreviations: OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome.

Anxiety and depression are elevated in women with PCOS, with consistent evidence presented in several systematic reviews with meta-analysis.^{121–125} In our community-based sample, among women with PCOS (the majority of whom had not previously been diagnosed), 50% had symptoms consistent with clinical depression (Center for Epidemiologic Studies Depression Scale) compared with 30% of their peers.⁴⁸

In one of the above systematic reviews,¹²⁵ clinical symptoms, including hirsutism, obesity, and infertility, were shown to contribute to higher emotional distress in women with PCOS, but did not fully account for the disparity. Elevated androgens have been associated with negative affect and depressive symptoms in women with PCOS,^{78,126} but the relationship between androgens and mood disorders in women remains controversial.^{124,127} As discussed, women with PCOS may have hyperresponsivity of the HPA axis, which is associated with impaired mental health, including depression.¹²⁸

In the community-based cohort of Australian women that we undertook, as mentioned, difficulty falling asleep and difficulty maintaining sleep were twice as common in women with PCOS compared to peers of similar age.⁴⁸ Depressive symptoms mediated both associations, but to varying degrees.

In a clinical sample of women with PCOS ($n = 114$), those with a history of depression had a threefold increase in disturbed sleep (as per the Patient Health Questionnaire).¹²⁹ In another study, women with ($n = 30$) and without PCOS ($n = 30$), matched for age and BMI, were recruited by advertisement in a Swedish community.¹³⁰ Symptoms of anxiety and depression were self-reported (using subscales of the Comprehensive Psychopathological Rating Scale for Affective Syndromes). Over 60% of women with PCOS had anxiety symptoms above a cut-point corresponding to clinical relevance, compared to 13% of controls, with the specific symptom of reduced sleep prominent.

As with anxiety and depression, it is likely that a bidirectional relationship exists between sleep and

QoL.¹³¹ This may be especially so in people with medical conditions.¹³²

QoL for girls and women with PCOS appears to be poorer than for their peers, although less is known about this than about specific conditions such as depression and anxiety. A systematic review and meta-analysis of five studies showed that women with PCOS had lower scores than their counterparts on all domains assessed by the Short Form-36 Health Survey, including physical and social function.¹³³ A recent systematic review¹³⁴ of QoL in adolescents and young women with PCOS identified nine studies that were too diverse in approach for meta-analysis to be performed. However, all studies reported a negative association between PCOS and QoL, with body weight issues conspicuous.

Distressing symptoms of PCOS are likely to contribute to poor QoL. In women more broadly, a systematic review with meta-analysis has demonstrated the profound impact of infertility on QoL.¹³⁵ Other stressors experienced by women with PCOS – that have received less attention – may contribute, including negative body image, poor self-esteem, poor sexual relations, reduced social support and low social engagement.^{136–138}

Lifestyle and health behaviors

Lifestyle factors and health behaviors, including smoking, consumption of alcohol and lack of physical activity, can contribute to impaired sleep. Tobacco smoking has been associated with altered sleep architecture, short sleep duration and poor-quality sleep, based on both self-reports and polysomnography.^{139,140} In nonalcoholics, the effect of alcohol consumption on sleep varies during the night, at first decreasing sleep latency and increasing the quality and quantity of NREM sleep, then as alcohol is metabolized, reducing NREM and fragmenting sleep.^{140,141} Alcohol is also associated with exacerbation of snoring and OSA.¹⁴⁰ Physical inactivity has been associated with reduced self-reported hours of sleep¹⁴² and increased risk of clinically diagnosed insomnia.¹⁴³ Furthermore, there is evidence that increased physical activity improves sleep quality.^{144,145}

There is some evidence that lifestyles and behaviors of women with PCOS are less healthy than those of other women of similar age and socioeconomic status. For example, in a case series of women with PCOS presenting at a reproductive health clinic, around half smoked cigarettes, substantially more than expected based on their demographic profile.¹⁴⁶ Consistent with this, in the US 2002 National Health Interview Survey, women who reported menstrual-related problems

were shown to be more likely than others to smoke and drink heavily.¹⁴⁷

Women with PCOS are less physically active than other women and may have difficulty in sustaining engagement in physical activity over the long term.¹⁴⁸ When interventions to improve physical activity among women with PCOS have been trialed, attrition rates have been high.¹⁴⁹ Barriers contributing to low physical activity in women with PCOS include lack of confidence in the ability to maintain activity, fear of injury and physical limitations.¹⁴⁸ It is also possible that there are physiological reasons for impaired exercise capacity in women with PCOS. For example, it has been shown that sedentary normal-weight women with PCOS (n = 14) have impaired cardiorespiratory capacity (maximal oxygen consumption and submaximal ventilatory thresholds) compared to age- and BMI-matched sedentary women without PCOS (n = 14).¹⁵⁰

Long-term cardiometabolic consequences of sleep disturbances in PCOS

There are few long-term studies of women with PCOS, with information especially lacking after menopause. However, available evidence suggests that women with PCOS may have relatively early onset of type 2 diabetes and other cardiometabolic disorders. This is not accounted for by the higher prevalence of obesity among women with PCOS, as highlighted in the studies described here. Drawing on wider literature, it is possible that sleep disorders may contribute to deterioration in the health of women with PCOS, although this has not been studied directly.

Detailed cardiovascular profiles of around 1000 women were obtained across 20 years in the CARDIA (Coronary Artery Risk Development in Young Adults) study undertaken in the US, commencing when participants were aged 18–30 years. Information on PCOS symptoms obtained 16 years from baseline was combined with androgen data from year 2 to classify women as having PCOS or not. Using data from year 5, women with PCOS (n = 42) had higher left ventricular mass index and larger left arterial diameter.¹⁵¹ By year 16, when women were aged 34–46 years, PCOS was associated with a twofold increase in incident diabetes (with almost a quarter of women with PCOS affected) and a twofold increase in dyslipidemia. Among women with normal BMI, those with PCOS (n = 31) had three times the rate of diabetes compared to those without PCOS.¹⁵² At year 20, women with PCOS (n = 55) had increased coronary artery calcification and intima-media thickness.¹⁵³

Australian hospital admission data from 1980 to 2011 have been used to compare 2566 women with a recorded diagnosis of PCOS to 25,660 age-matched women (identified using the electoral roll); most women in this study were aged under 40 years. Women with a diagnosis of PCOS were two to three times more likely to be hospitalized for adult-onset diabetes, hypertensive disorders, ischemic heart disease and cerebrovascular disease compared to women without PCOS. These findings remained statistically significant after adjusting for obesity.¹⁵⁴

In a retrospective cohort study, women with PCOS ($n = 319$) identified through hospital records were compared with age-matched women ($n = 1060$) identified through general practice records. After an average follow-up of 31 years, when approximately 80% of women were postmenopausal, those with PCOS had elevated prevalence of diabetes, hypertension and high cholesterol.¹⁵⁵ Another study with a small sample size and substantial losses to follow-up over 21 years found more hypertension and higher triglycerides in women with PCOS ($n = 25$ of 35) compared to women of similar age and BMI ($n = 68$ of 120).¹⁵⁶

Turning to the wider literature, a recent meta-analysis of cohort studies showed that OSA was associated with increased risk of type 2 diabetes after adjustment for age, sex and BMI (RR = 1.49, 95% CI 1.27–1.75, eight studies, 63,647 participants).¹⁵⁷ Other types of sleep disturbance were also associated with type 2 diabetes, notably – in view of our findings on women with PCOS⁴⁸ – difficulty initiating sleep (RR = 1.55, 95% CI 1.23–1.95) and difficulty maintaining sleep (RR = 1.72, 95% CI 1.45–2.05).

Sleep restriction has been demonstrated to result in increased food intake due to increased appetite, exceeding the energy amount needed to meet the requirements of extended wakefulness, and thereby resulting in weight gain.^{158–160} It has also been shown to decrease the ability to lose body fat with dietary restriction,^{158,161} and to alter glucose metabolism, with decreases in glucose clearance, insulin sensitivity and acute insulin response documented.^{158,162,163}

OSA is likely to increase the risk of diabetes through intermittent hypoxia and arousals, which result in impaired glucose tolerance through increasing sympathetic nervous system activity, HPA axis dysregulation, altered cytokine release and oxidative stress.^{164–167} OSA is also independently associated with hypertension, premature atherosclerosis and arterial stiffness and an increased risk of future myocardial infarction, stroke and cardiovascular mortality.^{166,168,169} This may be due to the combination of sympathetic nervous

system stimulation and endothelial dysfunction that result from OSA.^{170,171}

In studies of short duration, insulin–glucose metabolism and lipids are worse in women with PCOS who have OSA than among women with PCOS but not OSA, independent of BMI.^{52,54,59,172} A link between sleep disturbances and poor long-term cardiometabolic health among women with PCOS remains speculative, as direct evidence is lacking.

Management of sleep disturbances in PCOS

Referral to a sleep specialist allows diagnosis of clinical conditions such as OSA and insomnia, and subsequent treatment. OSA is generally diagnosed using overnight polysomnography to generate AHI.⁴⁰ Insomnia diagnosis ideally requires assessment by a clinical psychologist.¹⁷³ However, many sleep medicine clinics do not currently have the resources necessary for adequate diagnosis, such as the ISI questionnaire, sleep diaries and measures of daytime fatigue without sleepiness. It is important to recognize that OSA and insomnia are frequently comorbid,¹⁷³ and also that women with PCOS may have other forms of sleep disturbance.

Weight loss is generally recommended for overweight and obese people with OSA,⁴⁰ although recent research has indicated that weight loss may only decrease the severity of OSA in a minority of patients.¹⁷⁴ As described above, weight loss may be particularly difficult to achieve in many women with PCOS due to hormonal abnormalities and other factors. Weight loss in women with PCOS would improve insulin sensitivity and symptom profiles, including fertility, so research is needed to understand the type and intensity of support required to achieve this. Avoidance of alcohol and sedative medications, which may predispose the upper airway to collapse, is also frequently recommended for OSA.⁴⁰ Again, this poses a particular difficulty for women with PCOS in view of their anxiety and use of alcohol, possibly as a coping mechanism.¹⁷⁵

In cases of mild OSA, oral appliances, commonly known as mandibular advancement splints, which are custom-made to increase upper airway size and reduce the likelihood of airway collapse during sleep, may be recommended.⁴⁰ However, efficacy and acceptability of oral appliances in women with PCOS is yet to be explored.

A small amount of research has been conducted in women with PCOS about the benefits of continuous positive airway pressure (CPAP) treatment, involving wearing a mask over the nose during sleep to maintain airway patency. CPAP has

been shown to be a promising treatment for OSA in young obese women with PCOS, with improvements in insulin sensitivity, daytime diastolic blood pressure, and cardiac sympathovagal balance after eight weeks of treatment.¹⁷⁶ These results indicate the need for a larger, well-designed randomized controlled trial to assess the clinically relevant effects of CPAP treatment on markers of future cardiovascular risk in women with PCOS.¹⁷⁷

For the general OSA subpopulation (mostly men), there is now evidence from systematic reviews with meta-analysis that CPAP reduces blood pressure¹⁷⁸ and endothelial dysfunction, which promote the development of atherosclerosis.^{179,180} Thus, CPAP could have a role in primary prevention of vascular disease, despite recent findings that CPAP is not effective in reducing coronary events in those with preexisting vascular disease.¹⁸¹ Systematic reviews with meta-analysis have also indicated that insulin resistance can be improved with CPAP use, thereby possibly reducing the risk of development of type 2 diabetes in nondiabetic and prediabetic individuals.¹⁸

Importantly for women with PCOS, a systematic review with meta-analysis has provided evidence that CPAP treatment reduces depressive symptoms.¹⁸² A subsequent large, randomized controlled trial of over 2000 individuals with moderate-to-severe OSA and coronary or cerebrovascular disease demonstrated that CPAP was effective in increasing QoL as well as decreasing symptoms of depression and anxiety.¹⁸³

The American College of Physicians now recommends cognitive behavior therapy (CBT) as the most appropriate treatment for all adults with insomnia.¹⁸⁴ This treatment is also recommended as a first-line treatment for insomnia by the British Association for Psychopharmacology.¹⁸⁵ The efficacy of CBT in treating insomnia symptoms has been demonstrated in multiple systematic reviews with meta-analyses,^{186–189} but most sleep clinics do not have clinical psychologists available to provide this treatment. In view of the widespread mental health and other problems reported among women with PCOS, there is a good case for referral to a clinical psychologist who can assess and address problems holistically.

In recent years, trials have been undertaken to assess the efficacy of online delivery of CBT for insomnia, using highly structured internet programs as a means of overcoming the barriers to face-to-face delivery of treatment.¹⁹⁰ A recent systematic review with meta-analysis of 15 randomized controlled trials of internet CBT for insomnia found evidence of clinically significant improvements in symptoms, of the order achieved in face-to-face CBT.¹⁹⁰ Importantly, the ISI score of patients was found to be reduced overall by 21%,¹⁹⁰ and by 15% in a similar systematic review with meta-analysis.¹⁹¹ This option may appeal to women with

PCOS as cost-effective, but they should still be encouraged to consult a clinical psychologist or other professional support services for wider problems.

There are well-recognized hazards in using pharmacotherapy for the primary treatment of insomnia. Depending on the type of drug used, negative effects include carry-over daytime sedation, slowed reactions and memory impairment, as well as the potential for intensification of symptoms upon cessation of treatment.¹⁷³ Pharmacotherapy is only recommended short term.¹⁹² This is particularly pertinent for women with PCOS whose insomnia and other sleep disturbances are unlikely to be short term and are related to underlying factors that need to be addressed directly.

Women who experience sleep disturbances, but do not meet the criteria for clinical diagnosis of a sleep disorder, may benefit from sleep hygiene approaches. This includes behavioral and environmental recommendations for promoting sleep.¹⁹³ Avoidance of smoking and alcohol and regular physical activity are aspects of sleep hygiene that have already been described. Other recommendations include avoidance of caffeine, adhering to regular sleep and wake times and stress management.¹⁹³ Stress management techniques, such as mindfulness, have been shown to reduce presleep arousal and worry,¹⁹⁴ which may be beneficial for women with PCOS. Clinical anxiety requires psychological expertise, however.

As has been highlighted throughout this review, it is common for women with PCOS to experience symptoms that span multiple medical specialties. The management of sleep disturbances among women with PCOS should form part of an interdisciplinary model of care (summarized in Figure 5) with effective communication between care providers.¹⁹⁵ It is important that interdisciplinary care is patient-centered¹⁹⁵ and emphasizes a holistic approach to health and well-being.

Conclusion

There is mounting evidence for an association between PCOS and sleep disturbances that is complex and possibly bidirectional. This is not simply due to the tendency of women with PCOS to be obese, as associations are seen in PCOS women of normal weight and most associations are upheld after adjustment for BMI. This suggests poor sleep is part of the pathophysiology of PCOS. We view PCOS as a condition of severe metabolic stress that cascades into oxidative and emotional stress. We suggest that multidimensional treatment, including treatment to improve sleep, may improve metabolic function and could potentially prevent long-term cardiometabolic sequelae for these women.

We have identified some important gaps in the literature, with further research recommended. These include a need

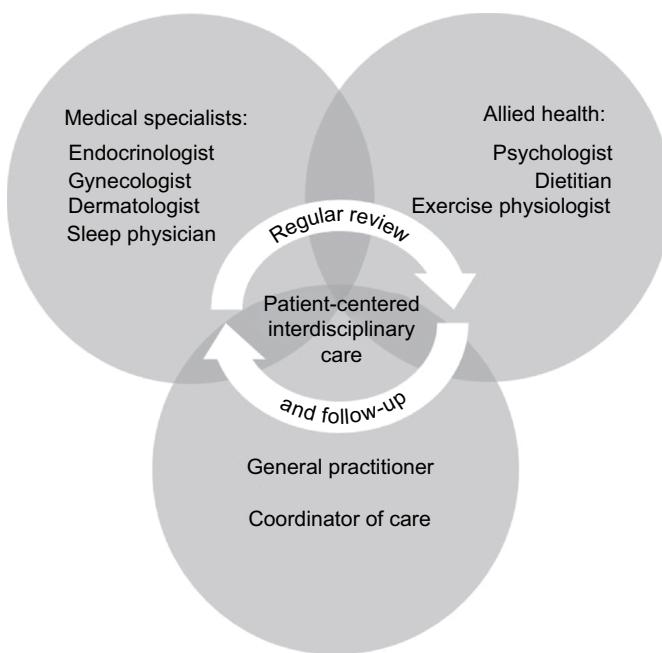


Figure 5 Model of interdisciplinary care recommended for management of sleep disturbances and disorders in women with PCOS.

Note: Teede HJ, Misso ML, Deeks AA, et al. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. *Med J Aust.* 2011;195(6 Suppl):S65–S112. © Copyright 2011 The Medical Journal of Australia – figure adapted and reproduced with permission.¹⁹⁵

Abbreviation: PCOS, polycystic ovary syndrome.

to fully describe HPA function in women with PCOS, and for further trials of insulin sensitizers and interventions designed to overcome the specific difficulties that women with PCOS have in sustaining physical activity. The implications for sleep deserve specific attention as well as the possibility that bidirectional processes can be harnessed so that improved sleep reduces metabolic stress in women with PCOS.

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Disclosure

The authors report no conflicts of interest in this work.

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Psychological Aspects in Communication with Patients on Departments of Medical Radiology

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Abstract

Frequently may be seen that in communication with patients coming to radiological departments for medical examination or treatment radiologic staff is somehow frustrated and insufficiently skilled. Purpose of study is to analyze conditions influence in communication between pts. and radiologic co-workers. In total 75 pts. And 25 radiologists passed 95 targeted personal interviews. Different views of pts. as well as radiologic staff were registered. Recommendations for radiologic co-workers to achieve optimal communication with pts. is of decisive value.

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Keywords: *communication, radiologic staff-patient relationship, ethic, compliance.*

1. Introduction

Frequently may be seen that in communication with the patients coming to department of radiology for medical examination and/or treatment interventions the radiologic staff is somehow frustrated and insufficiently skilled in its daily work. The purpose of our study is to analyze the situation and conditions influencing effective communication between the patients and radiologic co-workers by suitable interview methods and based on the results to optimize the communication skill of the radiologic staff (1,5).

2. Methods.

A special targeted questionnaire was developed by radiologist and clinical psychologist (with over 30, resp. 15 years of practical hospital experience on radiological departments) to interview: (1) patients referred for conventional X-ray studies, CT or MRI examinations or interventional procedures and (2) radiologic co-workers. In total 75 patients and 25 co-workers passed 95 targeted personal interviews (1).

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3. Findings and recommendations for clinical practice.

Between general psychological aspects following specifics of communication on radiologic departments were identified:

3.1. Different views on clinical position of patients as well as radiologic staff.

The view of the patient: I am coming or was sent for an examination or treatment into a place I do not know ; the place seems to be unfriendly and overcrowded by strange sophisticated technical devices – it stresses me". "I feel not being sufficiently informed as to what will happen to me and what will be done with me; thus, my position causes a serious psychical burden for me" (2).

The view of radiologic staff: "A patient was referred to our department, without clear enough questions from referring physician". "He/she is like a number in a queue, just a migrant more or less anonymous to us". "He/she is going to leave for further treatment to other place".

In order to respect above mentioned situation it is necessary to keep in mind the reality: It is evident that rational and effective communication between patients and radiologic co-workers as well as referring physician plays the decisive role in patient's management.

Recommendations for radiologic staff: effort to achieve optimal communication level with the patients and fasten on an "alliance" ("condition sine qua non").(1).

3.2. Elements and premises for radiologic staff for creating rational communication with the patients:

- Introduce yourself and your position, listen to the patient, create feedback.
- Explain clearly the reasons and targets of diagnostic or treatment procedures planned (their character and course, patient's benefit, risk, other alternatives of medical care, etc.).
- Create mutual understanding and trust, be open, fair and honest.
- Respect patients' privacy and intimacy of their somatic and psychical problems ("patient is not a thing").
- Plug-up your ability of empathy and respect ethical memento: "The ill – not the illness – must be the focal point of medical staff, including radiologists and co-workers' interest.

Recommendation: to strengthen empathy which is basic condition of "mutual understanding" (2,4,8).

3.3. Requirements concerning main communication forms:

- Speech communication – eye-contact, clear wording, ensuring feedback.
- Paralinguistic means ("metacommunication") – intonation, mimics, gestures, "haptic", touch communication etc.(4).

Recommendations: respect the rules, concentrate and control yourself.

3.4. How to inform the patients on diagnosis and/or necessary interventional treatment?

Patients' need to know about their disease reveals as ethical problem. Presumptions:

- Inform the patient, first of all, about positive technical course of procedures being performed, about diagnostic value and/or treatment results of carried-out studies and interventions.
- Patient's psychical state should be "matured" for final diagnostic information (reaction: compensation versus decompensation).

- Ethical approach: to inform the patients after their compensation, in right time, at right place, by physician's personal handling, in professional form (fairness, dignity, enough time, calm environment, acceptance and encouraging of discussion, listen to).
- Extend psychological support (4,5,7,8).

Recommendations: Main goal for radiologic staff: to support patient's compliance and informed consent!!

3.5 Patients' laws (keep in mind)!:

- To refuse information on diagnosis in effort to save and support positive psychological condition (important immunological factor).
- Patient's agreement is necessary for diagnostic information of partners, family members and public (6).

Recommendations: to avoid mistakes and misunderstanding in communication with the patients, radiologic co-workers and interdisciplinary collaborators.

4. Conclusions

For radiologic co-workers it is essential to train their skills in rational communication with the patients to improve the duality of patients' care based on our common understanding of ethical and humanistic principles.

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Article

The Association of a Mediterranean-Style Diet Pattern with Polycystic Ovary Syndrome Status in a Community Cohort Study

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Abstract: Polycystic ovary syndrome (PCOS) is a common condition in reproductive-aged women. While lifestyle management is first-line treatment in PCOS, the dietary intake of women with PCOS is unclear and there is no research assessing dietary patterns of women with and without PCOS. The aim of this study was to examine dietary patterns in a large cohort of women with and without PCOS. Data were from 7569 participants in the 1973–1978 cohort of the Australian Longitudinal Study on Women’s Health population assessed at 2009 (Survey 5) ($n = 414$ PCOS, $n = 7155$ non-PCOS). Dietary patterns were evaluated using factor analysis and multiple logistic regressions assessed their associations with PCOS status. Three dietary patterns were identified that explained 27% of the variance in food intake between women with and without PCOS: Non-core foods; Meats and take-away and Mediterranean-style. The Mediterranean-style dietary pattern was independently associated with PCOS status. On adjusted analysis for each 1 SD increase in the Mediterranean-style dietary pattern, there was a 26% greater likelihood that women had PCOS. This may indicate an improvement in the quality of dietary intake following a diagnosis of PCOS. Future research should examine the contribution of dietary patterns to the incidence and severity of PCOS and the potential for modification of dietary patterns in the lifestyle management of PCOS.

Keywords: polycystic ovary syndrome; diet; dietary patterns; Australia

1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine condition affecting 12%–18% of reproductive-aged women [1]. It is associated with reproductive (hyperandrogenism, anovulation, menstrual irregularity, infertility and pregnancy complications) [2], metabolic (increased risk factors for and prevalence of impaired glucose tolerance, type 2 diabetes and cardiovascular disease) [3–5] and psychological (worsened quality of life and increased risk factors for depression and anxiety) [6] features. There is a proposed bidirectional relationship between obesity and PCOS [7]. Women with PCOS have an elevated prevalence of obesity [8] and increased longitudinal weight gain [7]. Obesity also worsens the presentation and prevalence of PCOS [9]. Mechanisms include increasing the pathophysiological factor insulin resistance, which increases hyperandrogenism through augmenting ovarian androgen production and decreasing hepatic production of the androgen binding-protein sex hormone binding globulin [10,11]. Due to the key aetiological role of obesity

and insulin resistance in PCOS, weight management, defined as prevention of excess weight gain or achieving and maintaining a modest weight loss, is a key treatment strategy in PCOS. Evidence based guidelines recommend achieving this through a combination of diet, exercise or behavioural management [12].

The optimal dietary strategy as part of lifestyle management in PCOS remains controversial. We reported in a recent systematic review that the controlled clinical literature found no difference in the majority of anthropometric, reproductive, metabolic or psychological outcomes for a range of dietary approaches including higher protein, higher carbohydrate, lower glycaemic index or monounsaturated fat-enriched diets [13]. Despite this, a range of dietary approaches may be prescribed by health professionals [14]. While evidence-based National Health and Medical Council approved Australian guidelines outline the principles of dietary management for PCOS [12], the effect of these guidelines on actual dietary prescription by health professionals and subsequent dietary intake by women with PCOS is not known. In the absence of specific recommendations by health professionals, women with PCOS may also often seek non-evidence based sources of information on dietary management [15]. The effect of this on actual dietary intake is not known. We and others have reported subtle differences in dietary intake for women with PCOS compared to those without PCOS including a better dietary intake as indicated by elevated diet quality indices, fibre and micronutrient intake, lower glycaemic index and lower total fat or saturated fat intake or a poorer dietary intake indicated by poorer diet quality, increased fat, saturated fat and high glycaemic index food intake and decreased fibre intake compared to women without PCOS [16–21]. There however remains uncertainty as to the quality of dietary intake in women with PCOS.

Assessment of dietary patterns offers an additional way of comprehensively assessing dietary intake. Rather than assessing single nutrients in isolation, dietary pattern analysis identifies underlying dietary characteristics of the study population in which the consumption of foods that are eaten together can be derived. In particular, exploratory approaches or posteriori dietary pattern analyses such as principal components analysis, which are not hypothesis driven, groups correlated food groups into uncorrelated factors termed dietary patterns [22,23]. In pregnant populations, unhealthy dietary patterns in the pre-conception period were associated with increased risk for preterm birth [24] or gestational diabetes [25] and healthy, Mediterranean or prudent diet patterns were inversely associated with risk of developing hypertensive disorders during pregnancy [26] or gestational diabetes [27,28]. In non-pregnant populations, unhealthy/Western-type dietary patterns have been associated with increased risk of general and central obesity [29] and type 2 diabetes [30]; while a Mediterranean dietary pattern was associated with decreased prevalence of hypertension and metabolic syndrome [31] and a healthy dietary pattern containing vegetables, fruits and whole grains was associated with reduced risk for diabetes [30].

These findings are of potential relevance to PCOS given the increased prevalence of cardiometabolic conditions and pregnancy complications and the potential for clinical benefits with approaches such as the Mediterranean diet [32]. However, there has been limited research examining dietary patterns in women with and without PCOS. This could provide an understanding on both the association of dietary intake with the pathophysiology of PCOS as well as of the dietary changes that occur following a diagnosis of PCOS. The aim of this study was therefore to examine dietary patterns in a large cohort of women, with and without PCOS, participating in the Australian Longitudinal Study on Women's Health.

2. Experimental Section

2.1. Study Population

This study is based on data from the Australian Longitudinal Study on Women's Health (ALSWH), a longitudinal population-based study of three age cohorts of Australia women. Women were randomly selected from the national health insurance scheme (Medicare) database,

which includes almost all people who are permanent residents of Australia, with national recruitment and intentional over-sampling from rural and remote areas [33]. Further details of the methods and characteristics of the sample have been reported elsewhere [34–36]. The Human Research Ethics Committees of the University of Newcastle and the University of Queensland approved the study methods and informed written consent was obtained from each participant.

The current study uses data from the cohort of younger women (born 1973–1978) ($n = 14,779$ at Survey 1) who first completed a mailed survey in 1996 [37]. For this analysis, data are from Survey 5 (2009, $n = 8200$, 58% retention of baseline participants and 84% retention of those who completed the second survey). The greatest drop out was from Survey 1 to Survey 2. However, the impact of attrition on associations between variables has been found to be minimal [36].

As with our prior publications on health outcomes in PCOS, we analysed data from $n = 7569$ women who completed Survey 5 and responded to the question on PCOS diagnosis (“In the last 3 years have you been diagnosed with or treated for Polycystic Ovary Syndrome”) of which $n = 414$ were classified as PCOS and $n = 7155$ as non-PCOS [7]. The analyses in this study are based on cross-sectional analysis of dietary patterns in women with and without PCOS. No specific inclusion or exclusion criteria were applied to this cohort and all women were included irrespective of pregnancy, medication, country of birth and language spoken.

2.2. Anthropometric, Demographic and Physical Activity Variables

Self-reported height, weight and BMI were reported with overweight and obesity defined by the World Health Organization criteria ($\text{BMI} \geq 25 \text{ kg/m}^2$ for overweight and obesity, $\text{BMI} \geq 30 \text{ kg/m}^2$ for obesity) [38]. Demographic variables including parity, education, occupation and income were collected at Survey 5 and area of residence was measured at Survey 1. Physical activity was calculated as the sum of the products of total weekly minutes in categories of walking, moderate-intensity or vigorous-intensity physical activity and the metabolic equivalent value (MET) was assigned to each category: (walking minutes \times 3.0 METs) + (moderate-intensity physical activity minutes \times 4.0 METs) + (vigorous intensity physical activity minutes \times 7.5 METs). Outliers were truncated at 28 h/day for total physical activity.

2.3. Food Group Consumption

At Survey 5, self-reported dietary intake data were collected from the Dietary Questionnaire for Epidemiological Studies (DQES) Version 2, a FFQ developed by The Cancer Council of Victoria previously validated in young Australian women [39] as previously reported [19]. One hundred different foods (grams per day) were obtained from the FFQ and were assigned into 33 food groups (grams per day) based on a previous Australian study [24,40] for use in the dietary pattern analysis.

2.4. Dietary Pattern Analysis

Dietary patterns were derived using factor analysis with factor loadings extracted using the principal component method and varimax/orthogonal rotation. The number of dietary patterns identified was based on eigenvalues >1.5 , on identification of a break point in the scree plot, and on interpretability [41]. Using these criteria, a 3-factor solution was chosen and rerun with the resulting factor scores saved and converted to Z-scores for analysis. Items with factor loadings ≥ 0.25 were considered as the items of relevance for the identified factor. These items represent the foods most highly related to the identified factor [42]. Foods that cross-loaded on several factors were retained.

2.5. Statistical Analyses

All statistical procedures were performed using SPSS version 22. Frequencies and descriptive statistics were expressed as n (%) and as means (SD), respectively. All reported P values were 2-tailed, and a p -value < 0.05 was considered to be statistically significant. Before hypothesis testing, data were examined for normality, in which all independent variables were normally distributed.

Data were analysed by independent *t*-test to compare continuous variables and chi-square test to compare categorical variables between women with and without PCOS. Binary logistic regression analyses were used to test the association between PCOS (yes/no) and the independent variables for each dietary pattern (Z-score), with values presented as OR (95% CI). All logistic regression analyses were undertaken adjusting for potential confounders identified a priori, including maternal age, BMI, currently breastfeeding, number of children and waist circumference, or statistically, from association with PCOS on univariate analysis ($p < 0.05$). Multicollinearity was tested with binary regression analysis using the variance inflation factor (<5); no multicollinearity was observed between any of the independent variables. All model assumptions were validated with residual plots. Analyses were conducted using survey commands for analysing data weighted by area of residence to adjust for the deliberate over sampling in rural and remote areas.

3. Results

3.1. Participant Characteristics

Participant characteristics are reported in Table 1. The women with PCOS were around two months younger, were more likely to not have children and had a lower prevalence of currently breastfeeding compared to women without PCOS. As reported previously, women with PCOS also reported a higher BMI, weight and waist circumference than women without PCOS [7]. As previously reported [19], women with PCOS had an elevated energy and fibre intake and lower glycaemic index and percent energy intake from saturated fat compared to women without PCOS (data not reported). As previously reported [19], women with and without PCOS had similar physical activity levels (814 ± 874 vs. 820 ± 895 MET/min, $p = 0.75$).

Table 1. Characteristics for women with and without polycystic ovary syndrome.

	All <i>n</i> = 8200	PCOS <i>n</i> = 414	Non-PCOS <i>n</i> = 7155	<i>p</i>
Age (years) *	33.7 (1.5)	33.5 ± 0.1	33.7 ± 0.02	0.015
BMI (kg/m^2) *	25.8 (5.9)	29.0 ± 0.4	25.4 ± 0.1	<0.001
Weight (kg) *	71.3 (16.7)	79.6 ± 1.2	70.3 ± 0.2	<0.001
Waist circumference (cm) *	86.0 (14.3)	91.9 ± 1.0	85.7 ± 0.2	<0.001
<i>Smoking status</i> †				0.729
Never smoker	4972 (60.4)	256 (59.1)	4341 (60.3)	
Ex-smoker	2112 (25.6)	121 (27.9)	1829 (25.6)	
Smoke <10 cigarettes/day	574 (6.9)	26 (6.0)	517 (7.1)	
Smoke 10–19 cigarettes/day	372 (4.5)	20 (4.6)	319 (4.4)	
Smoke ≥20 cigarettes/day	205 (2.5)	10 (2.3)	183 (2.5)	
<i>Personal income</i> †				0.765
No income	724 (9.5)	41 (9.8)	634 (9.1)	
Low (>\$0–\$36,399)	2923 (38.5)	156 (37.5)	2562 (36.3)	
Medium (\$36,400–\$77,999)	2737 (36.1)	137 (32.7)	2398 (34.0)	
High (>\$78,000)	1207 (15.9)	71 (17.0)	1047 (14.9)	
<i>Highest qualification</i> †				0.762
No formal qual/year 10/12	1492 (18.4)	76 (18.1)	1301 (17.3)	
Equiv				
Trade/diploma	2040 (21.2)	100 (23.8)	1793 (23.9)	
Degree or higher	4565 (56.4)	245 (58.2)	3986 (53.1)	

Table 1. Cont.

	All n = 8200	PCOS n = 414	Non-PCOS n = 7155	p
<i>Marital status</i> †				
Married	5115 (62.2)	260 (59.9)	4455 (62.0)	
De facto	1233 (15.0)	64 (14.7)	1067 (14.9)	
Separated/divorced	422 (5.1)	21 (4.8)	373 (5.2)	
Widowed	14 (0.2)	0 (0)	14 (0.2)	
Never married	1445 (17.6)	89 (20.5)	1274 (17.7)	
<i>Number of children</i> †				
0	3134 (38.1)	205 (47.2)	2748 (36.1)	
1	1630 (19.8)	86 (19.8)	1409 (18.5)	
2–3	3228 (39.2)	132 (30.4)	2818 (37.0)	
≥4	243 (3.0)	11 (2.5)	213 (2.8)	
<i>Currently breastfeeding</i> †				
No	4817 (58.4)	223 (51.3)	4193 (55.0)	
Yes	277 (3.4)	7 (1.6)	240 (3.2)	
No child	3149 (38.2)	205 (47.1)	2761 (36.2)	

* Values represent mean (SD); † Values represent n (%); Data were analysed by independent t-test to compare continuous variables and chi-square test to compare categorical variables between women with and without PCOS; BMI: Body mass index.

3.2. Dietary Patterns

The dietary pattern analysis revealed three distinct patterns explaining a total 27% variance (Table 2). The first pattern was labelled *Non-core foods* as there were high factor loadings for cakes, biscuits, sweet pastries; confectionary; refined grains and also take-away foods and crisps. The second pattern was labelled *High meat and take-away* as fish (fried, processed, canned and cooked), processed meat, red meat, but also take-away food highly correlated in this pattern. The final pattern was labelled *Mediterranean-style* as Mediterranean type foods highly correlated to this pattern including a variety of vegetables, fruit and nuts, small correlations with fish, while crisps were inversely correlated. Participant characteristics across the quartiles of dietary pattern score are presented in Supplemental Table 1.

Table 2. Factor loadings for each of the identified pre-conception dietary patterns for women with and without PCOS.

Food Group	Non-Core Foods	High Meat and Take-Away	Mediterranean-Style
Cakes, biscuits, sweet pastries	0.661	0.010	0.020
Confectionary	0.629	0.089	0.020
Refined grains	0.483	0.239	0.146
Vegemite	0.483	0.106	0.068
Takeaway	0.467	0.402	-0.138
Crisps	0.466	0.199	-0.262
Juice	0.408	0.007	0.071
Tomato sauce	0.380	0.018	0.029
Processed meat	0.359	0.567	-0.190
Red meat	0.330	0.595	-0.088
Added sugar	0.325	-0.023	-0.120
Wholegrains	0.319	-0.113	0.408
Saturated spreads	0.291	-0.117	0.111
Poultry	0.280	0.520	-0.098

Table 2. Cont.

Food Group	Non-Core Foods	High Meat and Take-Away	Mediterranean-Style
Potato	0.279	0.009	-0.199
Nuts and nut spread	0.260	0.137	0.493
Fried fish	0.212	0.649	-0.064
Fresh fruit	0.150	-0.020	0.539
Tomatoes	0.081	-0.137	0.355
Legumes	0.066	0.018	0.207
Other vegetables	-0.008	0.114	0.618
Leafy green vegetables	-0.038	0.082	0.503
Eggs	-0.039	0.202	0.271
Processed fish	-0.040	0.510	0.376
Other fish	-0.042	0.620	0.260
Garlic	-0.055	0.033	0.435
Soya	-0.082	-0.040	0.393
Alcohol	-0.185	0.287	0.060
<i>Percentage variance explained</i>	13%	8%	6%

Dietary patterns obtained using factor analysis with factor loadings extracted using the principal component method and varimax/orthogonal rotation. Food groups with factor loadings <0.25 for all factors are not included in the table (cruciferous vegetables; yellow or red vegetables; low fat dairy; full fat dairy; and canned fruit).

3.3. Dietary Patterns and PCOS

Table 3 reports the results from logistic regression. In the crude analysis, for each 1 SD increase in the *High meat, fish, poultry and take-away* pattern, there was a 9% greater likelihood for women to have PCOS, however this association did not remain in the adjusted analysis. In the crude analysis, for each 1 SD increase in the *Mediterranean-style* dietary pattern, there was a 15% greater likelihood for women to have PCOS. This association was strengthened after adjusting for maternal age, maternal BMI, current breastfeeding, number of children, such that for each 1 SD increase in the *Mediterranean-style* dietary pattern, there was a 26% greater likelihood that the women reported had PCOS. There were no associations between the *Unhealthy, non-core foods* pattern and PCOS.

Table 3. Odds ratios for likelihood of PCOS according to the dietary patterns identified.

	OR *	95% CI	p	Adjusted OR * †	95% CI	p
PCOS						
Unhealthy, non-core foods	1.06	0.97, 1.16	0.22	1.03	0.94, 1.13	0.55
High meat, fish, poultry and take-away	1.09	1.00, 1.17	0.03	1.04	0.95, 1.13	0.43
Mediterranean-style	1.15	1.05, 1.26	0.02	1.26	1.15, 1.39	<0.001
Maternal age	-			0.92	0.85, 0.98	0.014
Maternal BMI	-			1.09	1.07, 1.10	<0.001
Current breastfeeding	-			1.00	0.96, 1.05	0.97
Number of children	-			0.88	0.75, 1.04	0.13

Associations between PCOS and dietary patterns (Z-scores) in crude and adjusted analyses carried out using binary logistic regression analyses; Referent category is not having PCOS; * Indicates change in risk per 1 SD increase in factor score; † Adjusted for maternal age, maternal BMI, current breastfeeding, number of children.

4. Discussion

We report here for the first time that women with PCOS have different dietary patterns compared to women without PCOS, in a large population-based cohort of women. Women with PCOS were more likely to consume a dietary pattern consistent with the Mediterranean diet; however there were

no differences in the other commonly consumed dietary patterns of unhealthy non-core foods or a pattern higher in meat.

The Mediterranean-style dietary pattern contains a number of foods similar to a Mediterranean diet which consists of fish, monounsaturated fats from olive oil, fruits, vegetables, wholegrains, legumes and nuts and moderate alcohol consumption [43]. It is also consistent with previously defined “Mediterranean” patterns in prior research comprising vegetables, fish, fruits, poultry, low-fat dairy products, and olive oil [44,45]. Surprisingly however, we found an inverse factor loading for poultry which is typically consumed in higher intakes in the Australian population compared to fish [46], which loaded on this pattern in moderate amounts for both processed (*i.e.*, tinned fish) and other fish (*i.e.*, cooked fish), while fried fish was inversely associated. It is to be noted that intake of olive oil is not collected in the food frequency questionnaire used in this study. Another surprising finding was that both low fat and high fat dairy foods did not correlate to any pattern. This might reflect the overall low consumption of dairy in men and women in the adult Australian population; yet this is consistent with a previous study in pregnant women where low fat dairy did not load on any of the three dietary patterns, and high fat dairy only moderately correlated with the vegetarian-type dietary pattern [24]. Nevertheless, non-core foods inversely loaded on this pattern such as take-away foods and crisps, as well as added sugar, which supports an overall healthier dietary pattern consisting of a number of Mediterranean foods. As we are the first to report that a Mediterranean-style dietary pattern was independently associated with increased likelihood of having PCOS, this discrepant finding may indicate the possible high level of women with PCOS seeking dietary knowledge with a subsequent adoption of healthy dietary patterns.

To date, there are few other studies reporting on the relationship between dietary patterns and other conditions co-existing with PCOS. In literature assessing infertile women, a large proportion of whom will likely have PCOS, a Mediterranean diet is associated with a higher chance of natural or assisted reproduction conception [44,47]. The adoption of a Mediterranean-style diet in PCOS may therefore have positive implications for the appropriate lifestyle management of chronic diseases associated with PCOS. Further studies are needed to expand on our findings on the association of dietary changes in those with a diagnosis of PCOS, the optimal means of conveying dietary education at diagnosis and the long-term maintenance of positive dietary changes.

We observed here that the two other identified dietary patterns, namely those consisting predominantly of non-core foods or a higher meat intake from either take-away/processed or non-processed sources explained a moderate proportion of variability in food intake in all participants (13% and 8% respectively). However, neither pattern was associated with PCOS status in the adjusted analysis. In association with higher weight and BMI in PCOS, this is a positive finding that is also consistent with the diagnosis of PCOS contributing to an improvement of dietary habits in keeping with population-based dietary guidelines of minimising discretionary or non-core food intake, reducing processed meats and consuming a moderate intake of protein [48].

While a Mediterranean diet is not a specifically recommended dietary intake for PCOS, emerging research suggests beneficial effects of certain components of this diet, such as elevated omega-3 fatty acids which are generally found in high amounts of oily fish. Although the specific types of fish consumed in our Mediterranean style dietary pattern cannot be extracted, both processed fish and cooked fish varieties contain some omega-3 fatty acids, likely contributing to a reasonable intake of omega-3 fatty acids in this population. The literature in PCOS focuses predominantly on omega-3 fatty acid supplementation studies which report improvements in outcomes including reductions in bioavailable androgens, triglycerides, blood pressure, glucose and surrogate markers of insulin resistance [49–52]. One recent study found that a Mediterranean diet pre-pregnancy was associated with a 42% reduced likelihood of developing hypertensive related disorders during pregnancy [26]; while higher consumption of sweets and seafood [25] or high intake of red meat, processed meat, refined grain products and sweets [27] during pregnancy was associated with a 23% and 63% increased risk of gestational diabetes. A Mediterranean dietary pattern has also been reported to be

associated with improved health outcomes including decreased inflammation [53] and prevalence of the metabolic syndrome [54], abnormal glucose tolerance [55] or depression [45]. As adverse health outcomes are commonly associated with PCOS [3,4,6], this dietary pattern may therefore result in health benefits. However, we have previously reported in this cohort that this improved diet quality occurred in conjunction with a modest increase in energy intake (+215 kJ/day) which could contribute to additional longitudinal weight gain [19]. The potential benefits of an improved dietary pattern may not outweigh the effects of increased energy intake and consequent weight gain with regards to effects on reproductive, and potentially metabolic and psychological, parameters.

Strengths to our study include the large population of women with and without PCOS from a community-based population in contrast to the majority of the existing research assessing diet and PCOS. This minimises selection bias. This is also more likely to capture a lower proportion of women with PCOS with a more severe clinical phenotype and a higher BMI who typically present to clinical services and are captured in research studies [56]. While the use of self-report PCOS is a limitation, the nature of this research means that it is not feasible to clinically verify PCOS or control status. It is also not possible to determine the PCOS phenotype or which diagnostic criteria were used in diagnosis. However, given that the Rotterdam criteria were first published in 2004 [57], it is also most likely that the majority of women self-reporting diagnosed PCOS in Survey 4, conducted in 2006, would have been diagnosed based on NIH criteria. There are also some other limitations to our study. We report here 58% participant retention compared to baseline levels 13 years prior which may indicate bias and limit generalisability. However, no differences between completors and non-completors has previously been reported indicating a likely minimal effect of attrition on outcomes [36]. Although the FFQ is a validated measure of assessing nutritional intake, we are not able to assess the contribution of dietary patterns to the development or severity of PCOS due to the study design and report here only associations between dietary patterns and PCOS status. Further, the total variance explained by each factor was intermediate compared with previous factor analyses conducted in different age groups [29,58,59]; however, the Kaiser-Meyer-Olkin measure of sampling adequacy was 0.78, exceeding the recommended value of 0.6; and Bartlett's test of Sphericity achieved statistical significance indicating the correlations in the data set are appropriate for factor analysis. Moreover, the food groups loading on the factors were varied and many were greater than the 0.25 cut-off value suggesting that our population had a varied diet that was, nevertheless, still specific to the identified factors. As the present study is the first of its kind in this population, further studies are required to refute or support our findings and future work is warranted assessing the contribution of dietary pattern intake to the severity or incidence of PCOS.

5. Conclusions

In conclusion, we report for the first time the independent association of PCOS status with self-reported dietary patterns, specifically a Mediterranean diet pattern. This may indicate an improvement in the quality of dietary intake following a diagnosis of PCOS. We also report no increase in dietary patterns high in non-core, meat or take-away foods despite a higher body weight. Combined with our prior research showing healthier intake but higher caloric consumption, it appears that women with PCOS may have a greater appetite and are more overweight, despite a healthier diet. Future research should examine the contribution of dietary patterns to the incidence and severity of PCOS and the potential for modification of dietary patterns in the lifestyle management of PCOS.

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The Effect of Lifestyle Intervention on Body Composition, Glycaemic Control and Cardio-respiratory Fitness in Women with Polycystic Ovarian Syndrome: A Systematic Review and Meta-Analysis

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"The Effect of Lifestyle Intervention on Body Composition, Glycaemic Control and Cardio-Respiratory Fitness in Women With Polycystic Ovarian Syndrome: A Systematic Review and Meta-Analysis"

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ABSTRACT

Introduction: Polycystic Ovarian Syndrome (PCOS) affects 18-22% women of reproductive age. We conducted a systematic review and meta-analysis to quantify expected benefits of lifestyle (exercise and dietary) interventions on various clinical outcomes in PCOS. **Methods:** Potential studies were identified by conducting systematic search of Pub Med, CINAHL and Cochrane controlled trials registry (1966 to April 2013) using key concepts of PCOS, exercise, dietary and lifestyle interventions. **Results:** Significant improvements were seen in women who received lifestyle intervention versus usual care, in body composition parameters of body mass index (BMI), mean difference (MD) -1.12 kg.m⁻² (95%CI -0.22 to -0.03, P=0.009), body weight MD -3.42 kg (95%CI -4.86 to -1.99, P<0.00001), waist circumference MD -1.64 cm (95%CI -2.09 to -1.19, P<0.00001), waist hip ratio MD -0.03 (95%CI -0.05 to -0.01, P=0.0002) and body fat % MD -1.71% (95%CI -3.10 to -0.32, P=0.02). Insulin improved significantly, MD -1.10 pmol/L (95%CI -2.05 to -0.16, P=0.02). Lipid profile improved, total cholesterol MD -0.09 mmol/L (95%CI -0.14 to -0.04, P=0.0007) and low density lipoprotein (LDL) MD -0.15 mmol/L (95%CI -0.23 to -0.07, P=0.0003). C-reactive protein (CRP) was significantly lower, MD -0.47 mmol/L (95%CI -0.80 to -0.15, P=0.004). Significant improvements were also observed in cardio-respiratory fitness with resting heart rate MD -1.89 beats.min⁻¹ (95%CI -2.90 to -0.88, p=0.0002) and peak VO₂ MD 5.09 ml.kg⁻¹.min⁻¹ (95% CI 3.13 to 7.05, P<0.00001). **Conclusions:** Our analyses suggest lifestyle intervention is optimal for improving body composition parameters, insulin, total and LDL-cholesterol, CRP and cardio-respiratory fitness in women with PCOS.

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INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) was first reported in the 1930s by Stein and Leventhal [1]. This is the most common endocrine disorder affecting up to 18-22% of reproductive age women [2]. PCOS is characterised by clinical or biochemical hyperandrogenism [excess androgens which lead to acne, scalp hair loss, excessive facial and body hair (hirsutism)], insulin resistance, oligo/amenorrhea (infrequent or no menstruation), polycystic ovaries and infertility or reduced fertility [3, 4]. Physical inactivity and obesity work together with the genetic post receptor defects and lead to insulin resistance and hyperinsulinaemia [5, 6]. Insulin resistance and increased insulin levels aggravate the symptoms of PCOS in relation to biochemical and clinical hyperandrogenism. It is not the entire body weight but the distribution of that weight as fat in android (abdominal, central or visceral) pattern that increases health risks and worsens PCOS symptoms. Visceral adipose tissues produce adipocyte related hormones – Adiponectin and Leptin, which are insulin antagonists and contribute towards insulin resistance [7]. Insulin resistance and obesity increase the risk of glucose intolerance, dyslipidemia and diabetes mellitus (DM) considerably, which in turn increases cardiovascular risks [8].

Elevated levels of androgens (testosterone, dehydroepiandrosterone and androstenedione) are not uncommon, and occasionally hyperprolactinaemia or hypothyroidism are present [9]. Most women with PCOS have elevated luteinizing hormone (LH) levels with normal oestrogen and follicle-stimulating hormone (FSH) production [10]. Increased insulin levels, obesity and hyperandrogenism contribute to the vicious cycle of anovulation which makes it hard for these women to conceive, often leading to depression and anxiety [11].

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Hyperinsulinaemia leads to excess androgen production, so lowering insulin levels by exercise training and weight loss (even as little as 5% of body mass) may reduce free testosterone levels and restore ovulatory cycles, resulting in improved menstrual regularity, ovulation, and pregnancy rates in many women with the disorder [12].

A systematic review was completed in 2009 by Harrison et al. [13] but these authors did not conduct data pooling. In 2011 a systematic review and subsequent meta-analyses was conducted by Moran et al.[14], but this analysis only included 6 published studies. Six more recent lifestyle studies for PCOS mean that the volume of pooled data has doubled and the number of outcome measures has been extended. We therefore conducted a systematic review and meta-analysis; the primary aim was to quantify the expected benefits of exercise training and dietary interventions on a range of clinical outcomes in women with PCOS.

METHODS

Search strategy

Potential studies were identified by conducting a systematic search using Pub Med, www.ncbi.nlm.nih.gov/pubmed (1966 to April 2013). A search strategy can be seen in the supplementary files. CINAHL and the Cochrane controlled trials registry were also searched (1966 to April 2013). The search strategy included the key concepts of PCOS, dietary therapy, lifestyle therapy and exercise training. These were combined with a sensitive search strategy to identify randomized controlled trials. Reference lists of papers found were scrutinized for new references. All identified papers were assessed independently by two reviewers (NS and LH). Searches of published papers were also conducted up until April 2013.

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Inclusions

Randomized, controlled trials of exercise alone or lifestyle (exercise and diet) intervention in people with PCOS were included. There were no language restrictions.

Exclusions

Animal studies, review papers and non-randomized controlled trials were excluded. Studies that did not have desired outcome measures or participants who were non-polycystic ovary syndrome patients in either exercise, lifestyle (exercise and diet) or usual care groups were excluded. Several authors were contacted and provided missing data, these data were used in the analyses. Incomplete data or data from an already included study was excluded. Studies using interventions other than lifestyle (e.g. electro acupuncture, ultrasound) were excluded.

Studies included in the review

Our initial search identified 201 manuscripts, examination of the latest editions of relevant journals yielded a further 32 manuscripts. Out of 233 studies, 28 were excluded at first inspection as duplicates, 182 were removed after reading titles or abstracts, 13 of these studies were not trials of lifestyle therapy in PCOS women, leaving 23 studies; 11 studies were excluded for various reasons (see Supplementary Table 3), 12 studies were included for analysis (see consort statement, Figure 1).

Data synthesis and Outcome Measures

Our lifestyle intervention groups were defined as exercise alone or exercise plus diet. Our definition of usual care (comparator) groups could include sedentary control, placebo, diet only or metformin. Analyses were only conducted on intervention versus comparator 1, see Table 1. Data on all outcomes measures were archived in a database. Outcome measures following interventions included body mass index (BMI), body weight, waist circumference

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(WC), percentage body fat, waist hip ratio, glycaemic parameters (insulin, glucose and homeostatic model assessment (HOMA) which quantifies insulin resistance), lipids, C-reactive protein (CRP) and cardio-respiratory fitness (peak oxygen consumption (peak VO₂) and heart rate).

Statistical analysis

Meta-analyses were completed for continuous data by using the change in the mean and standard deviation of outcome measures as we did not wish to assume randomization would adjust for baseline imbalance. Change in post-intervention mean was calculated by subtracting baseline from post-intervention values. Change in the standard deviation of post-intervention outcomes was calculated by using Revman 5.0 (Nordic Cochrane Centre Denmark). Data required was either (i) 95% confidence interval data for pre-post intervention change for each group or when this was unavailable (ii) actual P values for pre-post intervention change for each group or if only the level of statistical significance was available (iii) we used default P values (e.g. P<0.05 becomes P=0.049, P<0.01 becomes P=0.0099 and P = not significant becomes P=0.05). A random effects inverse variance was used with the effects measure of mean difference. Heterogeneity was quantified using Cochrane Q test [15]. Sensitivity analyses were conducted by removing studies of exercise and diet, leaving exercise only studies, for the outcomes BMI, WC and peak VO₂. The purpose of sensitivity analyses was to compare effect sizes of exercise alone with exercise and diet. Egger plots [16] were provided to assess the risk of publication bias (see supplementary files). Study quality was assessed by using a modified PEDro [17] score (out of 9 maximum score) as blinding participants difficult in lifestyle studies. We used a 5% level of significance and 95% confidence intervals, figures were produced using Revman 5.

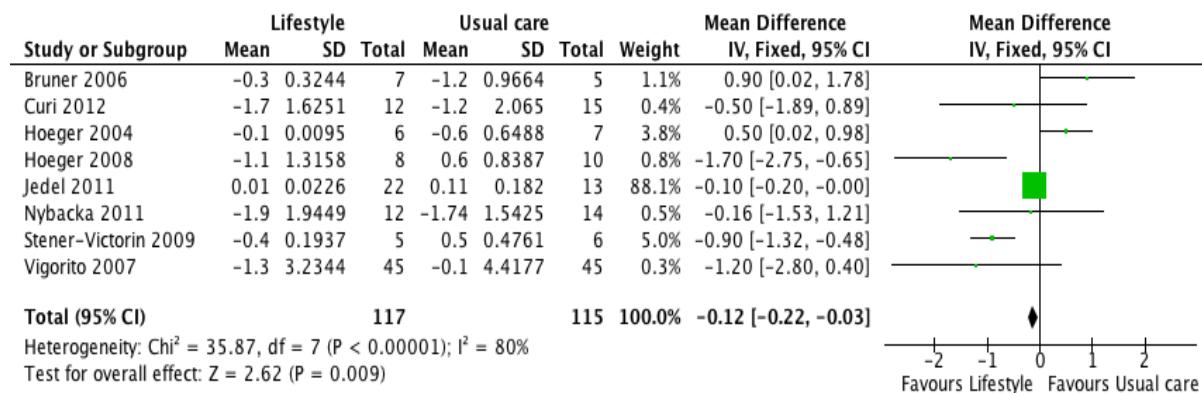
RESULTS

Our analyses included data from 12 studies [3, 4, 18-27], which yielded data on 668 women with PCOS. In seven studies the mean BMI indicated the participants were obese, three studies indicated women were overweight and in two studies it was unclear. Mean age of participants in all but one study was 21-32 years of age. Details of number of participants, duration of studies and withdrawals for included studies can be seen in Table 1. Supplementary Table 1 contains detailed descriptions of all interventions and comparator groups. Details of baseline characteristics of participants in included studies can be seen in supplementary files, Table 2. Details of the excluded randomized, controlled, trials [28-38] can be seen in supplementary file, Table 3.

Body Composition Parameters

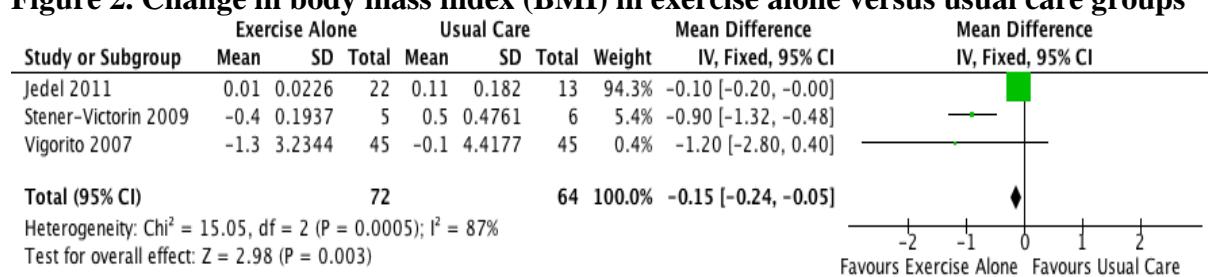
Analysis of change in BMI showed significant improvement in lifestyle versus usual care groups, mean difference (MD) -1.12 kg.m^{-2} (95%CI -0.22 to -0.03 , $P=0.009$), see Figure 1.

Figure 1. Change in body mass index (BMI) in lifestyle versus usual care groups



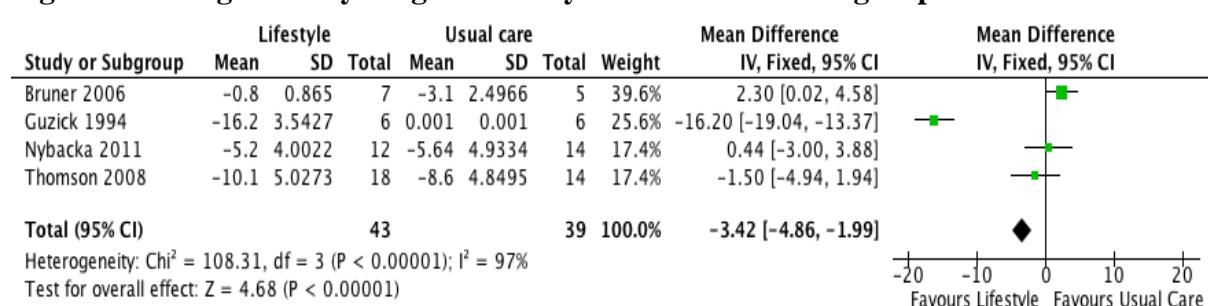
When studies using exercise plus diet were removed to distinguish between exercise alone and exercise plus diet groups, MD was -0.15 kg.m^{-2} (95% CI -0.24 to -0.05 , $P=0.003$), see Figure 2. Note the 95% CI's in figures 1 and 2 overlap considerably.

Figure 2. Change in body mass index (BMI) in exercise alone versus usual care groups



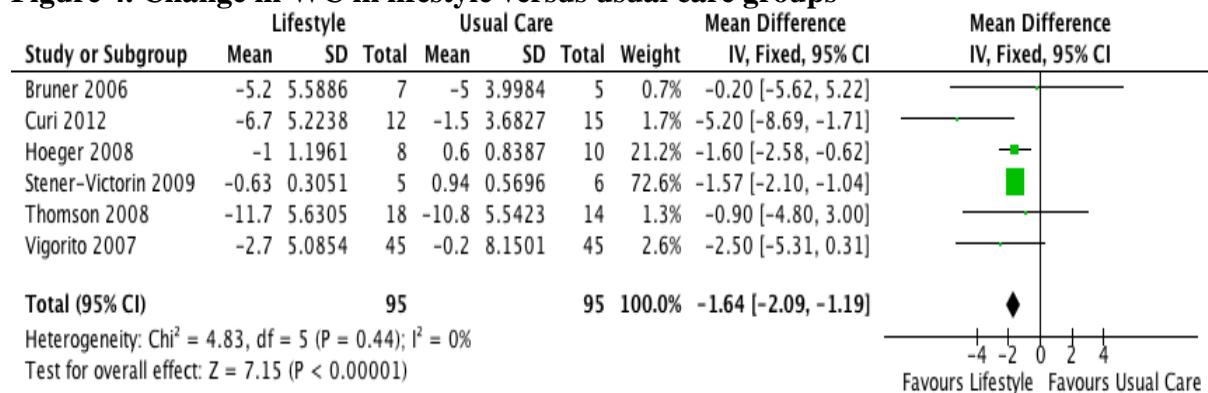
Analysis of change in body weight showed significant improvement in lifestyle versus usual care groups, MD -3.42 (95%CI -4.86 to -1.99, $P < 0.00001$), see Figure 3.

Figure 3. Change in body weight in lifestyle versus usual care groups



Waist circumference (WC) was significantly reduced for lifestyle versus usual care groups, MD -1.64 cm (95%CI -2.09 to -1.19, $P < 0.00001$), see Figure 4.

Figure 4. Change in WC in lifestyle versus usual care groups



When studies using exercise plus diet were removed to distinguish between exercise alone and exercise plus diet groups, MD was -0.51(95% CI -0.67 to -0.34, $P < 0.00001$), see Figure 5.

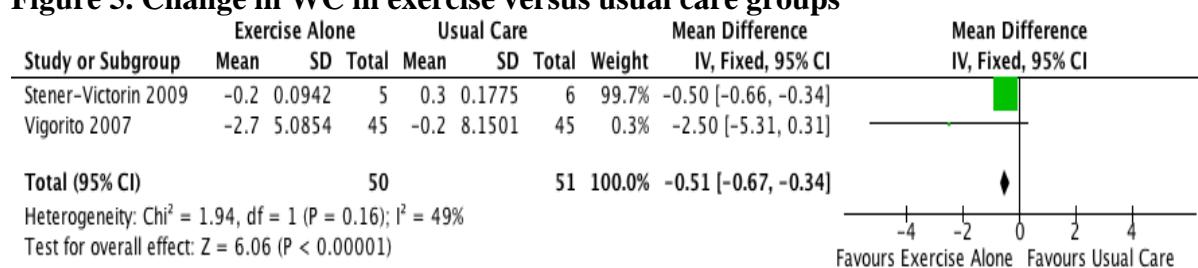
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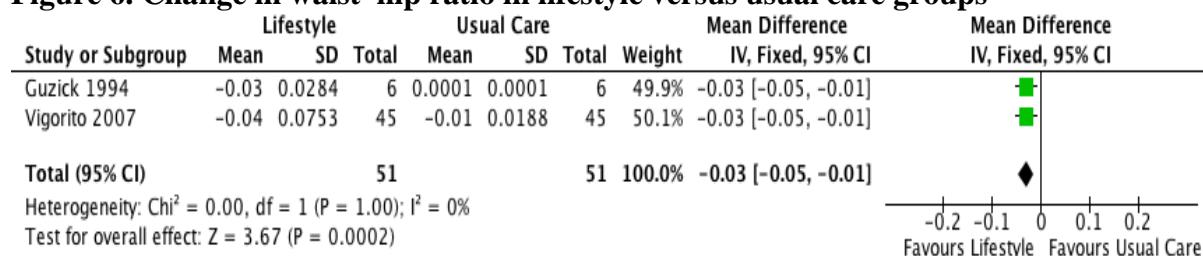
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Figure 5. Change in WC in exercise versus usual care groups



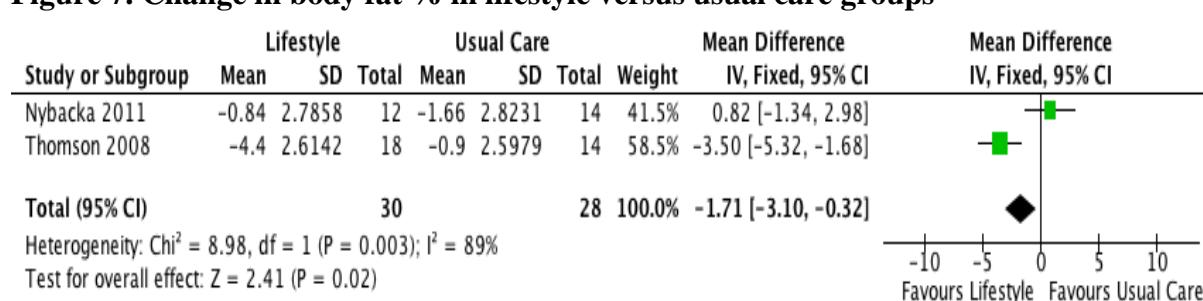
Waist-Hip ratio was significantly lower for lifestyle versus usual care groups, MD -0.03 (95%CI -0.05 to -0.01, $P=0.0002$), see Figure 6.

Figure 6. Change in waist–hip ratio in lifestyle versus usual care groups



Body Fat % was significantly lower for lifestyle versus usual care groups, MD -1.71% (95%CI -3.10 to -0.32, $P=0.02$), see Figure 7.

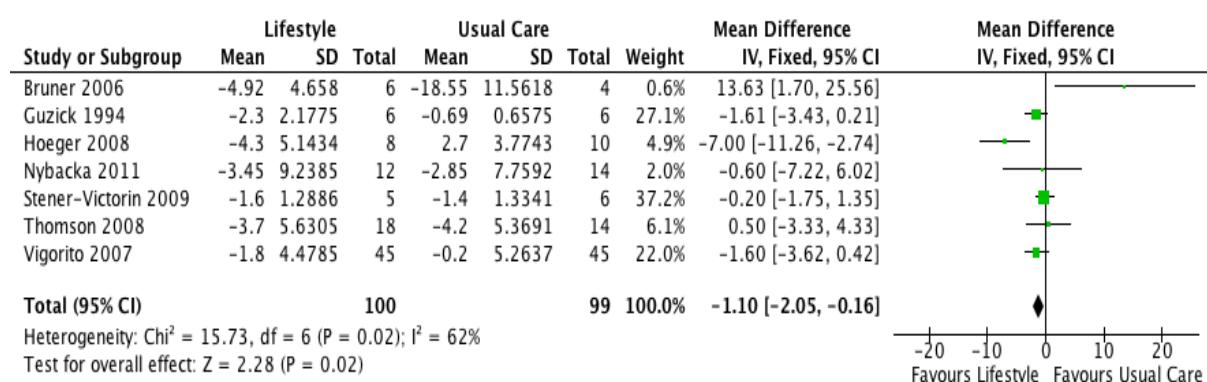
Figure 7. Change in body fat % in lifestyle versus usual care groups



Glycaemic Parameters

Insulin levels were significantly lower for lifestyle versus usual care groups, MD -1.10 pmol/L (95%CI -2.05 to -0.16, $P=0.02$), see Figure 8.

Figure 8. Change in insulin in lifestyle versus usual care groups



Glucose levels were not significantly lower for lifestyle versus usual care groups, MD

-0.02 mmol/L (95%CI -0.04 to 0.00, P=0.06), see supplementary file, Figure S1.

HOMA was not significantly different for lifestyle versus usual care groups, MD 0.10

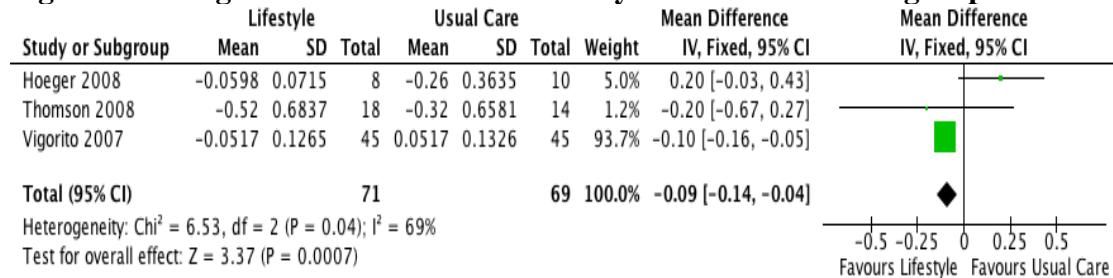
(95%CI -0.22 to 0.42, P=0.56), see supplementary file, Figure S2.

Lipid Profile

There was no significant difference in triglycerides between lifestyle versus usual care groups, MD 0.19 mmol/L (95%CI -0.04 to 0.42, P=0.11), see supplementary Figure S3.

Total cholesterol was significantly lower in lifestyle versus usual care groups, MD -0.09 mmol/L (95%CI -0.14 to -0.04, P=0.0007), see Figure 9.

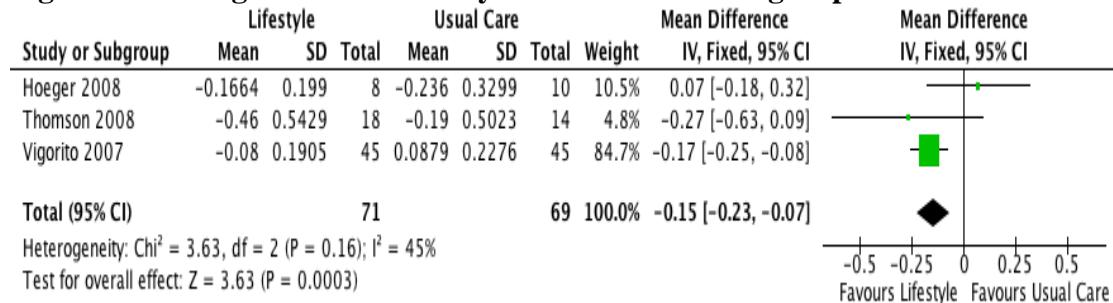
Figure 9. Change in total cholesterol in lifestyle versus usual care groups



LDL cholesterol was significantly lower in lifestyle versus usual care groups, MD -

0.15 mmol/L (95%CI -0.23 to -0.07, P=0.0003), see Figure 10.

Figure 10. Change in LDL in lifestyle versus usual care groups



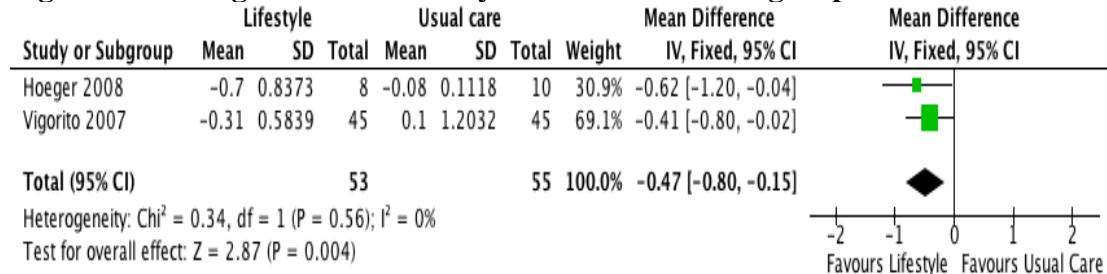
HDL was not significantly different in lifestyle versus usual care groups, MD -0.01

mmol/L (95%CI -0.04 to 0.02, P=0.51), see supplementary Figure S4.

C-Reactive protein (CRP)

Inflammatory marker CRP was significantly lower in lifestyle versus usual care groups, MD --0.47 mmol/L (95%CI -0.80 to -0.15, P=0.004), see Figure 11.

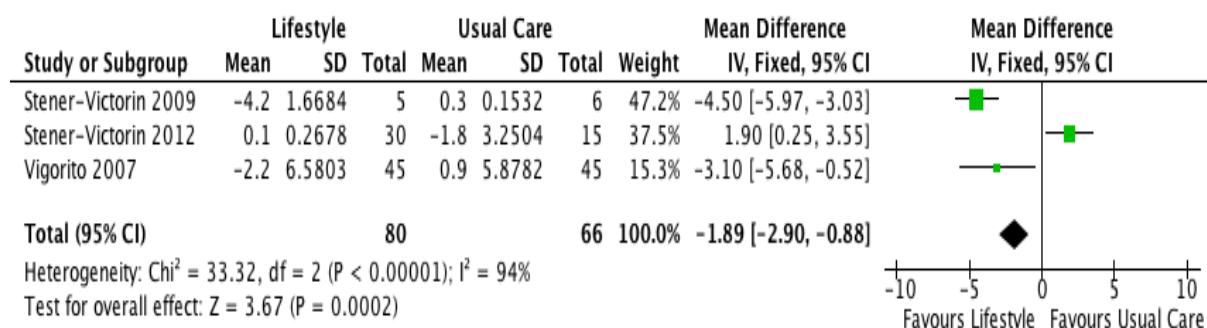
Figure 11. Change in CRP in lifestyle versus usual care groups



Cardio-respiratory Fitness

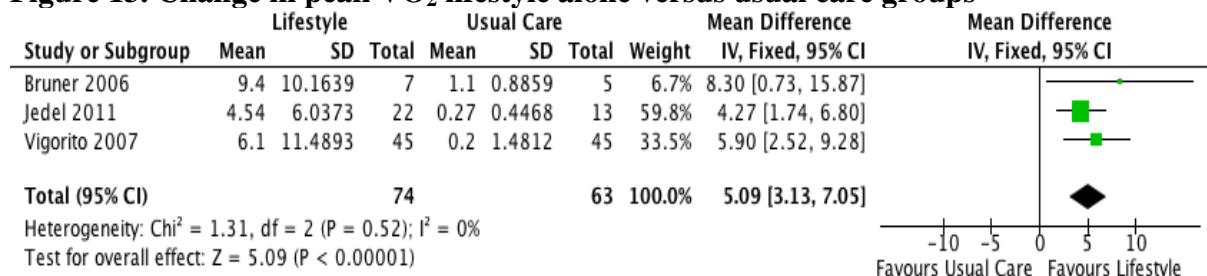
Resting heart rate was significantly lower in exercise alone versus usual care groups, MD -1.89 beats. min^{-1} (95%CI -2.90 to -0.88, P=0.0002), see Figure 12.

Figure 12. Change in resting heart rate in exercise alone versus usual care groups



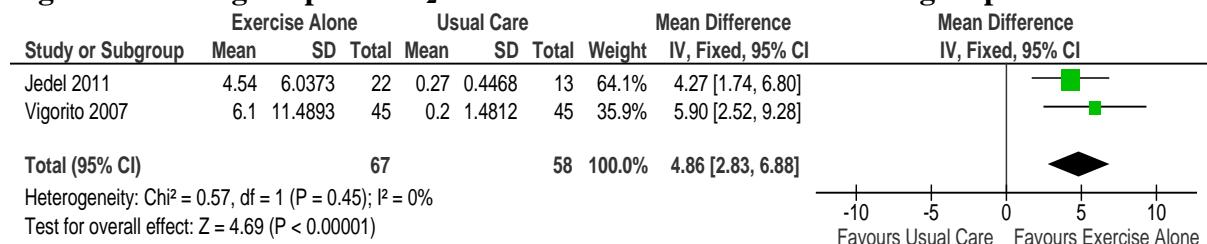
Peak VO_2 improved significantly for lifestyle versus usual care groups, MD 5.09 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (95% CI 3.13 to 7.05, $P < 0.00001$), see Figure 13.

Figure 13. Change in peak VO_2 lifestyle alone versus usual care groups



When studies using exercise plus diet were removed to distinguish between exercise alone and exercise plus diet groups MD was 4.86 (95% CI 2.83 to 6.88, $P < 0.00001$), see Figure 14.

Figure 14. Change in peak VO_2 in exercise alone versus usual care groups



STUDY QUALITY

In terms of study quality, median score was 7, with four studies scoring 6, four studies scoring 7, three studies scoring 8 and one study scoring 9, using a modified PEDro scale (out of 9). Details of the scores and PEDro scale are given in the supplementary file, Table 4. Egger plots showed little or no evidence of publication bias (see supplementary Files, Figures S5-S9).

DISCUSSION

This work presents a meta-analysis of the effectiveness of lifestyle (exercise and diet) intervention for polycystic ovarian syndrome (PCOS). These analyses were conducted using

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a range of prognostic markers of PCOS as outcome measures. There was a significant improvement in body composition parameters (BMI, body weight, waist circumference, waist-hip ratio and body fat %), total- and LDL-cholesterol, C-reactive protein, insulin and cardio-respiratory parameters (resting heart rate and peak VO₂). These data have clinical implications for improving reproductive function in overweight/obese women with PCOS using non-pharmacological methods.

Lifestyle with or without dietary intervention produced favourable changes in body composition measures; WC, waist-hip ratio, percentage body fat and BMI, suggesting that a large proportion of weight lost was adipose tissue. Previously, combined diet and exercise interventions for PCOS participants reported reductions in body fat but also muscle mass [23]. Previous work has suggested it is exercise, not dietary, intervention that provides the greatest changes in body composition and glycaemic control in women with PCOS [23]. Previous work also suggests modest weight reduction of about 5-10% might play the most significant role in restoration of ovulation and fertility in obese women with PCOS [21, 39]. The mean study duration of this analysis was 20 weeks; this duration may not be sufficient to achieve 5-10% weight loss.

Exercise alone has been shown to improve fertility [23, 40] and this is most likely mediated by improved insulin resistance [40]. Our analyses lend weight to the theory that insulin sensitivity is improved with regular exercise training in women with PCOS, although blood glucose was actually better in control groups. Our results suggest that optimal reductions in measures related to central obesity (waist circumference and waist-hip-ratio) require both exercise and dietary intervention. These reductions in central obesity are accompanied by improvements in measures of glycaemic control. Previous work has suggested that improved insulin sensitivity is closely related to improved waist circumference

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and waist-hip ratio, which in turn is related to android (central) body fat morphology [41].

Previous work has hypothesized that either through exercise alone, or in combination with appropriate dietary intervention, enhancements in insulin sensitivity is possible in women with PCOS.

Our analyses demonstrated improved peak VO₂ and reduced resting heart rate after completion of lifestyle therapy in women with PCOS. Vigorito et al. have previously shown that in overweight women with PCOS insulin sensitivity and peak VO₂ are positively correlated [27]. Moreover a 2006 review suggested: (i) Exercise may prevent reproductive complications associated with maternal obesity. (ii) Obesity increases the risk of infertility and miscarriage. (iii) Weight loss programs that incorporate diet and exercise are a cost-effective fertility treatment that may also reduce the probability of obesity-related complications during pregnancy. (iv) Regular exercise following conception may prevent excessive gestational weight gain and reduce post-partum weight retention [42]. Our measurements support the argument that higher levels of cardio-respiratory fitness are associated with better fertility. The magnitude of change in peak VO₂ demonstrated here would be noticeable to the participants and also clinically meaningful.

With respect to lipid profile, our analyses showed improvements in only Total- and LDL-cholesterol. Previous work has suggested that exercise induced changes in lipid profiles require a sustained lifestyle adherence program [43]. It may be that the included studies were not of sufficient duration to induce lipid improvements [14, 44], although reduced CRP levels indicate reduced systemic inflammation.

The sensitivity analyses for exercise only for the BMI, WC and peak VO₂ yielded very similar effect sizes and statistical significance as combined diet and exercise

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interventions. This suggests that exercise will improve these outcomes either in isolation or in combination with dietary intervention.

In summary, previous work has suggested that exercise is superior to dietary intervention for improving glycaemic control and body composition in women PCOS, our data support this, although intuitively a combined exercise and dietary intervention approach may yield superior results in trials lasting more than 20 weeks. We suspect there are currently insufficient published data to separate the effects of exercise or dietary intervention.

The limitations of this study are that exercise prescriptions vary slightly, and several studies used additional dietary interventions, although we conducted sub-analyses for BMI, WC and peak VO₂ to account for this. Meta-analysis of continuous data is problematic; we took the approach of adjusting for baseline difference in primary outcomes between allocation groups by measuring pre-versus post-intervention change. In many cases we were accurately able to calculate change in standard deviation, but in some cases where exact P-values were not provided in included study reports we had to use default values e.g. P<0.05 or P<0.001 in our calculations which may have introduced errors. Moreover these errors may have increased the measures of heterogeneity in our analyses which in some cases were high. Finally, we acknowledge that other factors, especially those related to volume of exercise (e.g. program duration) may explain some of the outcomes reported.

Conclusions

Our analyses suggest lifestyle intervention involving exercise are optimal for improving body composition parameters, insulin, lipid profile (especially total and LDL-cholesterol), CRP and cardio-respiratory fitness in women with PCOS.

Acknowledgments

None

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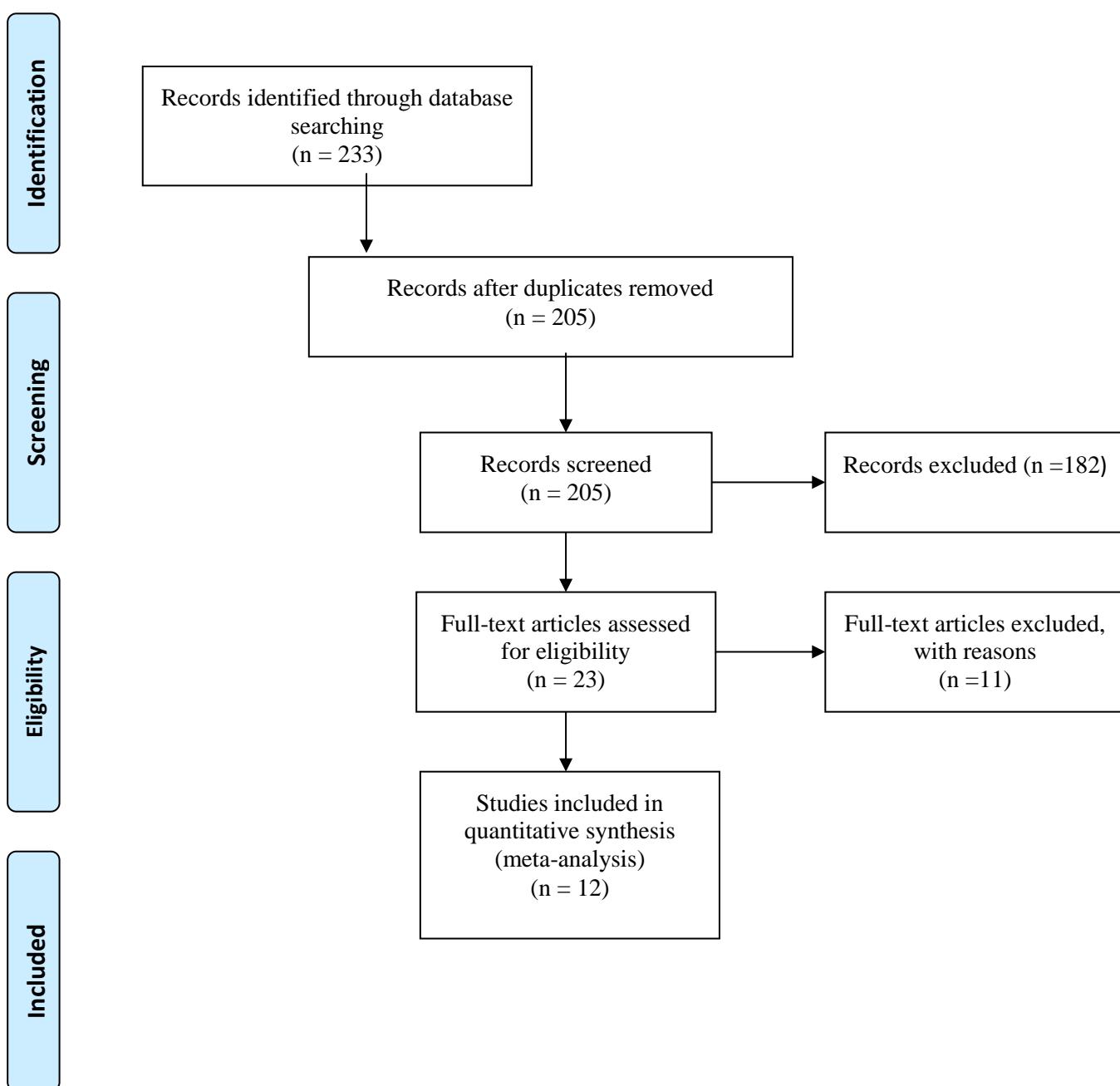
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Figure 1. Consort Statement.



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Table 1: Included lifestyle intervention studies, duration, number of participants, intervention and comparator groups.

Study	Duration of study	Total participants (lifestyle group)	Withdrawal (number of people)	Intervention	Comparator 1	Comparator 2	Comparator 3
Bruner 2006 [18]	12 weeks	12(7)	None	Lifestyle	Diet		
Curi 2012 [19]	6 months	40(12)	13	Lifestyle	Metformin		
Guzick 1994 [20]	12 weeks	12(6)	None	Lifestyle	Usual Care		
Hoeger 2004 [21]	48 weeks	38(6)	15	Lifestyle and placebo	Placebo	Metformin	Lifestyle & Metformin
Hoeger 2008 [22]	24 weeks	43(8)	9	Lifestyle	Placebo	Metformin	Oral contraceptive
Jedel 2011 [3]	16 weeks	84(22)	25	Lifestyle (Exercise only)	Usual care	Low frequency electro-acupuncture	
Nybacka 2011 [23]	4 months	57(12)	14	Lifestyle	Diet	Exercise	
Stener-Victorin 2009 [24]	16 weeks	20(5)	None	Lifestyle (Exercise only)	Usual care	Low frequency electro-acupuncture	
Stener-Victorin 2012 [25]	16 weeks	84(30)	10	Lifestyle (Exercise only)	Usual care	Low frequency electro-acupuncture	
Thomson 2008 [4]	20 weeks	94(18)	42	Lifestyle	Diet	Diet & combined aerobic-resistance exercise	
Thomson 2012 [26]	20 weeks	94 (16)	44	Lifestyle	Diet	Diet & combined aerobic-resistance exercise	

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Study	Duration of study	Total participants (lifestyle group)	Withdrawal (number of people)	Intervention	Comparator 1	Comparator 2	Comparator 3
Vigorito 2007 [27]	3 months	90(45)	None	Lifestyle (Exercise only)	Usual care		

Research article

Open Access

The information needs of women diagnosed with Polycystic Ovarian Syndrome – implications for treatment and health outcomes

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Abstract

Background: This paper reports the findings of an exploratory study about the information women diagnosed with Polycystic Ovarian Syndrome (PCOS) want to know about their condition and the consequences of this information for future treatment and health outcomes.

Methods: In-depth qualitative interviews regarding their information needs were undertaken with ten South Australian women diagnosed with PCOS. These women were aged 28–38 years and at differing stages of their fertility experience. The time since diagnosis ranged from 1–17 years. The main outcome measures sought were the identification of the information needs of women diagnosed with Polycystic Ovarian Syndrome (PCOS) during different periods of their lives; how and where they obtain this information, and the consequences of this information for future treatment and health outcomes.

Results: The women with PCOS in this study preferentially used the Internet for their information needs, as it had the advantages of convenience, privacy and accessibility, when compared with traditional mechanisms of information provision.

Conclusion: Giving a name to a collection of symptoms may bring relief and provide recognition that there really is a problem. However, with a diagnosis comes the need to have questions answered. A diagnosis of a chronic condition such as PCOS necessitates decision-making regarding possible treatment strategies and lifestyle choices. Information is needed in order to participate in shared decision making. The Internet proved to be a most versatile and beneficial source of information source for women with PCOS, if its limitations are taken into consideration.

Background

Polycystic Ovarian Syndrome (PCOS), the most common endocrine disorder in women [1], generates numerous health problems, usually commencing at puberty. PCOS affects approximately 5 to 10% of women of reproductive age in Australia [2].

The aetiology of PCOS is unclear: however, genetic inheritance may be implicated [3], and both insulin and androgen production are affected. Women diagnosed with PCOS have an increased risk of menstrual disorders, hirsutism, infertility, miscarriage, obesity, cardiovascular complications, endometrial cancer, and a seven fold greater risk of Type II diabetes [4].

The symptoms of PCOS may appear at any age during the reproductive life, and manifest in some groups of women differently to others. Women with PCOS may not seek assistance until they attempt to conceive, as this may be the first time they have not been under the influence of contraception, which may have masked the symptoms [5]. Symptoms such as obesity and hirsutism which were previously just annoying may get worse, and infertility may be a problem. Studies suggest symptoms vary by ethnicity. A 1999 study of Greek Caucasian women aged 17 to 45 years with PCOS (6.8% overall prevalence, n = 192), reported the prevalence of obesity at 38%, 29% experienced hirsutism with no menstrual disorders and 9.2% had menstrual disorders with moderate to severe hirsutism [6]. In Spanish Caucasian pre-menopausal women aged 18 and over, a study undertaken in 2000 found those with PCOS (6.5% overall prevalence, n = 154) had a prevalence of obesity of 36%, 40% had hirsutism, and 100% had menstrual disorders [7]. However, another 2000 study concerning women in the USA aged 18 to 45 years, white and black with PCOS (overall prevalence of 6.6%, n = 400) had a prevalence of 66% with menstrual disorders only, 19% with hirsutism only, and 14.7% experiencing both [8]. In Iranian girls aged 14 to 18 years, there was an overall prevalence of 3% with PCOS, and of these 6% had hirsutism, 7.4% had menstrual dysfunction, and 4.7% had severe acne [9].

In order to manage its impact, women with PCOS have a great need for information [10]. The physical and psychological problems associated with obesity and infertility, in particular, significantly affect quality of life [11]. Despite the huge increase in the availability of health information concerning PCOS, such as PCOS related books and websites, there has been little research in this area, particularly qualitative research. One of the few studies concerned with general health status of PCOS women examined questions important to women with PCOS. This 1998 study developed a tool to assess the quality of life of women with PCOS, in order to evaluate treatment outcomes [12]. Kitzinger & Willmott concentrated on women's own experience of PCOS within a feminist framework [13]. They found PCOS to be deeply stigmatising, and associated with considerable stress.

There is much consumer information available for many different aspects of health and disease, including PCOS. This information includes that developed by health professionals, advertising disguised as education, and also resources developed by support groups and individuals. The amount of information has increased and has recently become far more accessible with the advent of the Internet. The 1999 South Australian Health Omnibus Survey (n = 3013), a representative survey of people age fifteen years and above [14], found that the sources used to

answer health related question in the last twelve months included mostly Doctors (83.6%), with Internet (12.3%) ranked seventh out of ten categories. The same survey found that 77.5% of respondents only sought health information when they had a problem.

Another group specialising in research considering how people use the internet for health research, found that the users appreciated the convenience of being able to seek information at any hour, that they could get a wealth of information online, and that they could do research anonymously.[15]

However, this paucity of research around specific conditions is disappointing. Women with PCOS often deal with their symptoms for a long time, without a specific diagnosis [13]. Many of these women do not know where to look for information. Such women have both a right to more information about their condition and are likely to benefit considerably if information is available. Given questions regarding the reliability, adequacy and agenda behind various sources of potential health information, our hopes are that guidelines can be formulated which assist health care providers in assuring the highest quality of information for the greatest benefit to health consumers.

Methods

This study used in-depth qualitative interviews to explore the complexity and in-process nature of meanings, attached to PCOS [16]. Women were recruited for the study from two major sources. Initially, seven women were recruited from a previous nutritional study of PCOS, undertaken jointly by the Commonwealth Scientific Industrial Research Organisation's Division of Health Sciences and Nutrition (CSIRO HSN), and the University of Adelaide's Department of Obstetrics and Gynaecology [17]. These women had previously been diagnosed in accordance with the National Institute of Health (NIH) consensus criteria for clinical diagnosis of PCOS [18]. A second group of women were recruited from the Polycystic Ovarian Syndrome Association of Australia (POSAA), a support group for women with PCOS. All women recruited to the study had previously obtained a diagnosis, which provided them with a reference point in their life from which to build their stories.

Intensity sampling, a sampling technique aiming to select cases that manifest the experience being examined intensely, was used to identify potential recruits [19] The characteristics of participants are discussed below.

Women with PCOS were recruited into the study until no new themes were identified during the interviews. Recruitment took place from May to August 2002. Informed writ-

ten consent was obtained from all participants. Ethics approval was obtained from both the University of Adelaide and CSIRO HSN. Inclusion and exclusion criteria are described in Table 1.

Ten Australian women aged 28–38 years (mean age 32.4) were interviewed. The narrow age group of the participants in this study reflect the time at which fertility is of most concern in a woman's life, as many of the symptoms of PCOS are directly related to fertility, and this is often when women seek diagnosis. The women in this study were at differing stages of their fertility experience. A profile of these women is given in Table 2.

The interviews were carried out by the first author. The first author had previously been involved with a nutrition study, as both a subject and a study coordinator [17] and many of the women were recruited from this same study. Thus, the subjects knew that the author had PCOS, and camaraderie had been established prior to interview. The interviews were reflexive; as the first author had her own experience of the condition, she had been part of the experience of the women in the past, and this experience was the basis of the relationship formed through the interviews such that the subjects and the interviewer were willing to openly exchange their experiences. This also provided the first author with insights during the analysis that may have not otherwise occurred [16].

Interviews were carried out in the women's own homes. The original interview schedule was developed from a review of the literature surrounding PCOS, patient information and education. Questions were developed relating to when the subjects received information, where they obtained it, whether it was helpful, and in what form it came. Other questions were asked regarding the women's own particular experience of the condition, their health status, treatments they had embarked upon, and their own rationale and interpretation regarding the aetiology of the condition. After the piloting, the schedule was modified and, consistent with a grounded approach, it was further developed during the interviews as concepts, categories and themes were identified [16]. The full inter-

view schedule is provided in Table 3. A number of themes from the study are reported on, as they represent stages in the information collection process. These include Information and Diagnosis of PCOS, Information Sources, and Preferences for Information Provision. The time taken for the interviews was between 45 to 90 minutes, and all interviews were tape-recorded.

Each of the interviews was transcribed and reviewed by the first author, which enabled further familiarity with the emerging themes of the interviews. 'Framework' content analysis, an analytical process involving a number of distinct yet highly interconnected stages [20], was used to categorise themes for discussion. This method was chosen because of its ability to facilitate systematic analysis. After transcription, data was managed using QSR N6 Student software [21].

Results and discussion

Information and diagnosis of PCOS

The participants in this study often began their search for information in an environment of uncertainty.

I think one of the difficult things about it was because the symptoms are so diverse and I didn't feel like I had some of them. But I definitely had others of them so it was hard to actually work out whether it applied to me or not. And because no one gave me a definite "Yes, you have it", I still was saying well I don't know have I got it, no I haven't, you know, I don't know, this person says I haven't, this person says I have. So what was probably the most important thing was to find out, "Did I have it?" and what constituted the fact that I had it – so that was probably the most pressing thing. (Portia).

In order to "have an illness", there needs to be a recognition that problems being experienced are abnormal, and part of a greater disorder. In the case of PCOS, symptoms can be explained by other causes, such as stress, diet, lack of exercise and hormones. The path to diagnosis of an underlying cause is delayed, creating further problems with illness, fertility, state of mind and quality of life. Kitzinger and Wilmott refer to the frustration and anger PCOS

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria:	Exclusion Criteria:
<p>Female</p> <p>Previously diagnosed with Polycystic Ovarian Syndrome – (defined for this study as possessing two or more of these clinical features):</p> <ul style="list-style-type: none"> Criteria for Clinical Diagnosis of PCOS:³⁰ • Hyperandrogenism with or without skin manifestations • Irregular menses (oligo-ovulation or anovulation) • Absence of other androgen disorders (adrenal hyperplasia or tumour) • Polycystic ovaries on ultrasonography (not required for diagnosis but extremely prevalent). 	Non English speakers

Table 2: Profile of Participants

Pseudonym ^a	Age (Years)	Diagnosis (Years)	Marital Status	Education	Fertility Status
Cynthia	28	2	Single	Post school	Trying to conceive (TTC)
Martha	28	2	De facto	University	1 girl
Portia	35	1	Married	University	TTC
Holly	29	4	Married	University	2 boys
Michelle	29	3	Married	Pre matric	TTC, 2 miscarriages
Petra	36	12	Single	Post school	Not tried
Miranda	36	6	Married	Post school	4 miscarriages, adopting
Rebecca	38	4	Relationship	Pre matric	Starting to TTC
Jemima	30	7	Married	Post school	1 girl, 1 boy
Christine	35	17	Married	Post school	TTC, 1 miscarriage

^aPseudonyms are used to conceal the identity and preserve the confidentiality of the thoughts and experiences of the participants of this study.

women felt about delays in diagnosis, lack of information and an unwillingness of health professionals to take their symptoms seriously [13]. These findings demonstrate the dominant themes that women with PCOS face in their path to diagnosis.

Women suffering from PCOS present their initial problem, with differing symptoms that alone may not be cause for major concern. When associated with other symptoms, the effect is compounded and medical advice may be sought.

I had irregular periods as a teenager. My mother, finally after going from GP to GP, the GP just saying "Teenagers have irregular periods", found another GP who referred me to a gynaecologist, who did some tests, different blood tests, didn't do an ultrasound or anything. When I went back to see him he said, "Bit of a hormonal imbalance, come back and see me if you ever have trouble having children". As an 18 year old I thought "yeah right," and didn't think much more about it. (Jemima)

It was important to the women that someone recognised that they did have a problem. Radley talks about resolving the worry caused by uncertainty about signs and symptoms, by having others establish that one is really ill [22]. This social comparison provides a mechanism for the evaluation of one's symptoms. A medical confirmation of an illness can further reassure suspicions of an illness. In this sense, recognition of a problem validated the women's concerns.

Upset, I was upset when I found out. Relieved at the same time because finally I had a name for something that was wrong with me. (Cynthia)

Prior to obtaining verification of their symptoms, and due to their frustration at the delay in diagnosis, some of participants in this study approached the search for relevant information in a different way. Through past knowledge,

gathering of information, and sometimes coincidentally via acquaintances, some of the women suspected that their symptoms did in fact reflect something called Poly-cystic Ovarian Syndrome, and presented this idea to their doctors.

I was probably self-diagnosed in the end... In between seeing the gynaecologists, doing loads of blood tests, an ultrasound, I was in a bargain basement bookshop, they had a one-dollar book on infertility. I opened it up and looked up irregular periods, read through the thing it said PCOS and I said "Hey I've got that, I've got that, I've got that!" So I went along for my follow up appointment, and he said, "You've got a bit of a hormone imbalance." I said "Have I got PCOS?" and he said, "Yes". (Jemima)

Considering the prevalence of PCOS, surprisingly few participants had knowledge of the condition. Once they were given a name, some completely identified with the condition, after doing some initial research.

I didn't know anything,, never heard of PCOS. When I went to the first endocrinologist I said I'd been putting on weight, noticed hair growth, no periods, skin tags and skin discolouration and after I'd done all the reading, they were all the symptoms for PCOS. So I didn't know anything at first. (Holly)

Sources of information are presented in different ways. The women with PCOS in this study identified a range of sources, and these varied in terms of the women's levels of satisfaction, in terms of quality, their expectations, access and availability.

Information sources

Most women were diagnosed by general practitioners, gynaecologists or endocrinologists. Their expectation was that they would receive information about their condition through this initial source. Experience of the initial information that doctors gave them was varied. It has been

Table 3: Interview Schedule

Diagnosis of PCOS
Think back to when you first found out you had PCOS. Tell me about how you were diagnosed? <ul style="list-style-type: none"> • When did you find out? • Who told you? • Why do you think there was a problem/seek help in the first place? • What did they tell you? • How do you feel about what you found out? • What happened next?
Could you tell me what you knew about PCOS when you were told that you had it? <ul style="list-style-type: none"> • Where did you get that information? • Who told you where to look for information? • Were you interested then in finding out more information? • Have you sought information since then? • At the time, what kind of information did you want to know?
Information about PCOS
What do you understand now about PCOS? <ul style="list-style-type: none"> • What do you think causes PCOS? • What are the symptoms and long term effects? • What kinds of treatments are there? • How do you feel about having PCOS now?
What information have you collected about PCOS? <ul style="list-style-type: none"> • What have you learnt from this information? • What did you do with this information • What did you like/dislike about this information? • What is the best way of obtaining information? • What format would you like information presented?
Outcomes/Lifestyle
Do you think that the information you've had about PCOS has helped you take better care of yourself? How? <ul style="list-style-type: none"> • How do you think your general health will be affected in the future? • What information have you had about how PCOS affects getting pregnant? • From this information how do you think PCOS will affect your chance of getting pregnant?
Are there things you would like to know about PCOS for the future? Considering your life experiences, do you think you look for information in the same way as others? If you could start over again: <ul style="list-style-type: none"> • Who do you think is best to give you information about PCOS? • Where would you go to look first for information if you had no guidance? • Why do you think that is a good source? • What would you do differently about getting your information about PCOS?
Is there anything else you think may be important in order to understand your experience with information about PCOS that we should discuss?

shown that there are marked differences between the different specialties in the diagnosis and management of PCOS [23]. The women considered that some doctors did not know very much about PCOS and most were not satisfied with this information.

"Some of them have got no idea. I think we know more than them" (Michelle).

Kitzinger and Wilmott reported a similar finding, as women who have sought information about their condi-

tion upset the doctor-patient relationship balance, complain that they are more informed than the doctors in general, and do not receive positive responses when they suggest treatment options [13]. This finding has been reflected in other similar studies [24,25].

I went to my GP and he sent me on to an endocrinologist, and he told me that with the symptoms that I was telling him that I had, that I probably had PCOS and to go home and lose weight... When I went back to my doctor, he didn't actually know a lot about it. He didn't know a lot about

treatments for PCOS. He was very supportive, in our wishes to have children... I'm sure there are doctors out there now who know a lot more about PCOS, I don't know about GPs, I never got a lot of information about it from GPs, but I'm sure it's well known. (Holly)

Doctors focused on fertility issues as the main problems for those with PCOS, often with the worst-case scenario being emphasised. This was evident in both the women who were trying to conceive, and those where this was not yet an issue. The baseline health risks of the syndrome were not emphasised. Some women were left feeling as though they were powerless to do anything about their condition until they wanted children.

I think it's important to ensure that the medical profession are fully aware, both male and female doctors, and have that information on hand, that first port of call for people who need more information and then to have something on hand to make it easier for people to find out information. I felt like the doctor just did not explain it to me properly and I think doctors need to, I mean they do it with everything. If she'd sat there and told me what my major risks were or whatever, I probably would have taken some steps to do things differently. But from this there doesn't apparently to be anything much you can do until you start having children, then it becomes an issue but as far as the doctors are concerned, unless you've got worse symptoms with the hair and those other things, but if you don't have many symptoms, its all just a matter of just wait and see. (Rebecca)

Some of the participants realised that, at diagnosis, the main issues of PCOS were not of great concern to them. This meant that they might only have retained the information that was important to them.

I really can't begrudge the information my doctor gave me, my local GP. I mean, I'm sure that if I had wanted to take it further, she would have been happy to get other references and things for me. Like I said, it wasn't relevant. It was just I had a name. (Martha)

Those that did have positive experiences with their doctors thought that they were fortunate and this kind of experience was rare.

My local GP is very well up on it... The thing I enjoyed about talking to that doctor was that he seemed to know what I was talking about. The symptoms and things like that. He was the one who said to me this is how you feel, this is what's happening and he was spot on. And he didn't make me feel like I was an idiot. That it was all in my head. He was really, really good. (Michelle)

Information at initial diagnosis was sometimes provided in a take home format, such as a photocopied page out of a medical textbook.

All she basically did was give me the name of the condition and a couple of handouts describing what it was. That was it really. (Martha)

Those who hadn't receive pamphlets wanted some written information to aid in their understanding, after the initial information had been taken in. However, pamphlets were also seen as just part of a whole resource package. Pamphlets had a number of advantages, such as being short, portable, local, and providing information on how to find further information.

That little flyer was really good. I liked it because it was Australian. I found out since then that lots of the stuff differs between America and Australia. But also because it was simple and easy and it was something I could give my parents and family, which is really important. It's hard to explain it. (Portia)

Often looking for information might involve a trip to the library, where books and resources can be found. Local libraries however, did not seem to be helpful, and one participant even felt uncomfortable with the idea. In this study, using a library was associated with level of education. The two women who considered the library, or used it, both had a university education. The woman who did not consider this resource had left school before matriculation.

I don't actually go to the library and say "Hello, can you give me PCOS stuff." Not that I should be ashamed of it but if I don't know stuff then I feel a bit embarrassed asking. (Portia)

The information found in books was scarce, outdated or not at a suitable level for the consumer. Occasionally, information could be found in generalist women's health books, but this often referred to PCOS as a condition of "too many male hormones" [26], which may encourage the stigma of this condition. Sometimes the information provided in books was regarded as paternalistic [27], not providing the information needed for shared decision-making.

I never found a book totally on PCOS... Most of the books that were written by the male doctor type, books I thought were quite clinical and didn't tell the whole truth. This is on reflection because at the time you don't know these things. (Jemima)

Dedicated support groups for PCOS are fairly new in Australia. However, one of the participants had sought out information from an American support group via the Internet prior to the establishment of the Australian network. Three of the women interviewed were involved in the Polycystic Ovarian Syndrome Society of Australia (POSAA), established in 1998. Seven of the women had been involved in a clinical trial regarding PCOS, and this provided contact with other sufferers, as well as information and exercise sessions, designed by a fertility clinic [17]. These groups provided the participants with a very positive experience as it was the first time that they had met with other women who had PCOS. This provided the women with opportunities to share experiences with other sufferers, and for finding information regarding their condition on both an individual and a more general level.

It wasn't until I started doing the diet study that I started communicating with other people that had it and all of a sudden you know I came to accept that I had it, and wanted to know a lot more about it... I think the thing that I did that was really good was that I did the CSIRO study, because doors opened and the information I found. (Cynthia)

It was important for the women to be able to compare themselves with other sufferers. This gave them a frame of reference to rate their own symptoms. Some women came to believe that they were better off than other women with PCOS, which reassured them. The women found that networking with other women provided them with an opportunity to validate their experience, as well as supply them with practical information at their level, from other women with PCOS, and concerned their interests at the time.

I guess I've learnt the most from chatting with other women who've got it, and learning different things like maybe that is related to PCOS when before I thought it wasn't. I thought it was a different problem or whatever... Talking to other people is a huge thing. (Miranda)

Even taking all of the above sources into account, the Internet was the medium of choice for the participants to obtain their information about PCOS, as it had the advantages of other methods as a well as further benefits. However, while the Internet was considered the best way of obtaining information, it was not ideal for everyone. Nonetheless, the women who did not have easy access to the Internet thought that it would be the best way to obtain information, and were keen to use it. Seven of the participants had access to the Internet at home, two at work, and only one did not have any easy access. Five of

the participants used the Internet on a regular basis, and four only used it sporadically.

Finally when the Internet was connected in late 1997, that was the explosion when I connected up to the Internet and thought "My God! – look what we've discovered!"... I've got that many bookmarks on the Internet. Tried to just become informed... Online is good., but I understand that so many people it's not for them. (Jemima)

Although the participants were keen to use the Internet, they had variable responses to the information they found there. Some women found much valuable information, but some were disappointed with the quality, and others were not able to access the information they wanted. Often women found information on the Internet that they would not normally have received, and they shared this with their doctor. The Internet provided the women with evidence that they could present to their doctors, to which they would not otherwise have had access.

I did a lot of research on the Internet and found out a lot about different treatments for women with PCOS. But the treatments were mainly used in the United States, so I had to convince the gynaecologist that I could give it a go. (Holly)

The Internet had enabled communication via chat groups and email lists for some women. This interaction was similar to that found via support groups, yet it could remain anonymous. The participants found these very helpful.

That's the first thing I did was find out all the information and join a few email groups in Australia. I discovered there was a few PCOS groups, so I joined them... I've participated in some chat groups. (Holly)

Using the Internet did, however, require a degree of skill, and the women who were most proficient were more highly educated. In general, the participants were aware that much of the information on the Internet needed to be critically assessed.

I know how to sift through online material... It's a worry when some people present all sorts of witchcraft, heaps of the stuff and a lot of young naïve people do. (Jemima)

Some women also used the Internet in specific ways; obtaining information from support groups that provided email lists, newsletters and question and answer sessions. Information on the Internet was found to be available at different levels of understanding, and this was appreciated.

I think the thing about the Internet is that you don't have to read huge amounts at one time. You can have a little bit and absorb it and then have a little bit more of it. I don't know how you could do that any other way. So you can sort of go at a level when you're ready to. (Portia)

Preferences for information provision

There are likely to be a number of reasons for the participants' preference for the Internet as an information source. Firstly, frustration at the paucity of information available via traditional mechanisms to women with PCOS, may be one motivating factor for why these women preferred to obtain information via the Internet. Established health and medical information sources may be inadequate for the information that women want about PCOS. Women with PCOS need time to understand the complexities of their chronic condition. The average length of a medical consultation in Australia is 14.8 minutes [28], which may be inadequate for a condition such as PCOS. In addition, women diagnosed some while ago may not want to retell their story and going through tests again every time they change doctors for other opinions, or just to get new information. Many women have also had unpleasant prior experiences, which undermined their confidence in talking to doctors.

Secondly, many of the participants preferred the Internet because it is private and accessible from one's own home, rather than having to make contact with a library or with medical practitioners. Broom (2005) found that men with prostate cancer, had similar experiences, preferring to be anonymous in their pursuit of information. Women with PCOS find it an embarrassing disease and consequently they may seek anonymity when they look for information. They prefer not to discuss their hairiness, obesity and failure to become pregnant with others who would not understand or empathise with their experience. The women realised that they had many choices of information available to them through the Internet, and this did not seem to be daunting.

I like the way I can access the information, that I can do it all of the time, night and day...Because it's accessible, because there's lots of stuff on there, look up more than one thing. Because it's easy for me to use... I can do it privately as well. At least this way I can explore by myself. (Portia)

Finally, women with PCOS used the Internet because it provided them with a sense of control. This included control over the information that they received, the time they received it, the level of the information, and the amount of information. This finding was also reflected in men with prostate cancer by Broom (2005). This continues to upset the power balance between medicine and health consumers, as the women in this study were obtaining

their information outside the usual medical sphere, and on their own terms.

Information about PCOS has grown recently. Women with PCOS want the most up to date information at their fingertips, and the Internet makes this information accessible. Women can become familiar with this area of knowledge, and learn exactly where to look, depending on their information needs.

Because there's a lot on there, there's a lot of different groups and different opinions, and you can compare it. Different studies, its not just one person's opinion. (Michelle)

Women's information needs about PCOS evolve as different parts of their lives are emphasised. Frank (1995) refers to people with illnesses telling stories to work out their changing identities, and women with PCOS need to do this at many different points in their life [29].

I came across some real life stories, which weren't really good because all of them had unsuccessful rates of fertility, so it just upset me... I learnt, I'm not alone, its good to know people around you have it. It's also good to hear that there are some people that aren't doing so well and that there's also good to hear the people who are doing well, because you can sort of rate yourself between that and where you're at. (Cynthia)

Many of the women in this study also had a high level of education, which allowed them to make use of more specialized information resources such as electronic databases, and enabled them to venture into unfamiliar areas such as medicine in their search for information. Much of this information was designed for people with medical training, so was sometimes inappropriate for the average woman with PCOS. However, the women in this group were discerning, and were happy that this information was available to them. The women with the least education in this group made the least use of the Internet, and information resources in general, such as reading material. These women preferred talking with a doctor.

As PCOS is a hidden disease, women with PCOS often have no contact with other sufferers. Other recent studies regarding chronic disease information seekers have illustrated a preference for sources other than the Internet [30], such as social networks. Perhaps this is why women with PCOS seem to make use of Internet for their health information, as well as to network with other sufferers. The Internet provides an initial anonymity, an arena to discuss sensitive issues, and a reciprocal support network, that can be further developed once trust is gained.

Conclusion

Women with PCOS in this study, in addition to routinely using other information sources, preferred using the Internet. The Internet had the advantages that other sources provided, and a number of extra strengths. The Internet opened a world of information to these women, not just that which the doctor provided. It was convenient, private and highly accessible to most, and the information was available at a number of different levels. The women were also aware of the problems with the Internet. They knew that there was some skill involved in searching for and critically assessing information. Often the women would share the information with their doctors, in order to become involved with managing their health. They began to ask the "right" questions, that led to appropriate and efficient answers [31]. The age group of the women in this study reflects the beginning of the Internet literate generation; these women often had training and access to the Internet via their post school education, or at work. However, similar findings have been reported in other health information seeking groups such as older men with prostate cancer, now embracing the Internet also, such that online information provided empowerment, anonymity, but may upset the doctor-patient relationship [24].

There are some limitations to this study. The participants in this study present a group of women with PCOS who were already relatively confident with taking charge of their health care, via being involved in a clinical trial, and/or being involved in a PCOS support group. Other women, not in this environment, or even unaware of the implications of PCOS on their future health, may not be so assured in seeking information. The women in this group also represent a narrow age group, reflecting the age where fertility, rather than the other symptoms of PCOS, may be a major focus. The finding may not be representative of younger women, closer to their primary diagnosis, who may be even more Internet literate. These limitations to the study, particularly the characteristics of the participant group, mean that when discussing information needs, we can only generalise to a similar group of women. Other limitations of this study include the small sample size, and that only one form of data collection was used. The study could be strengthened using triangulation methods, extending to perhaps a questionnaire, and including the women in further discussions of the themes through focus groups. The results of the have also been reported back to participants and members of a PCOS support group.

How then should information be provided to women with PCOS? The medical practitioners may need to be provided with a "sample bag" of information to give to PCOS women at their diagnosis, and follow this information with a review session where the women can ask con-

sidered questions about their syndrome. The "sample bag" would need to have pamphlets for a quick run down of the condition and terminology, lifestyle information, support group contact information and a list of reputable web sites; so that further research can be carried out by the woman as her lifestyle and information needs changes over time.

Women with PCOS need to be consulted and involved with creating the design, and assessment of quality of information about their condition, so that this is relevant to their lifestyle. PCOS provides an ideal opportunity for directed health promotion, particularly in terms of diabetes and cardiovascular illnesses, as well as an opportunity for consumer involvement in decision-making, and development of clinical guidelines. The most important treatment that we know of for PCOS is promoting healthy lifestyle as early as possible. Women with PCOS need information and guidance about how to do this to enable them to take control of their own health.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

The research reported here was carried out while both the authors were based in the Discipline of Public Health, The University of Adelaide. The research was conducted by JCA for her Masters dissertation under the supervision of AJBM. All authors read and approved the final manuscript.

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The Molecular-Genetic Basis of Functional Hyperandrogenism and the Polycystic Ovary Syndrome

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The genetic mechanisms underlying functional hyperandrogenism and the polycystic ovary syndrome (PCOS) remain largely unknown. Given the large number of genetic variants found in association with these disorders, the emerging picture is that of a complex multigenic trait in which environmental influences play an important role in the expression of the hyperandrogenic phenotype.

Among others, genomic variants in genes related to the regulation of androgen biosynthesis and function, insulin resistance, and the metabolic syndrome, and proinflammatory genotypes may be involved in the genetic predisposition to functional hyperandrogenism and PCOS.

The elucidation of the molecular genetic basis of these disorders has been burdened by the heterogeneity in the diagnostic criteria used to define PCOS, the limited sample size of the studies conducted to date, and the lack of precision in the

identification of ethnic and environmental factors that trigger the development of hyperandrogenic disorders. Progress in this area requires adequately sized multicenter collaborative studies after standardization of the diagnostic criteria used to classify hyperandrogenic patients, in whom modifying environmental factors such as ethnicity, diet, and lifestyle are identified with precision.

In addition to classic molecular genetic techniques such as linkage analysis in the form of a whole-genome scan and large case-control studies, promising genomic and proteomic approaches will be paramount to our understanding of the pathogenesis of functional hyperandrogenism and PCOS, allowing a more precise prevention, diagnosis, and treatment of these prevalent disorders. (*Endocrine Reviews* 26: 251–282, 2005)

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I. Introduction

POLYCYSTIC OVARY SYNDROME (PCOS) is one of the most common endocrinopathies in women of childbearing age (1). PCOS is characterized by increased ovarian and adrenal androgen secretion (2); hyperandrogenic symptoms such as hirsutism, acne, and/or alopecia; menstrual irregularity; and, in a significant proportion of patients, insulin resistance (3).

The presence of male sexual secondary characteristics in women has been recognized from ancient times, but it was not until 1921 when Achard and Thyers (4) reported the association of hyperandrogenic symptoms with abnormalities in glucose metabolism, highlighting the presence of polycystic ovaries in some of their patients. However, only after the description of seven cases of amenorrhea and bilateral polycystic ovaries by Stein and Leventhal in 1935 (5) was PCOS considered a separate entity that interested clinicians and researchers worldwide.

Although for many years the interest in PCOS has been

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Abbreviations: AR, Androgen receptor; CRP, C-reactive protein; CYP, cytochrome P450; gp130, gp130 subunit of IL-6 receptor; HSD, hydroxysteroid dehydrogenase; INS, insulin gene; INSR, insulin receptor gene; IRS, insulin receptor substrate; LH β , β -subunit of LH; PAI-1, plasminogen activator inhibitor-1; PCOS, polycystic ovary syndrome; PON1, paraoxonase; PPAR- γ 2, peroxisome proliferator-activated receptor- γ 2; SORBS1, human homolog for the sorbin and SH3-domain-containing 1 gene; SNP, single nucleotide polymorphism; SRD5A, steroid 5 α -reductase; TNFR2, type 2 TNF receptor; VNTR, variable number of tandem repeats.

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focused on the cutaneous and reproductive manifestations of this disorder, the recent evidence suggests that metabolic and cardiovascular risk factors cluster in these patients (6–8). This evidence has renewed research efforts on hyperandrogenism and PCOS, including those directed toward the identification of the genetic and environmental factors involved in the pathogenesis of these prevalent conditions.

At present, there is no consensus on the criteria for the diagnosis of PCOS (Table 1). Most clinicians and researchers from the United States and from southern Europe use the criteria derived from the conference held at the National Institute of Child Health and Human Development (NICHD) in 1990: clinical and/or biochemical hyperandrogenism, menstrual dysfunction, and exclusion of specific etiologies (9). According to these criteria, the presence of polycystic ovaries on ultrasound examination is not needed for the diagnosis. On the contrary, most specialists from the other European countries, Asia, and Oceania rely mostly on the presence of polycystic ovaries on ultrasound examination for this diagnosis, whereas menstrual dysfunction is not required (10). A recent consensus workshop held in The Netherlands in 2003 under the auspices of the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine proposed a revision of the criteria for the diagnosis of PCOS, of which two of the following three would be needed: 1) oligo- and/or anovulation; 2) clinical and/or biochemical signs of hyperandrogenism; and 3) polycystic ovaries, together with the exclusion of other etiologies such as congenital adrenal hyperplasia, androgen-secreting tumors, or Cushing's syndrome (11, 12).

However, the term PCOS as used in the literature is not specific and has been applied to a wide range of hyperandrogenic women, including women with or without menstrual dysfunction or polycystic ovaries. For that reason, in the present review, we will use the more general term functional hyperandrogenism to define these patients presenting with androgen excess, including those diagnosed with PCOS according to any of the current definitions of the syndrome, in whom a specific etiology such as congenital adrenal hyperplasia or androgen-secreting tumors cannot be identified, and, whenever possible, we will describe the particular characteristics of the patients included in the different studies. Of note, we will not include idiopathic hirsutism in this definition, because this infrequent disorder, in which hyperandrogenemia, menstrual dysfunction, and ultrasonographic polycystic ovaries are not present, appears to be a separate entity in which increased skin activity of 5 α -reductase (resulting in increased conversion of testosterone into the more

potent androgen dihydrotestosterone), androgen receptor (AR) polymorphisms, and altered local androgen metabolism contribute to the development of hirsutism (13).

Functional hyperandrogenism and PCOS cluster in first-degree relatives of patients (14) and are inherited together with insulin resistance and metabolic disorders (15, 16). During the past decades, the inheritance of these disorders has been the subject of intense research (17–19), but many questions remain unanswered.

The pattern of inheritance is still unknown. Initially, an autosomal dominant model, including premature balding as the male phenotype, was proposed (20, 21), but later studies did not confirm this hypothesis. The heterogeneity of the populations, the large number of candidate genes studied to date (22), and the difficulty inherent to identifying the molecular genetic mechanism leading to a complex metabolic disorder such as PCOS, in which environmental factors play a major role (23, 24), provide an explanation for the fact that the molecular genetic basis of functional hyperandrogenism and PCOS remains largely unknown despite significant efforts.

The purpose of this review is to provide a systematic evaluation of the studies conducted to date in functional hyperandrogenism and PCOS and to suggest priorities and new strategies that may contribute to understanding the pathogenesis of these disorders.

II. Evidence Suggesting a Genetic Origin for Functional Hyperandrogenism and PCOS

A. Familial aggregation (Table 2)

The familial aggregation of PCOS, hyperandrogenemia, and associated metabolic abnormalities suggests a genetic origin for functional hyperandrogenism and PCOS. Back in 1968, Cooper *et al.* (25) studied the families of 18 Caucasian women with polycystic ovaries and clinical and biochemical traits associated with PCOS, and the families of 18 paired control women. The incidence of oligomenorrhea and polycystic ovaries was increased in first-degree relatives of PCOS patients compared with controls, and males in these families had increased hairiness according to a questionnaire, suggesting an autosomal dominant pattern of inheritance (25). Givens and colleagues (26–28) published a series of family-based studies in patients presenting with hirsutism, oligomenorrhea, and increased ovarian size, and they found familial aggregation of hyperandrogenic symptoms (hirsutism and oligomenorrhea) and of metabolic disorders (diabetes mellitus, dyslipidemia, arterial hypertension, and athero-

TABLE 1. Diagnostic criteria for the diagnosis of PCOS

NICHD criteria (9)	Ultrasonographic criteria (10)	Rotterdam criteria (11, 12)
1) Oligoovulation	1) Ultrasonographic polycystic ovaries	1) Oligo- and/or anovulation
2) Clinical and/or biochemical hyperandrogenism	2) Clinical and/or biochemical hyperandrogenism	2) Clinical and/or biochemical hyperandrogenism
Exclusion of secondary etiologies such as congenital adrenal hyperplasia, androgen-secreting tumors, and hyperprolactinemia.		
Criteria 1 and 2 must be present for the diagnosis of PCOS according to NICHD and ultrasonographic criteria. The Rotterdam criteria require the presence of two of the three individual criteria. All definitions require exclusion of secondary etiologies.		

TABLE 2. Studies of familial aggregation in functional hyperandrogenism and PCOS

Authors ^a	Phenotype in first-degree relatives	Suggested inheritance
Cooper et al. (25)	Women: oligomenorrhea and PCO	Autosomal dominant with variable penetrance
Wilroy et al. (26), Givens (27, 28)	Men: increased hairiness Women: hyperandrogenism and metabolic disorders	X-linked
Ferriman and Purdie (29)	Men: oligospermia and LH hypersecretion	Not determined
Hague et al. (30)	Women: infertility, oligomenorrhea, hirsutism	Not determined
Lunde et al. (31)	Women: PCO	Autosomal dominant
Carey et al. (20)	Women: hyperandrogenic symptoms	Monogenic
Jahanfar et al. (40, 41)	Men: premature baldness and increased hairiness	Polygenic
Norman et al. (36)	Women: PCO	Not determined
Legro et al. (33, 34, 39)	Men: premature baldness Twin studies: fasting insulin, androstenediol glucuronide, lipid profile Men: premature baldness, hypertriglyceridemia, and hyperinsulinemia Women: PCOS (NICHD), hyperandrogenemia, insulin resistance	Monogenic
Azziz et al. (14), Kahsar-Miller et al. (32)	Men: increased DHEA-S Women: PCOS (NICHD)	Not determined
Mao et al. (37)	Men: premature baldness	Not determined
Yildiz et al. (35)	Women: PCOS (NICHD) and insulin resistance Men: insulin resistance	Not determined

^a Authors are cited in chronological order. PCO, Polycystic ovaries on ultrasound examination; DHEA-S, dehydroepiandrosterone sulfate.

sclerosis). These authors suggested both a maternal and paternal pattern of inheritance, in which the latter showed higher penetrance and expression (26–28). Of note, in some of these male subjects, oligospermia and increased LH secretion were found pointing to an X-linked pattern of inheritance.

Ferriman and Purdie (29) studied first-degree relatives of hirsute women presenting with or without enlarged ovaries in gynecography. Compared with a control group, patients had an increased prevalence of oligomenorrhea and infertility, and the prevalence of hirsutism was increased in their female first-degree relatives. Hague et al. (30) studied the families of 61 patients with ultrasonographic polycystic ovaries and hyperandrogenic symptoms and found that 67% of the mothers and 87% of the sisters of probands were affected. Lunde et al. (31) studied the families of 132 Norwegian women with polycystic ovaries previously treated by ovarian wedge resection, who also had two or more of the following symptoms: menstrual irregularity, hirsutism, infertility, and/or obesity. A control group of 71 women and their families was used for comparison (31). Clinical manifestations of hyperandrogenism were found in 31.4% of the female relatives of the patients compared with only 3.2% of the female relatives of the controls (31). Among male relatives, premature balding and increased hairiness were found in 19.7% of the relatives of the patients, but only in 6.5% of the relatives of the controls (31). Azziz and colleagues (14, 32), using NICHD criteria for the diagnosis of PCOS, found that PCOS was present in 35% of the mothers and 40% of the sisters of PCOS patients.

In addition to hyperandrogenism, insulin resistance clusters in the families of hyperandrogenic women. Legro et al. (33), also using also NICHD criteria for the definition of PCOS, found that 22% of the sisters of patients actually had PCOS, whereas a further 24% of the sisters of these patients presented with hyperandrogenemia and regular menstrual cycles. This bimodal pattern suggested a monogenic defect

for hyperandrogenism (33). Additional studies from Legro et al. (34) recently demonstrated that in these families, insulin resistance is associated with hyperandrogenemia rather than with menstrual dysfunction. This suggests that insulin resistance and hyperandrogenemia share the same pathogenic mechanisms, whereas the presence of menstrual dysfunction needed for the diagnosis of PCOS may be only a matter of degree. Therefore, of PCOS sisters, those with PCOS and those presenting with hyperandrogenemia and regular menstrual cycles may actually have functional hyperandrogenism.

The finding of an increased prevalence of insulin resistance in families of PCOS patients has been replicated in the Turkish population. Yildiz et al. (35) recently studied 102 relatives of 52 PCOS patients defined by NICHD criteria and found that, compared with different population-based control groups matched for sex, age, and pre- or postmenopausal status with the relatives of PCOS patients, insulin resistance and disorders of carbohydrate metabolism were more frequent in the mothers, sisters, and brothers of PCOS patients, and that the mothers and sisters of PCOS women had increased serum androgen levels compared with the controls.

B. Male phenotype

The lack of a clearly defined male phenotype in families of PCOS patients has burdened the progress in the search for the genetic origin of functional hyperandrogenism and PCOS. Although initial studies suggested that male pattern premature balding was the male equivalent for PCOS (20, 29, 31, 36, 37), these findings have not been universally confirmed (38). More recently, increased serum dehydroepiandrosterone sulfate concentrations in the brothers of PCOS patients described above (39) and insulin resistance in the fathers and brothers of PCOS women (35) have been proposed as the male phenotype in PCOS families. However, there was a considerable overlap between male PCOS relatives and controls in serum dehydroepiandrosterone sulfate

levels and indexes of insulin resistance, and additional studies are needed to establish the actual usefulness of these abnormalities as markers of the syndrome in male relatives of PCOS patients.

C. Twin studies

There are very few data regarding PCOS in twins. Jahanfar *et al.* (40) studied 34 (19 monozygotic and 15 dizygotic) twin pairs, in which PCOS diagnosis was based on ultrasonographic and biochemical findings. Although 11 pairs were discordant for the presence of polycystic ovaries, model-fitting analysis suggested that fasting insulin level, serum androstenediol glucuronide, and body mass index were significantly influenced by genetic factors (40). A later report of this study suggested a genetic origin for an unfavorable lipid profile, especially for increased circulating concentrations of

lipoprotein (a), but only in twin pairs concordant for polycystic ovaries (41). These data point to a genetic component in the metabolic abnormalities associated with PCOS but suggest a polygenic etiology in which environmental influences play a significant role.

D. Environmental and other confounding factors

Familial aggregation of hyperandrogenism and PCOS strongly suggest a genetic origin for these disorders, but another possibility is that clustering of PCOS within families results from nongenetic inheritance related to certain environmental factors that are present in the affected families, and not in the families of unaffected women.

As exemplified in Fig. 1, insults during pregnancy may induce intrauterine growth retardation, which has been proposed to induce a thrifty phenotype in small for gestational

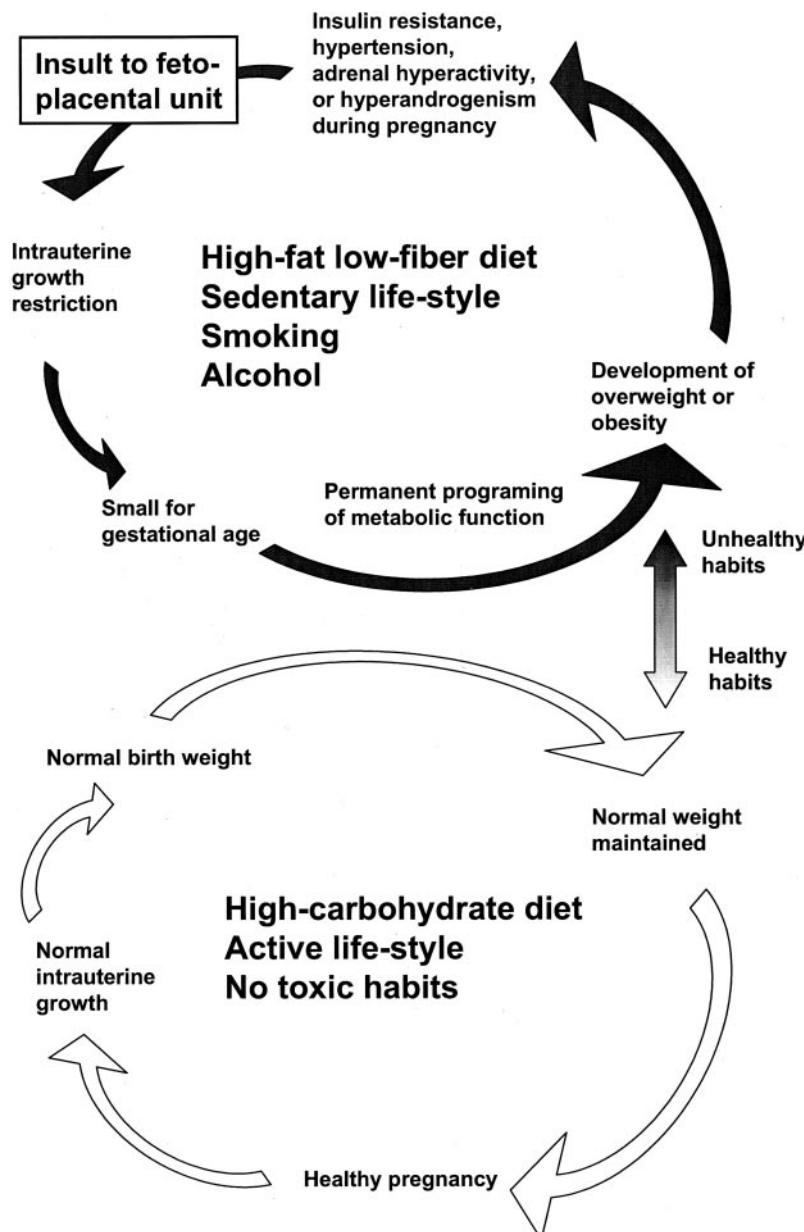


FIG. 1. Intrauterine growth retardation and insulin resistance as an example of nongenetic inheritance, markedly influenced by environmental factors. Insults during pregnancy may result in intrauterine growth retardation, inducing a thrifty phenotype in small for gestational age babies. These women are predisposed to suffer from insulin resistance and may develop hypertension, glucose intolerance, adrenal axis hyperactivity with relative cortisol excess, functional hyperandrogenism, and PCOS later in life, especially when these individuals are exposed to environmental factors such as sedentary lifestyle and a diet rich in saturated fat. These environmental factors may also cluster in certain families because exercising and diet are heavily influenced by parental habits. The metabolic abnormalities associated with the thrifty phenotype can induce further insult to the pregnancies of small for gestational age women, and the defect might be transmitted to another generation without the participation of any genetic abnormality. However, if small for gestational age babies maintain healthy habits, insulin resistance and its consequences might be avoided and, at least in theory, their fetuses will not be exposed to an unfavorable metabolic milieu during pregnancy, preventing nongenetic inheritance of these conditions.

age babies. These babies are predisposed to suffer from insulin resistance, which may result in hypertension, glucose intolerance, adrenal axis hyperactivity with relative cortisol excess, functional hyperandrogenism, and PCOS (42) later in life, especially when these individuals are exposed to environmental factors such as a sedentary lifestyle and a diet rich in saturated fat. These environmental factors may cluster in certain families because exercising and dieting are heavily influenced by parental habits.

The metabolic abnormalities associated with the thrifty phenotype can induce additional insult to the pregnancies of small for gestational age women, and the defect might be transmitted to another generation without the participation of any genetic abnormality. Therefore, the presence of more than one small for gestational age baby in a family may result from exposure of the mothers and their fetuses to the same unfavorable environmental conditions, rather than being related to genetic factors.

Yet it is important to highlight, as shown in Fig. 1, that if small for gestational age babies have healthy habits, insulin resistance and its consequences might be ameliorated, and, at least in theory, their fetuses will not be exposed to an unfavorable metabolic milieu during pregnancy, preventing nongenetic inheritance of these conditions. Nevertheless, intrauterine growth retardation may also be influenced by genetic variants, and the most probable scenario is that of an interaction between predisposing genetic abnormalities with unfavorable environmental conditions. Of note, even the influence of intrauterine growth restriction on the development of PCOS is debatable (43–45), considering that the presence of polycystic ovaries also has been related to above-average birth weight in babies born from obese, androgenized mothers (43–45).

There are very few data on the influence of environmental factors on the development of hyperandrogenism and PCOS, other than the triggering role for obesity on the development of these disorders (46). Although the prevalence of PCOS is similar in different countries, ethnic factors influence the clinical manifestations of the syndrome. In Caucasian premenopausal women, the reported prevalences of PCOS defined by NICHD criteria ranged from 4.7% in Alabama (47) to 6.5% in Spain (48) and 6.8% in the Greek island of Lesbos (49). Moreover, the prevalence in African-American women from Alabama (3.4%) was comparable with that in Caucasian women (47).

However, ethnicity influences the manifestations of PCOS. Carmina *et al.* (50) compared the clinical histories, physical examinations, ovarian morphology by ultrasound, insulin sensitivity, serum gonadotropin, and steroid profiles in 25 Japanese, 25 Italian, and 25 Hispanic-American women with PCOS. The three groups were homogeneous in terms of serum testosterone and adrenal androgen concentrations, insulin resistance, and polycystic ovaries, but Japanese women were less obese and did not present with hirsutism (50).

Dunaif *et al.* (51) found that insulin resistance is higher in Hispanic-Caribbean women with PCOS defined by NICHD criteria compared with Caucasian patients and with control women paired for age, weight, body composition, and ethnicity. Williamson *et al.* (52) recently reported a higher in-

cidence of obesity, dyslipidemia, and infertility, as well as a higher degree of insulin resistance in Maori and Pacific Islander PCOS patients, defined by ultrasonography and clinical symptoms, compared with European patients. In the United Kingdom, the prevalence of polycystic ovaries and type 2 diabetes is increased in Indian subcontinent Asian women (53). Compared with Caucasian women, PCOS patients of southeastern Asian origin presented with oligomenorrhea and were diagnosed at younger ages; hirsutism, acne, acanthosis nigricans, and subfertility were more prevalent, and patients were more insulin resistant (54).

These ethnic differences in the clinical presentation of PCOS may be related to environmental factors such as diet, exercise, and lifestyle. Of note, even the content of polyunsaturated or monounsaturated fatty acids in the diet may influence the metabolic manifestations of the syndrome (55). Thus, because of differences in the environmental factors triggering the development of PCOS, the genes contributing to PCOS patients may also be different, depending on the population studied. These considerations may also apply to the discrepant results of previous studies regarding the association of genomic variants with PCOS.

III. Classic Techniques Used in Molecular Genetic Studies

Before reviewing the molecular genetic studies conducted to date in functional hyperandrogenism and PCOS, we will provide a brief description of the techniques usually used for molecular genetic studies, focusing on the particular advantages and disadvantages of each technique.

A. Linkage analysis

Linkage analysis is a family-based molecular genetic technique that has permitted the identification of the genetic abnormalities leading to many monogenic Mendelian disorders (56). However, most complex metabolic disorders result from the interaction between multiple genes and environmental factors, making their identification much more difficult than in disorders with a Mendelian pattern of inheritance (57–63).

In linkage analysis, markers frequently located at intergenic regions of DNA are studied in multiple members of affected families. The cosegregation of alleles with a disease phenotype is studied, and the linkage of the disease with any marker focuses the search for genomic abnormalities to the DNA regions close to the polymorphic marker segregating with the disorder.

Linkage analysis is based on the meiotic recombination that occurs during ovogenesis and spermatogenesis. The closer two genomic markers are, the more seldom these markers are separated during meiotic recombination. The probability of recombination between two markers is an estimation of the distance between them, and is expressed in centimorgans (cM). Two markers are defined to be 1 cM apart if they become separated by recombination in 1% of meioses. One centimorgan is equivalent on average to 10^6 bp of physical distance. The markers usually studied in linkage studies

include microsatellites and single nucleotide polymorphisms (SNPs).

Classical or parametric linkage analysis requires the specification of a model for the disease or trait *a priori*, in terms of allelic frequencies, penetrance, and pattern of inheritance, and the result is expressed by the LOD score (64). The LOD score is the base 10 logarithm of the odds that two markers (one being the disease-causing or disease-associated genomic variant) are truly linked, divided by the odds that the observed set of data may result from chance if the markers are unlinked. Usually, significant positive proof of genetic linkage requires a LOD score of 3.0 or greater, corresponding to odds favoring linkage of at least 1000:1 at a given specified recombination frequency. Because the pattern of inheritance of functional hyperandrogenism and PCOS is complex and uncertain, nonparametric or model-free linkage analysis is required to ensure the power to detect linkage (22). In nonparametric linkage analysis, multiple DNA markers are obtained from siblings and, if possible, from their parents, and allele sharing between relatives is investigated (64). Allele sharing is defined as identity-by-state (having the same DNA sequence) or as identity-by-descent (when two alleles come from the same ancestral allele) (64). Nonparametric linkage scores use a similarity statistic defined by the average of the possibilities that relatives are identity-by-state (64). However, the number of meioses assessed, disease penetrance, knowledge of the marker coupling phase, and other relevant variables must be considered before reaching a clinically significant conclusion (65).

There are several factors that may limit the usefulness of linkage studies including, among others, the uncertainty about the pattern of inheritance, a variable penetrance of the genetic defect, the delay in the debut of the disease, possible errors in clinical diagnosis, gene to gene interactions, interaction with environmental factors, and the limited resolution of these techniques. The sample size needed to detect a particular effect varies inversely with the square of the effect (62), and therefore genes that contribute modestly to the phenotype may be missed because of the extremely large sample size needed to demonstrate the association. This is especially important given that PCOS affects women in reproductive age and is associated with reduced fertility, limiting the pedigrees and the generations studied to two (mothers and daughters) in most of the linkage analyses performed to date, resulting in small sample sizes within families (66, 67).

The resolution of linkage analysis may be improved using tests such as affected sibling-pair identity by descent analysis or the transmission disequilibrium test (68), allowing the detection of genes of modest effects that might be otherwise missed by linkage analysis. The transmission disequilibrium test involves genotyping the parents of the proband and the proband, and it determines whether or not the parent heterozygous for the putative allele transmits it more often to their affected children than other allele(s). These tests are frequently used to confirm the linkage already established but may also be useful when used without previous evidence for linkage (69).

Linkage with a polymorphic marker only serves to focus the search of the genomic abnormality associated with the

disorder to an area of approximately 1–2 cM, and locating the precise genetic defect may involve studying as many as 30–100 genes in the linked area. After obtaining linkage with a genomic region, the search of the particular genomic abnormality involved can be accomplished by fine-mapping of that region using additional markers, and by a candidate gene approach searching for variants in biologically appealing genes located there. This approach has been facilitated by the growing number of genes identified all across the genome, but frequently the demonstration that a gene has a causative role in a disease requires direct sequencing of the whole gene in affected and nonaffected individuals (70).

B. Case-control studies

These studies look for specific genetic markers or alleles that are more frequent in affected individuals (cases) compared with unaffected subjects from the same population (controls). These studies are focused on association of a genetic variant with a disease in a population and not on the mode of inheritance of a trait (71, 72). Association studies are preferable for finding "susceptibility" loci, low-risk alleles that are often found in relatively high frequencies in the general population, and do not result in robust signals in family-based studies (73). A positive association indicates an increased risk for the disease in subjects carrying the at-risk allele, which may have a causative role in the disorder or be in linkage disequilibrium with the gene actually causing the disease. Population stratification is a major problem in case-control studies, because the higher prevalence of particular alleles in different ethnic groups might bias the results and lead to false-positive associations. Moreover, case-control studies are especially prone to type II errors, that is, ruling out an association that is actually present in the population because of the small sample sizes often used in these studies.

In summary, linkage studies and case-control studies are both valid approaches for the study of the genetics of functional hyperandrogenism and PCOS, provided that the sample sizes of these studies are sufficiently large, the diagnostic criteria used to define affected and nonaffected subjects are clearly defined, and both ethnicity and differences in environmental factors are carefully considered.

IV. Studies in Pediatric and Adolescent Hyperandrogenism

Functional hyperandrogenism and hyperinsulinism may be detected early in life in affected women, even before pubertal development. As stated above, the presence of low birth weight in small for gestational age newborns, resulting from an unfavorable environment during intrauterine life and/or to defective maternal nutrition, has been related to the development of insulin resistance (74), disorders of glucose tolerance (75), hypertension, and cardiovascular disease (76–79) later in life.

The association of low birth weight with the development of hyperinsulinism and type 2 diabetes mellitus has been confirmed in different populations (80, 81), and these children present with an accelerated growth and increased body mass index during adolescence.

Although environmental factors may be an important contributor to the restriction of fetal growth in small for gestational age newborns, genetic factors may also be involved in this association (82). According to this hypothesis, affected fetuses might suffer insulin resistance because of the influence of several unknown genes or genomic variants. Insulin resistance would lead to restriction of intrauterine growth and abnormal fetal vascular development, ultimately leading during adult life to increased vascular resistance and endothelial dysfunction. The compensatory increase in circulating insulin concentrations would contribute to the abdominal deposition of fat, and inflammatory cytokines and other mediators secreted by abdominal adipocytes would perpetuate insulin resistance and endothelial dysfunction, leading to abnormal glucose tolerance, atherosclerosis, and cardiovascular disease (82).

However, the analysis of the influence of genomic variants on the association of birth weight and insulin resistance has yielded conflicting results. Dunger *et al.* (83) analyzed a variable number of tandem repeats (VNTR) polymorphism in the insulin gene (*INS*) at 11p15.5. This VNTR polymorphism consists of a repeated sequence of 14 to 15 bp (ACAGGGGT-GTGGGG), and is located at -596 bp of the start of transcription site (84). Among Caucasians, these alleles have been typed as class I (small, with 28–44 repeats, frequency approximately 70%), class II (intermediate, rare), and class III (large, with 138–159 repeats, frequency approximately 30%). The VNTR polymorphism in the *INS* promoter regulates the transcriptional rate of the gene (85) and probably that of the gene encoding IGF-II (84–89). Newborns homozygous for class III alleles, which are those associated with increased transcription of the *INS*, presented with increased head circumference, length, and weight at birth as compared with babies homozygous for class I alleles, possibly favoring newborn survival. On the contrary, data from the same researchers suggested that the maternally inherited 16,189 mitochondrial DNA variant, which increases the risk for type 2 diabetes mellitus, was associated with restrained fetal growth, thereby favoring maternal survival by decreasing birth-related morbidity and mortality (90). Therefore, other genetic and environmental factors are possibly involved in the relationship between birth weight and the development of insulin resistance and type 2 diabetes mellitus in adulthood.

Given the association of insulin resistance with functional hyperandrogenism, Ibáñez *et al.* (91) have proposed that low birth weight is related to the development of premature pubarche, and of functional hyperandrogenism during adolescence, insulin resistance being the underlying disorder common to both conditions. Retrospective analysis of a cohort of patients presenting with premature pubarche showed, especially in those girls who developed hyperinsulinemia and functional ovarian hyperandrogenism at adolescence, a lower birth weight compared with a control group, suggesting that low birth weight, premature pubarche, and functional hyperandrogenism are different manifestations of a unique disorder originating during prenatal life (92–95), but becoming clinically apparent peripubertally (42).

Additional analysis of this cohort showed that adolescent

girls who had anovulation and higher androgen levels were those with lower birth weight (96) and also confirmed the association of adrenal androgen excess, low birth weight, premature pubarche, and hyperinsulinemia (97).

In conceptual agreement, an exaggerated adrenal response to adrenocorticotropin stimulation, similar to that described in women with functional hyperandrogenism and PCOS, has been found in girls with premature pubarche, suggesting that this disorder can be considered an early manifestation of the syndrome (98). However, the relationship of low birth weight with hyperandrogenism and PCOS has not been universally confirmed. Jaquet *et al.* (99) compared a large population of young women born with intrauterine growth retardation with age-matched healthy controls, and although low birth weight was associated with insulin resistance, androgen levels were similar in both groups of women. Moreover, birth weight had no influence on the presence of hyperandrogenic symptoms suggestive of PCOS in a large cohort of Finnish women recently reported (100).

Given the association of functional hyperandrogenism and insulin resistance in children and adolescents, several genomic variants related to insulin resistance and the metabolic syndrome have been studied in these patients, mostly by the group of Ibáñez in Spain and the group of Witchel in Pittsburgh.

The VNTR locus at the *INS* has been studied in girls with a history of premature pubarche (101). Although class I and class III alleles were equally distributed in patients and controls, patients carrying class I alleles presented with lower birth weight and lower insulin sensitivity compared with patients homozygous for class III alleles (101).

The common Gly⁹⁷²Arg variant in the gene encoding the insulin receptor substrate 1 (*IRS-1*), which has been shown to influence insulin resistance and glucose tolerance in adult PCOS patients (102, 103), has also been studied in adolescents (104). The frequencies of heterozygosity for the Gly972 allele were 31% among girls with a history of premature pubarche, 40% among girls with hyperinsulinemic ovarian hyperandrogenism, and only 19% among healthy control subjects. Carriers of Gly972 alleles presented with decreased sex hormone-binding levels (104).

The human homolog for the sorbin and SH3-domain-containing-1 gene (*SORBS1*), which encodes for an important signaling molecule in insulin-stimulated glucose uptake in the mouse, might play a role in human disorders with insulin resistance. The Ala228 allele of the Thr²²⁸Ala polymorphism of *SORBS1* is a protective factor for both obesity and diabetes (105). However, alleles of the Thr²²⁸Ala polymorphism of *SORBS1* were equally distributed in a multiethnic group of healthy adolescents compared with those presenting with premature pubarche and/or functional hyperandrogenism (106).

The Arg64 allele of the Trp⁶⁴Arg polymorphism in the β_3 -adrenergic receptor gene is associated with abdominal obesity and resistance to insulin and may contribute to the early onset of type 2 diabetes mellitus (107). However, Witchel *et al.* (108) found no differences in the distribution of Trp⁶⁴Arg alleles in the girls presenting with premature pubarche and/or functional hyperandrogenism described above compared with healthy adults, and neither was an

TABLE 3. Candidate genes involved in androgen biosynthesis, transport, action, and their regulation, in functional hyperandrogenism (FH) and PCOS

Gene	Variant/locus	Design	Subjects	Phenotypic trait	Association
CYP17					
Carey et al. (125)	-34T/C	FBS/case-control	PCOS/MPB	PCOS	Yes
Gharani et al. (129)	-34T/C	Case-control	PCOS	PCOS/increased T levels	No
Techatraisak et al. (131)	-34T/C	Case-control	PCOS	PCOS/increased T levels	No
Liovic et al. (133)	-34T/C	Case-control	PCOS	PCOS	No
Urbaneck et al. (132)	D10S192	FBS (TDT)	PCOS	PCOS	No
Diamanti-Kandarakis et al. (128)	-34T/C	Case-control	PCOS	Increased T levels	Yes
Marszalek et al. (130)	-34T/C	Case-control	PCOS	PCOS and hormone profile	No
SF1, DAX-1, StAR protein					
Urbaneck et al. (132)	D8S1821 (StAR)	FBS (TDT)	PCOS	PCOS	No
Calvo et al. (144)	Mutation scanning (SF-1, DAX-1, StAR protein)	Case-control	Hirsutism	Hyperandrogenism	No
CYP11B2					
Zhao et al. (207)	-344T/C	Case-control	PCOS	PCOS	Yes
CYP21					
Hague et al. (148)	HLA: ↑ DRW6 and ↓ DR7	Case-control	PCOS/CAH	PCOS	Yes
Witchel et al. (112, 113)	Heterozygosity for CYP21 mutations	Case-control	PP/FH	Hyperandrogenic symptoms in children and adolescents	Yes
Escobar-Morreale et al. (147)	Heterozygosity for CYP21 mutations	Case-control	FH	Origin of androgen excess	No
HSD3B2					
Chang et al. (155)	Mutation scanning	Case series	PP/hirsutism	↑ 17-Hydroxypregnenolone	No
Nayak et al. (111)	Case-control	Case-control	PP, FH (adolescents)	PP, FH	No
Urbaneck et al. (132)	D1S514	FBS (TDT)	PCOS	PCOS	No
HSD17B					
Moghribi et al. (159)	HSD17B3 G289A	Case-control	PCOS	PCOS	No
Urbaneck et al. (132)	HSD17B1, HSD17B2, HSD17B3 (D9S1809)	FBS (TDT)	PCOS	PCOS	No
CYP19					
Gharani et al. (140)	CYP19(tttta)n/D15S103	FBS/case-control	PCOS	PCOS	No
Urbaneck et al. (132)	CYP19	FBS (TDT)	PCOS	PCOS	No
LHβ					
Rajkhowa et al. (169)	Trp ⁸ Arg and Ile ¹⁵ Thr	Case-control	PCOS	Increased in obese PCOS	Yes
Liao et al. (174)	G1502A	Case-control	PCOS	PCOS	No
Tapanainen et al. (170)	Trp ⁸ Arg and Ile ¹⁵ Thr	Case-control	PCOS	Reduced in obese PCOS	Yes
Ramanujam et al. (172)	Trp ⁸ Arg and Ile ¹⁵ Thr	Case-control	Menstrual disorders	Menstrual disorders	Yes
Elter et al. (173)	Trp ⁸ Arg and Ile ¹⁵ Thr	Case-control	PCOS	PCOS	No
Takahashi et al. (175)	-894C/T, -1018G/C, -1036C/A, -1098C/T and -1423C/T	Case-control	Ovulatory disorders	Ovulatory disorders	Yes
FSHβ					
Tong et al. (176)	TAT/TAC in codon 76	Case-control	PCOS	Obesity and PCOS	Yes
FSH receptor					
Urbaneck et al. (132)	D2S1352	FBS (TDT)	PCOS	PCOS	No
Tong et al. (177)	Thr ³⁰⁷ Ala/Ser ⁶⁸⁰ Asn	Case-control	PCOS	PCOS	No
Takakura et al. (178)	Exons 6, 7, 9, and 10	Case-control	PCOS	PCOS	No
GnRH receptor					
Cohen et al. (179)	Mutation scanning	Case series	PCOS	PCOS	No
Dopamine receptor					
Legro et al. (181)	MscI polymorphism	Case-control	PCOS	PCOS	Yes
Kahsar-Miller et al. (182)	MscI polymorphism	Case-control	PCOS	PCOS	No
SHBG					
Urbaneck et al. (132)	D17S1353	FBS (TDT)	PCOS	PCOS	No
Hogeveen et al. (184)	P156L	Case-series	PCOS, hirsutism, and ovarian failure	PCOS, hirsutism, and ovarian failure	Yes
Xita et al. (185)	(TAAAAA)n	Case-control	PCOS	PCOS and SHBG levels	Yes
Cousin et al. (186)	(TAAAAA)n	Case series	Hirsutism	SHBG levels	Yes
	Asp ³²⁷ Asn	Case series	Hirsutism	SHBG levels	Yes
Glucocorticoid receptor					
Witchel and Smith (188)	Mutation scanning, N363S	Case-control	PP, FH (adolescents)	PP, FH	No
Kahsar-Miller et al. (189)	N363S	Case-control	PCOS	PCOS/adrenal androgens	No
Calvo et al. (187)	Mutation scanning	Case series	Adrenal FH	Adrenal androgen excess	No

TABLE 3. *Continued*

Gene	Variant/locus	Design	Subjects	Phenotypic trait	Association
AR					
Legro et al. (198)	(CAG)n	Case-control	Hyperandrogenism	Hirsutism	Yes
Sawaya and Shalita (200)	(CAG)n	Case-control	Hirsutism, acne	Clinical hyperandrogenism	Yes
Vottero et al. (202)	X-inactivation	Case-control	Hirsutism	Idiopathic hirsutism	Yes
Urbanek et al. (132)	AR	FBS (TDT)	PCOS	PCOS	No
Mifsud et al. (201)	(CAG)n	Case-control	PCOS	PCOS and normal T levels	Yes
Calvo et al. (204)	(CAG)n/X-inactivation	Case-control	Hirsutism	Idiopathic hirsutism	No
Hickey et al. (203)	(CAG)n/X-inactivation	Case-control	PCOS	PCOS and T levels	Yes
Ibáñez et al. (116)	(CAG)n	Case-control	PP	PP and ovarian hyperandrogenism	Yes
UDP-glucuronyltransferase 2B15					
Tomboc and Witchel (117)	D85Y	Case-control	PP, FH (adolescents)	PP, FH	No

Authors are cited in chronological order. CAH, Congenital adrenal hyperplasia; FBS, family-based study; MPB, male premature baldness; PP, premature pubarche; T, total testosterone; TDT, transmission disequilibrium test; X-inactivation, skewed X chromosome inactivation.

influence of this polymorphism on the body mass index of these girls. Similarly, the study of the common Pro¹²Ala polymorphism in the gene encoding the peroxisome proliferator-activated receptor- γ 2 (*PPAR*- γ 2), which influences insulin sensitivity in Caucasians (109), has been studied in children with premature pubarche and in adolescent hyperandrogenic girls, but no association was found with any of the *PPAR*- γ 2 alleles and hyperandrogenism (110).

In addition to genes related to insulin resistance, those encoding for the steroidogenic enzymes involved in androgen biosynthesis and the genes encoding several molecules involved in androgen metabolism and action have been considered candidate genes to explain premature pubarche and adolescent hyperandrogenism.

Witchel and colleagues from Pittsburgh conducted a series of studies focused on the steroidogenic enzymes involved in androgen synthesis, which are shared by the adrenal and the ovaries. These authors have found that children with premature pubarche and adolescent girls with hyperandrogenism were heterozygous for mutations in *CYP21*, the gene encoding for 21-hydroxylase, and in the gene encoding 3 β -hydroxysteroid-dehydrogenase (*HSD3B2*), more frequently than nonhyperandrogenic controls (111–113). In these patients, *CYP17* mutations were ruled out as the cause of androgen excess (114). However, because congenital adrenal hyperplasia is an autosomal recessive disease requiring mutations in both alleles—in homozygosity or double heterozygosity—of *CYP21* or of *HSD3B2*, it is unclear how carrying only one defective allele of these genes in these clinically symptomatic heterozygotes contributes to the hyperandrogenic phenotype (113). Moreover, defective *CYP21* and *HSD3B2* alleles were found only in a minority of these patients, and the authors concluded that other genomic variants were also involved in the pathogenesis of these disorders (111–113).

To further explore this possibility, Witchel et al. (115) evaluated the prevalence of the common variants and mutations in *CYP21*, *HSD3B2*, *IRS-1*, β_3 -adrenergic receptor gene described above, and the glucocorticoid receptor gene within their series of children with premature pubarche and adolescent hyperandrogenism. They found that the prevalence of these variants and mutations was clearly increased when

compared with 15 healthy controls, suggesting that the occurrence of multiple sequence variants in these genes might contribute to the development of hyperandrogenism.

Finally, the AR and uridine diphosphate-glucuronyltransferase 2B15, an enzyme involved in androgen inactivation, have been considered candidate genes for premature pubarche and adolescent hyperandrogenism. The study of the AR gene CAG repeat polymorphism suggested that shorter AR gene CAG numbers, indicative of increased androgen sensitivity, were associated with premature pubarche (116), whereas the allele frequencies of the D85Y polymorphism in uridine diphosphate-glucuronyltransferase 2B15 gene were similar in patients and in controls (117).

In summary, studies conducted to date in girls with premature pubarche and adolescent hyperandrogenism suggest a polygenic etiology for these disorders, which can be considered predictors of functional hyperandrogenism and PCOS later in life.

V. Studies in Hyperandrogenic Adults

Most if not all the studies conducted to date to elucidate the genetics of functional hyperandrogenism and PCOS have used a candidate gene approach, because no genome-wide scan has been conducted comparable with those done for other complex metabolic disorders, such as type 2 diabetes mellitus. Although many genes have been considered candidates to explain PCOS inheritance, most studies have included genes related to androgen biosynthesis and action and their regulation, genes involved in insulin resistance and associated disorders, and lately genes involved in chronic inflammation and atherosclerosis.

A. Genes involved in androgen biosynthesis, transport, and action, and their regulation (Table 3)

1. *CYP17*. The limiting step in androgen biosynthesis in the ovary and adrenal gland is an enzyme termed P450c17 α , which possesses both 17 α -hydroxylase and 17,20-lyase activities. Therefore, P450c17 α may catalyze the conversion of pregnenolone and progesterone into 17-hydroxypreg-

nenolone and 17-hydroxyprogesterone, respectively, and of these steroids into dehydroepiandrosterone and androstenedione, although in humans only the conversion of Δ^5 steroids has been demonstrated (118).

Rosenfield *et al.* (2, 119, 120) proposed several years ago that women with functional hyperandrogenism and PCOS had an exaggerated adrenal and ovarian responsiveness, and that increased activity of P450c17 α was responsible for the enhanced androgen synthesis and secretion. They proposed the increase in serum 17-hydroxyprogesterone in response to the GnRH analog nafarelin as the marker of functional ovarian hyperandrogenism (119). Studies using adrenal stimulation with ACTH and ovarian stimulation and suppression with the long-acting GnRH triptorelin also suggested that most hyperandrogenic women have increased P450c17 α activity in the adrenal and ovary (121–123), and that the increased adrenal P450c17 α activity was not influenced by ovarian function (122). Moreover, P450c17 α expression and activity are increased in ovarian theca cells from PCOS women, defined by NICHD criteria, compared with those from nonhyperandrogenic controls (124).

Given these findings, the gene encoding the P450c17 α enzyme, *CYP17*, was considered a candidate gene in early studies. *CYP17* is located in chromosome 10q24.3 (125, 126), and its promoter contains a T/C SNP at –34 bp from the start of transcription site that might modulate enzyme activity. Some studies suggested that this polymorphism was associated with the presence of polycystic ovaries on ultrasound (125), and PCOS patients homozygous for C alleles of this polymorphism presented with increased serum testosterone levels (127, 128). Other studies failed to confirm these observations, suggesting that this base change is a polymorphism without functional consequences for the development of polycystic ovaries and hyperandrogenism (129–131). Also, no evidence for linkage or association was found between PCOS, defined by NICHD criteria, and the *CYP17* locus in a family-based study that included mostly families of European ancestry from the United States (132). Moreover, no abnormalities were found after single-strand conformational polymorphism analysis of the entire coding region of *CYP17* in a small sample of PCOS patients with or without exaggerated 17-hydroxyprogesterone response to a GnRH analog (133), ruling out *CYP17* as a major candidate gene for the pathogenesis of PCOS and functional hyperandrogenism. However, posttranscriptional hyperphosphorylation of the serine residues of P450c17 α by a defective serine kinase might increase the 17,20-lyase activity of this enzyme, contributing to hyperandrogenism (118, 134). Confirmation of this hypothesis is still pending (135).

2. *CYP11A*. Ovarian theca cells from women with PCOS defined by NICHD criteria overexpress all the steroidogenic enzymes involved in androgen biosynthesis (136, 137), and these cells secrete increased amounts of progesterone, 17-hydroxyprogesterone, testosterone, and androstenedione compared with theca cells from nonhyperandrogenic women (136, 138).

The initial step in adrenal and ovarian steroidogenesis is the conversion of cholesterol into progesterone, which is catalyzed by the cholesterol side chain cleavage enzyme. The

CYP11A gene, located at 15q24, encodes the cholesterol side chain cleavage enzyme and has therefore been considered a candidate gene for functional hyperandrogenism and PCOS (139). It has been proposed that a VNTR polymorphism, consisting in repeats of a (ttta)n pentanucleotide at –528 bp from the ATG start of translation site in the *CYP11A* promoter, plays a role in the pathogenesis of PCOS (140). Evidence for linkage with the *CYP11A* locus was found in 20 pedigrees presenting with PCOS, based mostly on the presence of polycystic ovaries or male pattern premature balding, and the absence of the more common four-repeats allele (this VNTR appears with four, six, eight, and nine repeats in Caucasians) was associated with hirsute PCOS patients and with higher serum testosterone levels (140). Diamanti-Kandarakis *et al.* (141), using NICHD criteria for the definition of PCOS, confirmed its association with absence of four-repeat alleles in Greek patients. In women from the United States, nine-repeat alleles were more frequent in PCOS patients, defined by oligomenorrhea and polycystic ovaries, and four- and six-repeat alleles were more frequent in controls, but these allelic differences did not influence *CYP11A* expression in theca cells (142).

Other studies failed to demonstrate linkage with the *CYP11A* locus in PCOS patients defined by NICHD criteria (132) or association of *CYP11A* VNTR alleles with functional hyperandrogenism (143). Moreover, in a small sample of hirsute hyperandrogenic patients from Spain (144), no consistent genomic abnormalities have been found in the entire *CYP11A* coding region, nor in the genes encoding the steroidogenic acute regulatory protein, steroidogenic factor-1, and dosage-sensitive sex reversal-adrenal hypoplasia gene on the X chromosome gene-1 (DAX-1), which are also involved in the first step of steroidogenesis and its regulation. The family-based study cited above failed also to demonstrate linkage or association with the steroidogenic acute regulatory protein (132). Finally, Gaasenbeek *et al.* (145) recently failed to confirm any influence of *CYP11A* VNTR alleles on polycystic ovaries and on serum testosterone levels in a series of experiments involving a large number of subjects, concluding that the existence of associations between *CYP11A* promoter variation and androgen-related phenotypes had been substantially overestimated in previous studies, including their own preliminary report cited above (140).

3. *CYP21*. An exaggerated serum 17-hydroxyprogesterone response to ACTH stimulation is a common finding in women with PCOS or functional hyperandrogenism (121, 146). This finding prompted several groups to study *CYP21*, which encodes the 21-hydroxylase enzyme catalyzing the conversion of 17-hydroxyprogesterone into 11-deoxycortisol; increased serum 17-hydroxyprogesterone levels are the biochemical marker for 21-hydroxylase deficiency. This type of congenital adrenal hyperplasia is an autosomal recessive disease resulting from homozygosity or double heterozygosity for missense or nonsense mutations in *CYP21* and is characterized by hyperandrogenism with or without mineralocorticoid deficiency.

However, whether or not heterozygous *CYP21* mutations influence functional hyperandrogenism and PCOS is still matter of debate. As stated above, girls presenting with pre-

mature adrenarche and adolescent hyperandrogenism carry *CYP21* mutations more frequently than nonhyperandrogenic controls (112). Clinically symptomatic heterozygotes for *CYP21* mutations present with a phenotype that resembles that of PCOS (113), but it is unclear whether all carriers of *CYP21* mutations have an increased risk of having PCOS. Moreover, in hyperandrogenic women carrying *CYP21* mutations there is no clear concordance between the *CYP21* genotype and the functional origin of androgen excess (147).

Finally, the presence of polycystic ovaries in ultrasound scans has been associated with increased frequency of DRW6 and decreased DR7 human leukocyte antigen haplotypes, whereas 21-hydroxylase deficiency is associated with the Bw47, B14, or DR1 haplotypes (148). Moreover, in families of patients with 21-hydroxylase deficiency, polycystic ovaries segregate independently from adrenal dysfunction (149).

4. *HSD3B2*. This enzyme catalyzes the conversion of Δ^5 steroids into Δ^4 steroids in the adrenal and in the ovary. Mutations in *HSD3B2* result in a rare form of classic congenital adrenal hyperplasia, causing various degrees of salt wasting in both sexes and incomplete masculinization of the external genitalia in genetic males because both adrenal and ovarian steroidogenesis are severely impaired (150). Biochemically, this disorder is characterized by a marked increase in serum 17-hydroxypregnенolone and dehydroepiandrosterone concentrations (150).

Mild increases in these steroid precursors, and in the ratio of Δ^5 to Δ^4 steroids, are not infrequent in hyperandrogenic patients, and hyperandrogenic patients presenting with increased 17-hydroxypregnенolone concentrations and/or increased Δ^5 to Δ^4 ratios after adrenal stimulation with cosyntropin were initially considered to have a nonclassic form of *HSD3B2* deficiency (151–153). However, these mild increases in serum 17-hydroxypregnенolone concentrations and in the Δ^5 to Δ^4 ratios were interpreted by others as an exaggerated adrenal response to cosyntropin stimulation without a genetic origin (154). Molecular analysis of *HSD3B2* of hyperandrogenic patients presenting with increased Δ^5 steroids and increased Δ^5 to Δ^4 ratios revealed no abnormalities (155, 156), ruling out the existence of a nonclassic form of *HSD3B2* deficiency in these women. In conceptual agreement, a marker close to the *HSD3B2* locus was not in linkage or association with PCOS, defined by NICHD criteria, in the American family-based study cited above (132).

5. *17 β -Hydroxysteroid dehydrogenases.* 17 β -Hydroxysteroid dehydrogenase type III is also known as 17-ketosteroid reductase. This enzyme catalyzes the conversion of androstanedione into testosterone in the testis. Up to 20 mutations in *HSD17B3* have been identified as the cause of male pseudohermaphroditism because of testosterone deficiency (157). Pang et al. (158) hypothesized that genetic females with ovarian 17-ketosteroid reductase deficiency would probably have a normal female phenotype at birth and normal pubertal breast development but would present at puberty with virilization and menstrual disorders because of the sudden increase of the ovarian secretion of androstanedione. However, no mutations have been identified in *HSD17B3* in Caucasian and African-American women presenting with PCOS

defined by NICHD criteria (159). Also, no evidence for linkage or association with the type 1, type 2, and type 3 17 β -hydroxysteroid dehydrogenase loci was found in the American family-based study cited previously (132).

6. *Aromatase.* This enzyme, encoded by *CYP19*, is responsible for the conversion of C19 steroids (androgens) into C18 steroids (estrogens). Aromatase activity may be decreased in granulosa cells and follicles from women with PCOS, and the possible androgen excess resulting from this decreased activity might contribute to abnormal follicle development (160, 161). Although mutations in *CYP19* have been associated with multicystic ovaries in a case report, the clinical picture was that of hypergonadotropic hypogonadism (162). Moreover, no evidence for linkage of *CYP19* with PCOS was found in studies conducted in the United Kingdom (140) and in the United States (132).

7. *11 β -Hydroxysteroid dehydrogenase type 1 and hexose-6-phosphate dehydrogenase.* These enzymes regulate the inactivation of cortisol into cortisone at the tissue level. 11 β -Hydroxysteroid dehydrogenase type 1 converts cortisol into cortisone directly, and endoluminal hexose-6-phosphate dehydrogenase regenerates reduced nicotinamide adenine dinucleotide phosphate in the endoplasmic reticulum, thereby influencing the directionality of 11 β -hydroxysteroid dehydrogenase type 1 activity. Mutations in the genes encoding 11 β -hydroxysteroid dehydrogenase type 1 and hexose-6-phosphate dehydrogenase have been recently shown to cause cortisone reductase deficiency (163), and because the phenotypic features of affected women resemble those of PCOS, these genes should be considered candidates to explain the pathogenesis of PCOS. However, this possibility has not been explored in any series of patients with functional hyperandrogenism and PCOS to date.

8. *Gonadotropins.* In as many as 40% of PCOS patients, LH hypersecretion is present (164). The gene encoding the β -subunit of LH (*LH β*), which is responsible for LH specificity, has been explored in PCOS and hyperandrogenic women. Initially, two point mutations, Trp⁸Arg and Ile¹⁵Thr, were identified as the cause of an immunologically abnormal *LH β* molecule (165). These mutations induce structural changes in the mutant *LH β* molecule (166) and have a 15% prevalence worldwide, although with significant differences depending on the population studied (167). The resulting *LH β* molecule has an increased *in vitro* activity and a decreased *in vivo* half-life compared with the wild-type molecule (168).

This *LH β* variant has been associated with increased serum testosterone, estrogen, and SHBG levels in healthy women, but not in PCOS patients (169). Furthermore, the prevalence of this *LH β* variant is reduced in obese women with PCOS, suggesting a protective role against the development of hyperandrogenic symptoms in these women and a possible usefulness in determining the risk for PCOS in obese women (170, 171). However, no association with PCOS, hyperandrogenism, or serum androgen or estrogen concentrations has been found in other studies (172, 173).

Other variants in the *LH β* gene might influence hyperandrogenism and PCOS. A Gly¹⁰²Ser mutation in exon 3 has been related to menstrual disorders in Chinese women (172,

174). Finally, in Japanese patients with ovulatory disorders, several SNPs in the promoter of the LH β gene (-894C/T , -1018G/C , -1036C/A , -1098C/T , and -1423C/T) are more frequent than in normal ovulatory women (175).

Polymorphisms in the FSH β -subunit gene have also been reported to influence PCOS. In Chinese women, homozygosity for a thymine-cytosine substitution in exon 3 (codon 76, TAT to TAC) has been found more frequently in PCOS patients, as defined by oligomenorrhea and polycystic ovaries, compared with nonhyperandrogenic women, especially in obese patients, and correlating with higher serum androgen concentrations (176). In these women, two SNPs in the gene encoding the FSH receptor, Thr³⁰⁷Ala and Ser⁶⁸⁰Asn, showed similar allele distribution among PCOS patients and controls (177). Moreover, the search for mutations in exons 6, 7, 9, and 10 of the FSH receptor gene, which have been shown previously to inactivate the receptor, yielded negative results in Japanese patients with oligomenorrhea and polycystic ovaries (178). This locus was not in linkage or association with PCOS in a family-based study conducted in the United States (132). Finally, mutations in the gene encoding the GnRH receptor have not been found in PCOS patients, defined by NICHD criteria (179).

9. Dopamine receptor. Given that dopamine is involved in the hypothalamic control of gonadotropin secretion, the association between polymorphisms in the dopamine receptor and disorders of ovulation and fertility has been studied. Legro *et al.* (180) reported that SNPs in exons 5 and 6 of the gene encoding the type 2 dopamine receptor influenced serum gonadotropin and prolactin levels, as well as parity and prevalence of miscarriage in women of Hispanic ancestry. In these women, a genomic variant in the type 3 dopamine receptor was associated with hyperandrogenic chronic anovulation and resistance to clomiphene citrate (181), but this association was not confirmed in a large series of non-Hispanic women (182).

10. SHBG. SHBG regulates the access of testosterone and estradiol to target tissues. Decreased SHBG concentrations are characteristic of hyperandrogenic women, contributing to increased tissue androgen availability (183). Despite the fact that evidence for linkage or association was not found between a marker close to the SHBG locus and PCOS in a family-based study conducted in the United States (132), a missense Pro¹⁵⁶Leu mutation in the SHBG gene, resulting in abnormal glycosylation and secretion of a SHGB mutant that retains binding capacity (184), has been detected in a women presenting with severe hyperandrogenism during pregnancy. However, it is seldom found in unselected hyperandrogenic women (184).

Recently, an association between a (TAAAA)n polymorphism in the promoter of the SHBG gene and PCOS has been reported (185). Longer alleles (more than eight repeats) were frequent in Greek PCOS patients, defined by NICHD criteria, whereas nonhyperandrogenic women presented with a higher frequency of shorter alleles (185). Furthermore, in the PCOS group, carriers of the longer allele genotypes had lower SHBG levels than in those with shorter alleles (185). Therefore, this polymorphism might be related to the low

SHBG levels characteristic of PCOS, facilitating androgen availability to target tissues. Cousin *et al.* (186) studied the (TAAAA)n polymorphism in hirsute women and found strong disequilibrium linkage with an Asp³²⁷Asn SNP in exon 8 of SHBG, 327Asn alleles being associated with eight-repeat (TAAAA)n alleles, and resulting in increased serum SHBG levels when compared with subjects homozygous for 327Asp alleles. Moreover, longer (TAAAA)n alleles resulted in decreased serum SHBG levels when compared with six-repeat alleles (186), in conceptual agreement with the results in PCOS women described above (185).

11. Glucocorticoid receptor. Mutations in the glucocorticoid receptor gene result in a compensatory increase in circulating ACTH, resulting in excess secretion of adrenal androgens. Therefore, the glucocorticoid receptor has been studied as a candidate gene for functional hyperandrogenism and PCOS. However, genomic abnormalities and polymorphisms in the glucocorticoid receptor gene do not appear to influence the pathogenesis of functional hyperandrogenism (187, 188) and PCOS (189).

12. Steroid 5 α -reductase (SRD5A). This enzyme catalyzes the conversion of testosterone into the more potent androgen dihydrotestosterone. SRD5A1 and SRD5A2 are the two isoforms of the enzyme. Mutations in SRD5A2 result in male pseudohermaphroditism (190, 191). Because total SRD5A activity is increased in polycystic ovaries (192), the genes encoding the SRD5A isoforms can be considered candidate genes for functional hyperandrogenism and PCOS. To date, no data have been published regarding the possible involvement of molecular genetic variants in these genes in hyperandrogenic disorders.

13. AR. The AR is a member of the superfamily of ligand-activated transcription factors that regulate many biological processes and is encoded by a gene located at Xq11–12 (193, 194). The AR has three functional domains responsible for transactivation, for ligand binding, and for binding to DNA. Exon 1 contains a VNTR polymorphism consisting of (CAG)n repeats, which encodes for a polyglutamine tract in the N-terminal transactivation domain of the AR protein (195).

The number of CAG repeats in the normal population varies between 11 and 31, with 20 repeats being the most frequent (196). The number of CAG repeats is inversely related to the transactivation of the AR and its activity (197). Thus, the decreased number of CAG repeats has been proposed to increase androgen activity at target tissues, favoring hirsutism (198), premature pubarche, and ovarian hyperandrogenism (116) in women, infertility in men (199), as well as androgen-dependent skin disorders in both men and women (200). A decreased number of AR gene CAG repeats has been suggested to explain the normal serum androgen levels found in some women with polycystic ovaries, infertility, and oligomenorrhea, in whom the hyperandrogenic symptoms would result from the intrinsic increase in the AR activity (201).

One of the two X chromosomes in every cell of a woman undergoes inactivation, a process that involves methylation of DNA and occurs in a random fashion. Skewed inactivation

of X chromosome with the larger CAG repeat, favoring expression of the shorter allele, has been proposed to play a role for idiopathic hirsutism and PCOS (202, 203). However, we have shown that both the number of CAG repeats and the prevalence of skewed X chromosome inactivation were equally distributed in hirsute patients with or without hyperandrogenemia and in healthy women (204). Moreover, no evidence for linkage or association with PCOS was found with the AR locus in the family-based study conducted in the United States cited above (132).

14. Aldosterone synthetase. The renin-angiotensin system may be hyperactive in women with PCOS (205, 206). Recently, a –344T/C SNP in the promoter of the gene encoding aldosterone synthetase, *CYP11B2*, has been proposed to influence the pathogenesis of PCOS, because C alleles are more frequent in these patients than in healthy controls (207). Interestingly, women homozygous for C alleles presented with increased plasma renin activity and increased serum angiotensin II, aldosterone, and testosterone levels compared with women homozygous for T alleles, suggesting that this polymorphism influences the activity of aldosterone synthetase and also contributes to androgen excess (207).

B. Genes involved in insulin resistance and associated disorders (Table 4)

1. Insulin receptor gene (*INSR*). The presence of insulin resistance is common in PCOS (3) and is frequent in other hyperandrogenic patients (208–210). Therefore, the genes encoding the *INSR* and those encoding several molecules involved in postreceptor signaling have been studied in hyperandrogenic patients.

The *INSR* is a heterotetrameric glycoprotein consisting of two α - and two β -subunits, and it is encoded by a gene located at chromosome 19. A marker relatively close (1 cM) to *INSR*, D19S884, has been reported in association with PCOS, defined by NICHD criteria, using the transmission disequilibrium test in a family-based study (132), and in a case-control study (211), both conducted in the United States. However, this association was not confirmed in PCOS patients from Spain and Italy using a case-control design (212). In conceptual agreement with the latter, the 22 exons of *INSR* have been sequenced in PCOS patients with negative results (213). *INSR* contains several polymorphisms, yet most of them are silent polymorphisms or are located in intronic regions and are present with similar frequencies in patients with polycystic ovaries and hyperandrogenism and in controls (214).

Recently, Siegel et al. (215) have observed a C/T SNP at the tyrosine kinase domain of *INSR* associated with PCOS defined by NICHD criteria. This SNP could be a susceptible variant for PCOS, or it could be in linkage disequilibrium with another *INSR* polymorphism; such an association must be confirmed in future studies.

Studying cultured skin fibroblasts and muscle samples from PCOS patients defined by NICHD criteria, Dunaif et al. (216) found increased *INSR* serine phosphorylation, which decreases its protein tyrosine kinase activity, in as many as 50% of the cases. Subsequent studies in these patients con-

firmed *in vivo* the defect in insulin signaling, using serial skeletal muscle biopsies obtained during euglycemic glucose clamp studies (217). However, the search for mutation in the tyrosine kinase domain of the *INSR* gene did not show abnormalities other than polymorphisms in exon 17, which were not associated with insulin resistance (218). Therefore, the still unidentified factor responsible for the increased phosphorylation of the serine residues of the *INSR* appears to be extrinsic to the receptor and might also contribute to the increased serine phosphorylation of P450c17 α also found in some PCOS patients (118).

2. IRS-1 and IRS-2. After insulin binding, autophosphorylation of tyrosine residues results in the activation of the *INSR*, and tyrosine kinase activity phosphorylates intracellular substrates such as IRS-1 and IRS-2 (3). PCOS women present a defect in insulin receptor signaling characterized by a decreased IRS-1-associated phosphatidylinositol 3-kinase activity (217). Two common SNPs in the genes encoding insulin-receptor substrates, Gly⁹⁷²Arg in *IRS-1* and Gly¹⁰⁵⁷Asp in *IRS-2*, are susceptibility genes for type 2 diabetes mellitus (219, 220); they have been studied in PCOS patients, despite the fact that evidence for linkage or association with PCOS was not found with *IRS-1* in a family-based study conducted in the United States (132).

Carriers of Arg972 *IRS-1* alleles presented with increased fasting insulin levels compared with women homozygous for Gly972 alleles, whereas carriers of Asp1057 *IRS-2* alleles presented with increased glucose and insulin levels 2 h after an oral glucose load and had an increased prevalence of glucose intolerance compared with subjects homozygous for Gly1057 alleles (102). However, a subsequent study in a larger series of PCOS patients showed only the effect of the Gly¹⁰⁵⁷Asp polymorphism in *IRS-2* on glucose tolerance, and no effect of the Gly⁹⁷²Arg polymorphism in *IRS-1* (103). Surprisingly, the effect was just the opposite found previously, because the 2-h glucose values were actually increased in subjects homozygous for Gly1057 alleles when compared with carriers of Asp1057 alleles (103). Additional studies are needed to confirm the influence of these polymorphisms on glucose tolerance and insulin resistance in PCOS.

3. INS. The presence of pancreatic β -cell dysfunction in women presenting with PCOS appears to have a genetic origin (221). Therefore, *INS* has been studied in women with PCOS and functional hyperandrogenism. Waterworth et al. (222) found that women with menstrual disturbances and/or hirsutism and polycystic ovaries, who were homozygous for class III alleles, were more frequently anovulatory and had increased body mass index and fasting insulin compared with women homozygous for class I alleles. Moreover, class III alleles were associated with symptomatic women (222, 223). Paternal transmission of class III alleles from heterozygous fathers to anovulatory PCOS patients is more frequent than maternal transmission of the allele (222–224), and class III alleles predisposed these patients to both PCOS and type 2 diabetes mellitus. However, later case-control studies in European Caucasian women, conducted outside the United Kingdom, have failed to reproduce these results (225, 226), and the *INS* locus was not associated with PCOS in a linkage study in American PCOS patients (132).

TABLE 4. Genes involved in insulin resistance and associated disorders, in functional hyperandrogenism (FH), and PCOS

Gene	Variant/locus	Design	Subjects	Phenotypic trait	Association
<i>INSR</i>					
Sorbara et al. (213)	Mutation scanning	Case series	PCOS	Insulin resistance	No
Conway et al. (218)	Mutation scanning	Case series	PCOS	Insulin resistance	No
Urbanek et al. (132)	D19S884 and other loci	FBS (TDT)	PCOS	PCOS	Yes
Talbot et al. (214)	Mutation scanning	Case-control	PCOS	Insulin resistance	No
Tucci et al. (211)	D19S884	Case-control	PCOS	PCOS	Yes
Siegel et al. (215)	C10923T	Case-control	PCOS	Lean PCOS patients	Yes
Villuendas et al. (212)	D19S884	Case-control	PCOS	PCOS	No
<i>IRS 1 and 2</i>					
Urbanek et al. (132)	<i>IRS1</i>	FBS (TDT)	PCOS	PCOS	No
El Mkadem et al. (102)	Gly ⁹⁷² Arg (<i>IRS-1</i>)	Case-control	PCOS	↑ Insulin resistance	Yes
Ehrmann et al. (103)	Gly ¹⁰⁵⁷ Asp (<i>IRS-2</i>)	Case-control	PCOS	↑ 2 h Insulin and glucose (OGTT)	Yes
Ibáñez et al. (104)	Gly ⁹⁷² Arg (<i>IRS-1</i>)	Case series	PCOS	Insulin and glucose levels	No
Ibáñez et al. (104)	Gly ¹⁰⁵⁷ Asp (<i>IRS-2</i>)	Case series	PCOS	↓ 2 h Glucose (OGTT)	Yes
Ibáñez et al. (104)	Gly ⁹⁷² Arg (<i>IRS-1</i>)	Case-control	PP	PP, ovarian hyperandrogenism and ↓ SHBG	Yes
<i>INS</i>					
Waterworth et al. (222)	<i>INS</i> VNTR	FBS/case-control	PCOS/MPB	PCOS and MPB	Yes
Urbanek et al. (132)	<i>INS</i> VNTR	FBS (TDT)	PCOS	PCOS and T levels	No
Eaves et al. (224)	<i>INS</i> VNTR	FBS (TDT)	PCOS	PCOS	Yes
Michelmore et al. (223)	<i>INS</i> VNTR	FBS/case-control	PCOS	Insulin resistance and T levels	Yes
Ibáñez et al. (101)	<i>INS</i> VNTR	Case-control	PP	Birth weight and insulin sensitivity	Yes
Calvo et al. (225)	<i>INS</i> VNTR	Case-control	FH	FH	No
Vankova et al. (226)	<i>INS</i> VNTR	Case-control	PCOS	PCOS, insulin secretion and action	No
<i>IGF system</i>					
Urbanek et al. (132)	<i>IGF-I</i> , <i>IGF-IR</i> , <i>IGFBP-1</i> and <i>IGFBP-3</i>	FBS (TDT)	PCOS	PCOS	No
San Millán et al. (229)	<i>IGF-2</i> (<i>ApaI</i>)	Case-control	PCOS	PCOS	Yes
San Millán et al. (229)	<i>IGF-IR</i>	Case-control	PCOS	↑ Fasting glucose and insulin resistance	Yes
	<i>IGF-I</i> , <i>IGF-II</i> R	Case-control	PCOS	PCOS	No
<i>PPAR-γ2</i>					
Urbanek et al. (132)	D3S1263	FBS (TDT)	PCOS	PCOS	No
Witchel et al. (110)	Pro ¹² Ala	Case-control	PP/FH	Weight gain	Yes
Hara et al. (245)	Pro ¹² Ala	Case series	PCOS	↓ Insulin resistance in PCOS	Yes
Korhonen et al. (246)	Pro ¹² Ala	Case-control	PCOS	PCOS	Yes
Orio et al. (247)	CAC ⁴⁷⁸ CAT	Case-control	PCOS	PCOS, obesity, and leptin levels	Yes
San Millán et al. (229)	Pro ¹² Ala	Case-control	PCOS	PCOS	No
San Millán et al. (229)	Pro ¹² Ala	Case-control	PCOS	PCOS	No
<i>PON1</i>					
San Millán et al. (229)	-108 C/T	Case-control	PCOS	PCOS	Yes
San Millán et al. (229)	Leu ⁵⁵ Met	Case-control	PCOS	↑ Insulin resistance and BMI	Yes
San Millán et al. (229)	Gln ¹⁹² Arg	Case-control	PCOS	PCOS	No
<i>SORBS1</i>					
Witchel et al. (106)	Thr ²²⁸ Ala	Case-control	PP/FH	PP/FH, obesity	No
San Millán et al. (229)	Thr ²²⁸ Ala	Case-control	PCOS	↑ BMI	Yes
<i>β₃-Adrenergic receptor</i>					
Witchel et al. (108)	Trp ⁶⁴ Arg	Case-control	PP/FH	PP/FH, obesity	No
<i>Calpain-10</i>					
Ehrmann et al. (263)	UCSNP-43, -19, and -63	FBS/case-control	PCOS	PCOS and insulin levels	Yes
Haddad et al. (264)	UCSNP-43, -44, -19, and -63	FSB/case-control	PCOS	PCOS and insulin levels	No
Escobar-Morreale et al. (265)	UCSNP-43	Case-control	Hirsutism	Hirsutism score	Yes
González et al. (266, 267)	UCSNP-44	Case-control	Hirsutism	PCOS, idiopathic hirsutism, FH	No
González et al. (266, 267)	UCSNP-45	Case-control	Hirsutism	Idiopathic hirsutism	Yes
González et al. (266, 267)	UCSNP-43, -44, -19, and -63	Case-control	PCOS	PCOS	Yes
<i>Glycogen synthetase</i>					
Rakjhowa et al. (268)	XbaI polymorphism	Case-control	PCOS	PCOS and insulin sensitivity	No
<i>Resistin</i>					
Urbanek et al. (269)	-420C/G	FBS (TDT)	PCOS	PCOS, obesity, and insulin resistance	No
<i>Leptin and leptin receptor</i>					
Oksanen et al. (270)	Mutation screening of leptin gene, polymorphisms in leptin receptor gene	Case-control	PCOS	PCOS and obesity	No

TABLE 4. *Continued*

Gene	Variant/locus	Design	Subjects	Phenotypic trait	Association
<i>Apolipoprotein E</i>					
Heinonen et al. (271)	Alleles E2, E3, and E4	Case-control	PCOS	PCOS	No
<i>PC-1</i>					
San Millán et al. (229)	Lys ¹²¹ Gln	Case-control	PCOS	PCOS	No
<i>PTP1B</i>					
San Millán et al. (229)	981C/T and 1484 insG	Case-control	PCOS	PCOS	No
<i>Adiponectin</i>					
San Millán et al. (229)	45T/G and 276G/T	Case-control	PCOS	PCOS	No

Authors are cited in chronological order. BMI, Body mass index; FBS, family-based study; IGF-IR, IGF-I receptor; IGF-IIR, IGF-II receptor; IGFBP, IGF binding protein; MPB, male premature baldness; OGTT, oral glucose tolerance test; PC-1, plasma cell differentiation antigen glycoprotein; PP, premature pubarche; PTP1B, protein tyrosine phosphatase 1B; T, total testosterone; TDT, transmission disequilibrium test.

4. IGF system. IGFs, their receptors, binding proteins, and proteases are important for the normal development of the ovary (227). IGFs stimulate ovarian cellular mitosis and steroidogenesis, inhibit apoptosis, and might be related to the development of functional hyperandrogenism and PCOS (228).

No evidence for linkage with PCOS was found for markers close to the genes encoding IGF-I and IGF-binding proteins 1 and 3 in a family study conducted in the United States (132). San Millán et al. (229) recently found an association of PCOS with homozygosity for G alleles of the *ApaI* polymorphism in *IGF-II*, but not with a dinucleotide polymorphism in *IGF-I*, a trinucleotide polymorphism in the *IGF-I receptor*, or with an ACAA-insertion/deletion polymorphism at the 3' nontranslated region of the *IGF-II receptor*, previously described (230–232). G alleles of the *ApaI* polymorphism in *IGF-II* have been attributed to increased IGF-II mRNA in leukocytes compared with A alleles (233), and possibly result in increased liver IGF-II expression and secretion (234). Given that IGF-II stimulates adrenal (235, 236) and ovarian (237) androgen secretion, the increased frequency of homozygosity for these alleles might contribute to hyperandrogenism in some PCOS patients, provided we assume that G alleles may increase IGF-II expression at the ovary, as reported for other tissues. In the same case-control study involving PCOS patients cited above (229), we found that subjects homozygous for 90-bp alleles of a trinucleotide repeat polymorphism in the gene encoding IGF-I receptor had increased fasting glucose levels and fasting insulin resistance index compared with subjects carrying 93-bp alleles, but no association of any genotype with PCOS.

5. PPAR-γ2. Activation of PPAR-γ by using the insulin sensitizer drugs, thiazolidinediones, has been one of the most important advances for the treatment of type 2 diabetes mellitus in past years. As described above, insulin resistance is a common finding in hyperandrogenic patients, and thiazolidinediones improve insulin sensitivity, hyperandrogenism, and ovulation in women with PCOS (238–243).

The Pro¹²Ala SNP in *PPAR-γ2* has been studied in women with PCOS, despite the fact that evidence for linkage or association with PCOS was not found for a marker close to the *PPAR-γ2* gene, in a family-based study conducted in the United States (132). Ala12 alleles of the *PPAR-γ2* gene favor weight gain in obese adults (244) and in obese hyperandro-

genic girls and adolescents (110). Also, Ala12 alleles preserve insulin sensitivity in Caucasian men (109) and in Caucasian women presenting with PCOS defined by NICHD criteria (245). Recently, a marginally significant decrease in the frequency of the Ala12 allele has been reported in women with polycystic ovaries from Finland (246), but this result has not been confirmed in a small case-control study of PCOS patients conducted in Spain (229) or in a recently published study in Italian PCOS patients defined by NICHD criteria and ultrasonography (247). In the latter, a silent C to T substitution at position 142 in exon 6 was differentially distributed in PCOS patients and controls, T alleles being more frequent in women with PCOS (247). This silent polymorphism was not in linkage disequilibrium with the Pro¹²Ala polymorphism, but the possibility of an association with other unknown genomic variant in the *PPAR-γ2* gene was not explored (247). Nevertheless, both Ala12 and T142 alleles are relatively uncommon (less than 20%) in normal and hyperandrogenic populations (229, 245–247), and therefore their putative influences on insulin sensitivity and/or hyperandrogenism would be restricted to a small number of PCOS patients.

6. Paraoxonase (PON1). We have recently explored the –108C/T, Leu⁵⁵Met, and Gln¹⁹²Arg polymorphisms in the gene encoding serum PON1 in PCOS patients defined by NICHD criteria. The PON1 gene is expressed mainly in the liver and encodes for serum PON1, which is an antioxidant high-density lipoprotein-associated enzyme. Liver PON1 mRNA expression is influenced by genetic and environmental factors, and both androgens and proinflammatory mediators decrease liver PON1 expression (248). Interestingly, both androgen excess and proinflammatory genotypes contribute to the pathogenesis of PCOS (249–251).

Homozygosity for T alleles of the –108C/T polymorphism in *PON1* was more frequent in patients compared with nonhyperandrogenic women (229). As expected from the association with PCOS, subjects homozygous for –108T alleles of *PON1* presented with increased hirsutism scores, total testosterone, and free testosterone and androstenedione concentrations compared with carriers of –108C alleles (229). Moreover, in a logistic regression model, homozygosity for –108T alleles of *PON1* was associated with a 7.1 odds ratio (95% confidence interval, 2.1–23.8) of having PCOS (229).

The –108C/T polymorphism is responsible of approximately 23% of PON1-expression levels in some cell systems, in which –108TT constructs showed reduced PON1 expression compared with –108CC constructs (252). We thus speculated that homozygosity for –108T alleles, hyperandrogenism, and proinflammatory genotypes might contribute to reduced PON1 expression, resulting in a higher oxidative stress in these women. The latter has been found in PCOS patients (253).

Oxidative stress may impair insulin action (254). Therefore, reduced serum PON1 activity might contribute to the insulin resistance of PCOS patients. This hypothesis is supported by the finding of reduced serum PON1 activity in other insulin-resistant disorders such as type 2 diabetes mellitus (255, 256) and cardiovascular atherosclerotic disease (257, 258). If confirmed in future studies, the association of homozygosity for –108T alleles of *PON1* with PCOS might contribute to explaining the insulin resistance and the increased risk for atherosclerosis associated with this syndrome (259).

In our study (229), subjects homozygous for Met55 alleles presented with increased body mass index and indexes of insulin resistance compared with carriers of Leu55 alleles, further suggesting the involvement of *PON1* in PCOS, despite the fact that the Leu⁵⁵Met and Gln¹⁹²Arg polymorphisms in *PON1* were not associated with PCOS.

7. Human homolog for the sorbin and SH3-domain-containing-1 gene (*SORBS1*). In addition to the studies in adolescents cited above (106), we have recently studied the Thr²²⁸Ala polymorphism in adult PCOS patients. Allele frequencies were similar in PCOS patients and nonhyperandrogenic women, but carriers of Ala228 alleles of *SORBS1* presented with increased body mass index compared with subjects homozygous for 228T alleles (229), in conceptual agreement with a large study conducted in Europe (260).

8. Calpain-10. This enzyme is a cysteine protease that plays a role in insulin secretion and action (261). The 112/121-haplotype combination of University of Chicago single nucleotide polymorphism (UCSNP)-43, UCSNP-19, and UCSNP-63 polymorphisms in the gene encoding calpain-10, located at 2q37.3, has been reported to increase the risk for diabetes (262). Ehrmann *et al.* (263) found no association between this haplotype and any of the phenotypic features of PCOS in Caucasian nondiabetic PCOS patients, defined by NICHD criteria, whereas the 112/121-haplotype was significantly associated with higher insulin levels in response to an oral glucose tolerance test in African-American, nondiabetic PCOS women. Moreover, when considering Caucasian and African-American, nondiabetic PCOS patients as a whole, the 112/121 haplotype was associated with a 2-fold increase in susceptibility to PCOS.

However, the association of *calpain-10* SNPs with PCOS, as defined by polycystic ovaries, hyperandrogenism, and/or anovulation, was not confirmed by Haddad *et al.* (264) in 330 PCOS patients from the United Kingdom. We have studied three common polymorphisms in the calpain-10 gene in 97 Spanish hyperandrogenic patients and 37 controls, including UCSNP-43 (265). C alleles at the UCSNP-45

locus were associated with idiopathic hirsutism, but neither the UCSNP-43 nor the UCSNP-44 was associated with hyperandrogenism or PCOS (265). However, in a different population from the south of Spain, González *et al.* (266, 267) recently reported an association between PCOS and UCSNP-44. Additional studies are needed to clarify this issue, especially because the physiological roles of calpain-10 remain mostly unknown.

9. Genes encoding for other molecules related to insulin resistance and associated disorders. Among other genes tested, no association has been reported in PCOS with genomic variants in the genes encoding glycogen synthetase (268), resistin (269), leptin and its receptor (270), apoprotein E (271), or with variants in the genes of plasma cell differentiation antigen glycoprotein, protein tyrosine phosphatase 1B, and adiponectin (229).

C. Proinflammatory genotypes (Table 5)

Chronic inflammation is involved in the development of metabolic syndrome and cardiovascular disease (272, 273), and serum inflammatory markers cluster in patients with cardiovascular disease, suggesting a role in the pathogenesis of atherosclerosis (272, 273).

Inverse correlations have been reported between indexes of insulin sensitivity and inflammatory markers such as circulating levels of TNF- α (274), soluble type 2 TNF receptor (TNFR2) (275), IL-6 (276), C-reactive protein (CRP) (276), and soluble intercellular cell adhesion molecule-1 (276).

Adipose tissue plays a central role in the relationship between cytokines and insulin resistance. The expression of TNF- α and TNFR2 in adipose tissue is increased in obesity (277, 278). TNF- α expression correlates with indexes of insulin resistance and decreases with weight loss in parallel with the improvement in insulin sensitivity (277). Similar results have been reported for IL-6 (279). Moreover, inflammatory cytokines may induce insulin resistance by direct actions on insulin-signaling postreceptor molecules (280) or by inducing central obesity through activation of the hypothalamic-pituitary-adrenal axis (281).

Because obesity and insulin resistance are common findings in hyperandrogenic women (3), chronic inflammation might be involved in the pathogenesis of functional hyperandrogenism and PCOS. In animal models in which polycystic ovaries were induced by neonatal administration of estradiol, the production of TNF- α and IL-6 was increased in ovaries and in peritoneal macrophages (282). The concentrations of IL-12 were decreased, and production of IL-13 and the number of activated lymphocytes were increased in follicular fluid of women with PCOS (283).

The study of serum inflammatory markers in PCOS has resulted in conflicting reports. Increased CRP levels have been reported in PCOS patients defined by NICHD criteria (284, 285). Similarly, increased serum IL-6 (286) and TNF- α (287–289) concentrations have been reported in women with PCOS or functional hyperandrogenism.

However, we have recently reported that obesity, and not PCOS, appears to be the major determinant of the increase in serum CRP and IL-6 in premenopausal women, and this and other inflammatory markers such as serum TNF- α , soluble

TABLE 5. Proinflammatory genotypes, functional hyperandrogenism (FH), and PCOS

Gene	Variant	Design	Subjects	Phenotypic trait	Association
<i>TNF-α</i>					
Milner et al. (296)	-308G/A	Case-control	PCOS	PCOS	No
Mao et al. (297)	-308G/A	Case-control	PCOS	PCOS	No
Escobar-Morreale et al. (288)	-308G/A	Case-control	FH	↑ Serum androgens and 17-hydroxyprogesterone levels	Yes
Korhonen et al. (298)	-1196C/T, -1125G/C, -1031T/C, -863C/A, -857C/T, -316G/A, -238G/A, and -163G/A -850C/T	Case-control	FH	FH	No
<i>TNFRSF1B</i>					
Peral et al. (250)	Met ¹⁹⁶ Arg 1663G/A, 1668T/G, and 1690T/C	Case-control Case-control	PCOS/FH PCOS/FH	PCOS/FH PCOS/FH	Yes No
<i>IL-6</i>					
Villuendas et al. (249)	-597G/A and -174G/C	Case-control	FH	FH and adrenal hyperactivity in GG homozygotes	Yes
Mohlig et al. (291)	-572G/C and 373A(n)T(n) -174G/C	Case-control Case-control	FH PCOS	FH ↓ Serum androstenedione in -174GC genotype	No Yes
<i>gp130</i>					
Escobar-Morreale et al. (251)	Gly ¹⁴⁸ Arg	Case-control	PCOS/FH	PCOS/FH	Yes
<i>IL-6Rα</i>					
Escobar-Morreale et al. (251)	CA-repeat polymorphism	Case-control	PCOS/FH	Obesity	Yes

Authors are cited in chronological order. gp130, 130-kDa IL-6 Signal transducer; IL-6R, IL-6 receptor; TNFRSF1B, gene encoding TNFR2.

TNFR2, or soluble intercellular cell adhesion molecule-1 are not increased by PCOS when controlling for confounding factors such as smoking and obesity (290). Similar findings have been published recently by Mohlig et al. (291). These results cast doubt upon the usefulness of these serum inflammatory molecules as markers of the inflammatory process associated with hyperandrogenism. On the contrary, another novel inflammatory marker of cardiovascular risk, IL-18, is increased in serum both by obesity and by PCOS, suggesting that this molecule may be a useful marker of inflammation in PCOS patients (292).

Given that proinflammatory genotypes influence obesity, type 2 diabetes mellitus, and insulin resistance-related disorders (273), over the past years our group has studied genomic variants in the genes encoding several inflammatory mediators and their receptors. Some of these variants are associated with functional hyperandrogenism and PCOS.

1. *TNF-α*. TNF-α induces reproductive changes that closely resemble those found in patients with PCOS and functional hyperandrogenism. TNF-α facilitates the effects of insulin and IGF-I on the ovary in a dose-dependent and additive fashion (293), stimulating proliferation and steroidogenesis in rat theca cells *in vitro* (293, 294). Moreover, TNF-α may be involved in apoptosis and anovulation in the rat ovary (295).

We have recently studied serum TNF-α levels and nine common polymorphisms (-1196C/T, -1125G/C, -1031T/C, -863C/A, -857C/T, -316G/A, -308G/A, -238G/A, and -163G/A) in the TNF-α gene in 60 hyperandrogenic women and 27 healthy controls matched for body mass index (288). As a group, hyperandrogenic patients presented with increased serum TNF-α levels, but this increase was only present in lean patients when compared with lean controls, and not in obese patients (288).

No differences between patients and controls were found in the allele frequencies of any of the polymorphisms studied

(288). In conceptual agreement, -308G/A alleles were equally distributed between patients with polycystic ovaries and hyperandrogenic symptoms and controls in other studies (296, 297), and similar results were reported for the -805C/T polymorphism in the TNF-α gene (298). However, when considering patients and controls as a whole in our series, carriers of -308A alleles presented with increased serum androgen and 17-hydroxyprogesterone levels before and after stimulation with the GnRH analog leuprolide (288). Therefore, polymorphisms in the TNF-α gene do not appear to play a major role in the pathogenesis of functional hyperandrogenism and PCOS but might be a modifying factor for phenotypic traits associated with these disorders.

2. *TNFR2 gene (TNFRSF1B)*. TNFR2 mediates most of the metabolic effects of TNF-α (299). We have recently studied serum soluble TNFR2 levels and several polymorphisms in the *TNFRSF1B* in women with functional hyperandrogenism, including PCOS defined by NICHD criteria (250).

TNFRSF1B has been studied in several metabolic disorders. The 1690T/C variant in exon 10 has been described to influence body mass index and insulin resistance (300). The CA-repeat polymorphism in intron 4 and the Met¹⁹⁶Arg polymorphism in exon 6, which are in strong linkage disequilibrium, influence serum lipid levels (301–303) and diastolic blood pressure (302); linkage studies suggest that the *TNFRSF1B* locus is associated with hypertension (302) and familial combined hyperlipidemia (301). Moreover, the CA-repeat polymorphism has been recently proposed as a contributing factor to coronary artery disease (304).

In our series, the uncommon 196Arg allele of the Met¹⁹⁶Arg (676T/G) polymorphism in exon 6 of *TNFRSF1B* was more frequent in patients with PCOS compared with healthy controls (250). When the study was extended to include Italian subjects, this variant was more frequent not only in PCOS patients but also in women with hyperandrogenic hirsutism and regular

menstrual cycles (250). However, the Met¹⁹⁶Arg polymorphisms did not influence any phenotypic trait associated with hyperandrogenism, insulin resistance, or obesity when studying patients and controls separately (250).

We also studied three SNPs in the 3'-untranslated region of *TNFRSF1B* in exon 10, 1663G/A, 1668T/G, and 1690T/C, which were not associated with hyperandrogenism (250). Serum soluble TNFR2 levels were not increased in hyperandrogenic women compared with controls, but they were influenced by the interaction between the 1663G/A and 1668T/G variants. We hypothesized that the Met¹⁹⁶Arg variant in *TNFRSF1B* might contribute to PCOS by modulating TNF- α actions at target tissues.

3. IL-6. Among cytokines, IL-6 circulates in plasma and acts in distant tissues (305). TNF- α stimulates IL-6 secretion by adipocytes, and mounting evidence suggests that IL-6 is also implicated in insulin resistance and associated syndromes (273, 306–308). Although serum IL-6 levels are not increased in women presenting with functional hyperandrogenism and PCOS (249, 290), IL-6 concentrations are increased in peritoneal fluid in clomiphene-resistant, anovulatory PCOS patients, suggesting a role in the pathogenesis of hyperandrogenic disorders (309).

We recently studied four common polymorphisms in the promoter of the IL-6 gene (−597G/A, −572G/C, −373A(n)T(n), and −174G/C) in 85 hyperandrogenic patients and 25 healthy women (249). The −597G/A and −174G/C variants were in strong disequilibrium linkage. When considering the three biallelic SNPs, five haplotypes were found (relative frequencies in parentheses): GGG (0.505), AGC (0.377), GGC (0.059), GCG (0.055), and GCC (0.005). The frequency of the GGG haplotype was increased in patients (0.559) compared with controls (0.320), and conversely, the frequency of the AGC haplotype was reduced in patients (0.318) compared with controls (0.580) ($P < 0.02$). Homozygosity and heterozygosity for −597G and −174G alleles were more frequent in controls, and controls carrying these alleles presented with increased serum IL-6, cortisol, 11-deoxycortisol, and 17-hydroxyprogesterone levels, and a tendency toward increased serum total testosterone levels compared with controls homozygous for −597A and −174C alleles. These findings suggest a protective role for the latter against IL-6 excess, adrenal hyperactivity, and hyperandrogenism. The −572G/C and −373A(n)T(n) were not associated with hyperandrogenism or with any androgen-related phenotypic trait (249). In conceptual agreement, Mohlig *et al.* (291) recently reported that the heterozygous −174G/C genotype in PCOS patients was associated with lower serum androstenedione levels.

4. IL-6 receptor. This is a heterodimeric receptor consisting of two membrane-bound glycoproteins: an 80-kDa IL-6 binding unit and a 130-kDa IL-6 signal transducer (IL-6 receptor β or gp130). gp130 is a transducer chain shared by other cytokines and is responsible for signal transduction of the chain-ligand complex through the Janus kinase/signal transducer and activator of the transcription pathway (310).

We have recently studied common polymorphisms in both subunits of the IL-6 receptor in a series of 145 hyperandrogenic women and 45 controls from Spain (251). The uncommon

Arg148 allele of the Gly¹⁴⁸Arg polymorphism in the gp130 gene was more frequent in controls compared with hyperandrogenic patients, and controls carrying Arg148 alleles had lower 11-deoxycortisol and 17-hydroxyprogesterone concentrations, a lower response of androstenedione to 1–24 adrenocorticotropin, and an almost statistically significant decrease in free testosterone levels, suggesting that, as occurred for the IL-6 polymorphisms described above, Arg148 alleles in the gp130 gene have a protective effect against androgen excess and adrenal hyperactivity (251). When considering patients and controls as a whole, a microsatellite CA-repeat polymorphism in the 80-kDa IL-6 binding unit locus was associated with obesity. The frequency of the common 149-bp allele was markedly increased in obese women compared with controls, further supporting the involvement of inflammatory genotypes in obesity and related syndromes (251).

Overall, our studies over the past years suggest that chronic inflammation underlies the pathogenesis of functional hyperandrogenism and PCOS, as has been proposed for other disorders associated with insulin resistance, and that proinflammatory genotypes may be involved.

D. Other candidate genes

1. Follistatin. This protein binds to activin, inhibiting its action both *in vivo* and *in vitro* (311). Activin and follistatin are expressed in multiple tissues, including pituitary, ovary, adrenal, and pancreas (312, 313). In the ovary, activin promotes follicular development and inhibits androgen secretion by theca cells (314). Conversely, transgenic mice overexpressing follistatin present with follicular arrest and infertility (315), characteristics frequently found in hyperandrogenic women.

However, the expression of human inhibin/activin subunit, follistatin, type 2 activin receptor mRNAs, and their encoded proteins in ovarian follicles from PCOS patients suggested that an increase in the availability of activin, relative to inhibin, was actually present in the arrested follicles in PCOS patients (316). Moreover, the location of the mRNAs of the follistatin subunits is not altered in PCOS (317).

Initial molecular genetic studies in humans by Urbanek *et al.* (132) suggested evidence for linkage between the *follistatin* locus and PCOS, as cited above. Subsequent studies by these authors (318) have failed to confirm the involvement of the follistatin gene with PCOS in a large multiethnic study. The coding regions and some introns of the follistatin gene were sequenced, disclosing at least 17 polymorphisms; however, 16 of them were rare, making a significant contribution of these variants to the pathogenesis of hyperandrogenism unlikely (318). Moreover, the only common polymorphism found, located in exon 6 but not translated, was not associated with PCOS when correcting for multiple testing, and the authors concluded that contributions to the etiology of PCOS from the follistatin gene, if any, are probably small (318).

In conceptual agreement, no mutations in the follistatin gene have been found in Chinese PCOS patients defined by menstrual dysfunction, hyperandrogenism, and polycystic ovaries (319), and the only mutation found in our series of patients from Spain, a silent G951A variant, was equally distributed in PCOS patients and in healthy women (320).

2. *Thrombophilic factors.* Women with PCOS have increased miscarriage rates, as happens in women with inherited thrombophilic conditions. The secretion of plasminogen activator inhibitor-1 (PAI-1) in adipose tissue is enhanced by inflammatory cytokines and by insulin (321–323). In agreement, the increased circulating PAI-1 levels found in PCOS patients decrease after treatment with insulin sensitizers (324). Homozygosity for 4G alleles of the –675 4G/5G polymorphism in the gene encoding PAI-1, which modulates PAI-1 activity, have been reported in association with obesity (325) and PCOS (326). We have found a similar trend in our series on Spanish women, although the difference in allele frequencies did not reach statistical significance, possibly because of small sample size (229).

Other genetic abnormalities associated with thrombophilia have been studied in PCOS. Tsanadis *et al.* (327) recently reported that the prevalence of antithrombin III, protein S and protein C deficiencies, factor V Leiden, prothrombin G20210A factor, and methylene tetrahydrofolate reductase 677C/T mutations is not increased in Greek patients with polycystic ovaries, menstrual dysfunction, and hyperandrogenism when compared with nonhyperandrogenic controls. Similar results have been found for the methylene tetrahydrofolate reductase variant in Italian women (328).

3. *Microsomal epoxide hydrolase.* Two SNPs, Tyr¹¹³His and His¹³⁹Arg, in the gene encoding the detoxifying enzyme microsomal epoxide hydrolase have been studied in women with PCOS, defined by the presence of polycystic ovaries and hyperandrogenic symptoms (329). Although none of the polymorphisms was associated with PCOS, the presence of the His113-Arg139 haplotype was associated with an odds ratio for PCOS of 2.28 and 95% confidence interval of 1.1–4.8 (329). However, it is unclear how changes in the activity of this enzyme might relate to functional hyperandrogenism and PCOS, and therefore, this result should be considered with caution unless confirmed in future studies.

4. *Bone morphogenetic proteins.* The intraovarian bone morphogenetic protein system is involved in the control of granulosa cell proliferation and cytodifferentiation and plays a role in oocyte development (330). The genes encoding the growth differentiation factor 9 and bone morphogenetic protein 15 have been studied in Japanese women with polycystic ovaries, but no missense mutations have been found in these women (331).

VI. Hyperandrogenism, PCOS, and Survival Advantage

The increasing prevalence of complex metabolic disorders in developed countries raised the possibility that, from an evolutionary perspective, the pathogenetic mechanisms underlying these disorders might have provided survival advantages (332). However, these previously beneficial mechanisms may lead to disease with prolonged life expectancy or when these subjects are exposed to the present lifestyle in Western countries.

As suggested by Witchel *et al.* (333) for congenital adrenal hyperplasia, which is one of the most common inherited disorders with carrier frequencies of approximately 10% in

all world populations studied to date and a relatively common cause of hyperandrogenism in children and adults, the presence of hyperandrogenism in women might have provided survival advantage for these women and their children.

The rapid maturation of the reproductive axis found in these subjects, together with the increase in assertive behavior resulting from increased androgen secretion, might be advantageous during times of environmental stress (333–335). Moreover, the relative infertility of these women could increase the interval between pregnancies, decreasing the birth rate and favoring maternal and infant survival (333). In addition to the lower rate of pregnancies secondary to oligoovulation, pregnancies may also occur at an older age, favoring the survival of these women. In agreement, an early beginning of fecundity is associated with higher mortality rates in animal models (335).

Yet survival advantage may also contribute to explaining the association of hyperandrogenism with other disorders related to insulin resistance. Human metabolism may be genetically adapted to the dominant conditions that have predominated for ages: near-continuous physical activity, a diet rich in carbohydrates and proteins yet poor in fat, and long periods of famine or food shortage (336–338). Survival was therefore favored by a combination of thrifty genotypes and phenotypes, in which insulin resistance played a central role (Fig. 2).

Insulin resistance increases glucose availability for brain metabolism. It also increases salt and water retention and sympathetic tone and induces endothelial dysfunction, favoring an increase in blood pressure, obviously beneficial when trauma occurs. Similarly, the increased coagulability and decreased fibrinolysis associated with insulin resistance are defensive mechanisms against bleeding. But more important is that insulin resistance favors obesity, protecting against starvation, and obesity contributes to a proinflammatory state through the secretion of several cytokines, contributing to the defense against infection, and possibly to the development of functional hyperandrogenism and PCOS.

When the environmental conditions change and access to food is not restricted, significant trauma and epidemics seldom occur, and life expectancy increases markedly, these defensive mechanisms are no longer beneficial, and the price to pay is atherosclerosis and cardiovascular disease (Fig. 2).

For the reasons outlined above, it is not surprising that the genomic variants associated with obesity, type 2 diabetes mellitus, and other disorders in which insulin resistance plays a major role are frequently associated with functional hyperandrogenism and PCOS. However, genomic variants-associated insulin resistance may contribute to hyperandrogenism only indirectly, by inducing insulin resistance and hyperinsulinemia and/or by direct actions at the adrenal or the ovary. For example, TNF- α induces insulin resistance by interfering with IRS-1-mediated insulin signaling (280) and also has reproductive actions that closely resemble those found in patients with PCOS and functional hyperandrogenism, as summarized above (293, 294).

Therefore, the precise elucidation of the mechanisms underlying these associations requires studies of the functional consequences of the genomic variants associated with hy-

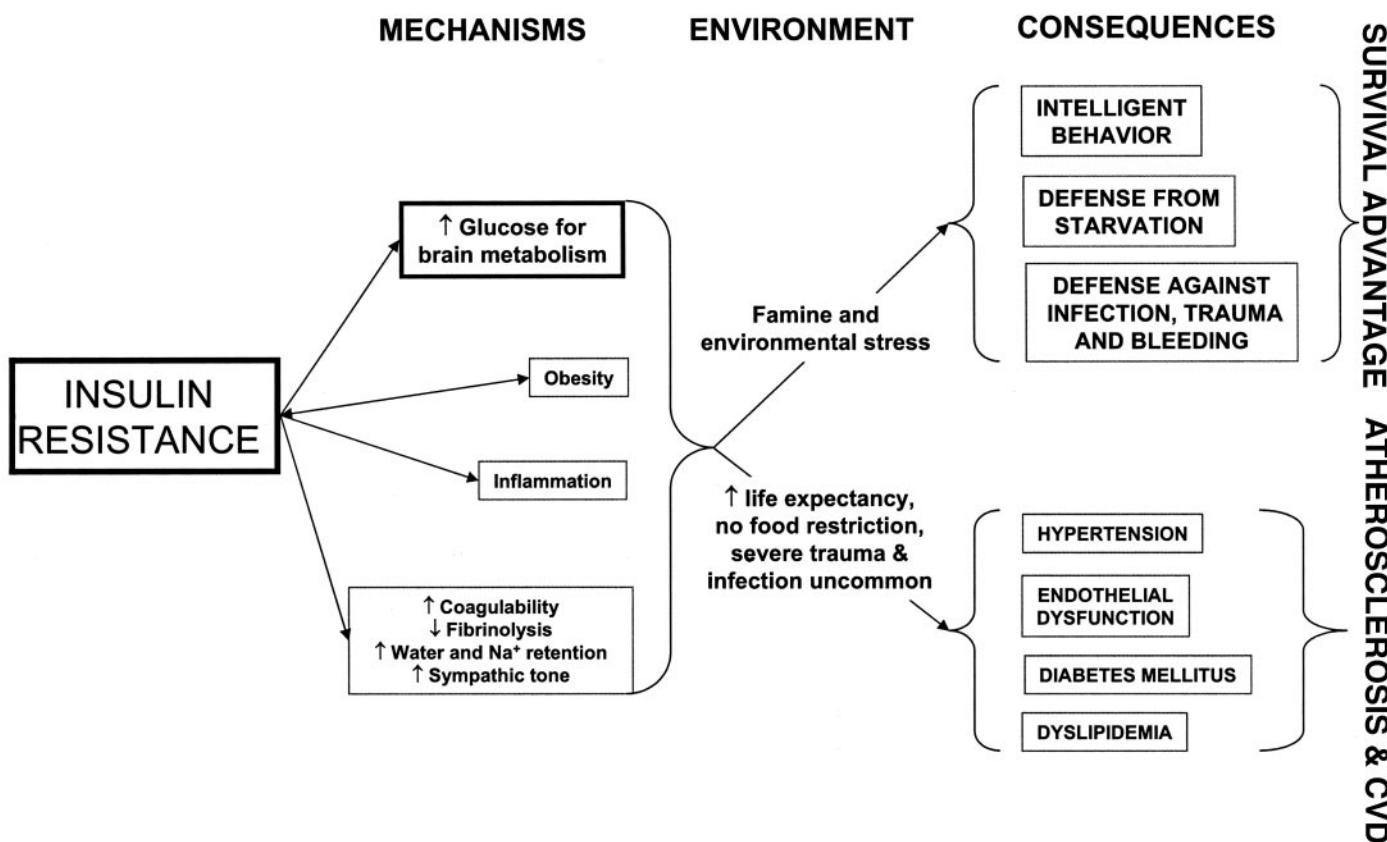


FIG. 2. Insulin resistance, survival advantage, and disease. Insulin resistance and related pathogenic mechanisms may have been selected during evolution because of survival advantage during times of environmental stress. However, with the sudden change in life conditions occurring during the last century in most developed countries, where access to food is not restricted, severe trauma and infection are relatively uncommon, and life expectancy has increased markedly, these mechanisms are no longer beneficial and result in atherosclerosis and cardiovascular disease (332). CVD, Cardiovascular disease.

perandrogenism in different target tissues, especially when some of the genomic variants appear to facilitate insulin resistance and hyperandrogenism, whereas others may protect against these disorders.

At present, the emerging picture for the molecular genetic mechanisms leading to functional hyperandrogenism and PCOS is that of a complex interaction between predisposing and protective genomic variants, and the strong impact of modifying environmental factors including diet, exercise, and lifestyle (Fig. 3).

VII. Explanations for the Lack of Reproducible Association of Hyperandrogenism and PCOS with Molecular Genetic Abnormalities and Genomic Variants

To date, most of the associations between genomic variants and functional hyperandrogenism or PCOS failed to replicate when studied in different populations. An immediate consideration is that most studies conducted to date have been modest with regard to the number of subjects included. A small sample size, leading to a lack of statistical power to detect the modest effects that genomic variants possibly play in the pathogenesis of a complex disorder such as functional hyperandrogenism, might explain the negative

results found in many cases when efforts have been made to confirm previous studies. Although at present there are no doubts about the need of studies with large sample sizes, lack of consistency of the reported findings is not limited to hyperandrogenism and is a recurrent problem in the study of many complex metabolic disorders (339). Therefore, other factors might also contribute to the discrepancies observed when studying candidate genes for hyperandrogenism in different populations, summarized below.

A. Ascertainment issues

One of the essential requirements for the effectiveness of molecular genetic studies is a clear definition of the phenotype under study. This has not been the case for functional hyperandrogenism and PCOS. As an example, the linkage studies cited above (140, 222) of *CYP11A* and *INS* in women from the United Kingdom relied mostly on the use of ultrasonography for the diagnosis of PCOS, and this series included "ovulatory" PCOS patients. On the contrary, a linkage study conducted in the United States relied on the NICHD criteria (132), in which chronic anovulation is strictly required for the diagnosis of PCOS (9). Given the considerable differences in the criteria used to define the phenotype, it is unlikely that the genes associated with the disease would be the same in both studies.

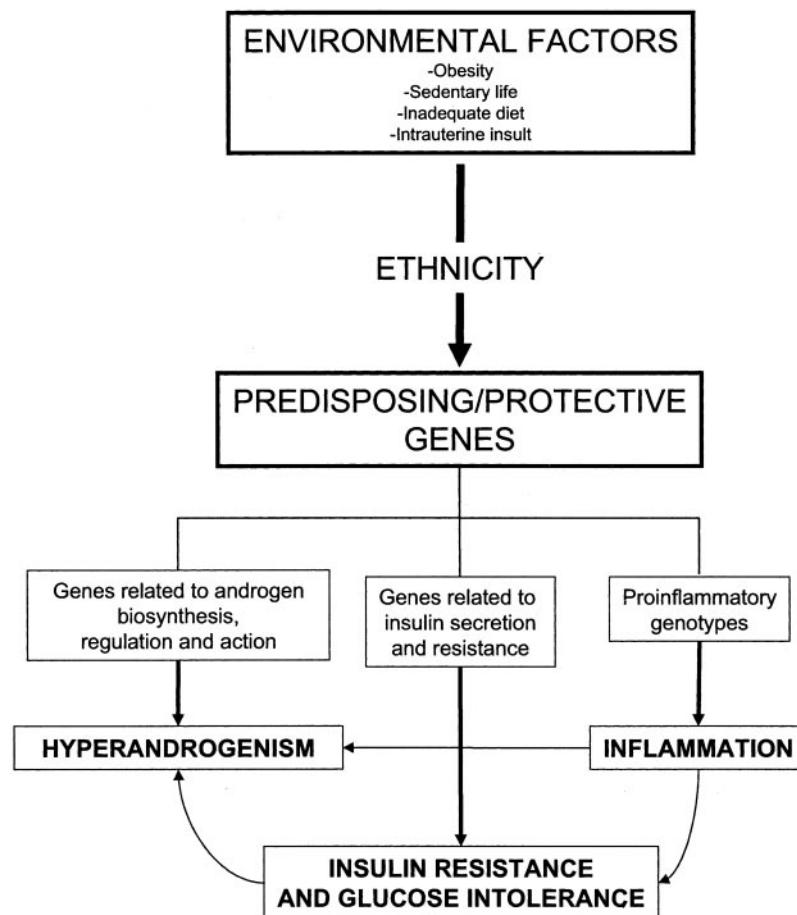


FIG. 3. A unifying hypothesis for the association of hyperandrogenism, inflammation, and insulin resistance. Environmental factors, influenced by ethnicity, act on a delicate balance between predisposing and protective common genetic variants that have been selected during evolution because of previous survival advantage. The genes involved in the pathogenesis of hyperandrogenism may vary depending on the particular and/or ethnic factors that predominate in the different populations studied, providing an explanation for the phenotypic variability of hyperandrogenic disorders.

Moreover, the spectrum of disorders covered by the criteria derived from the Rotterdam Consensus Workshop (11, 12) is even broader than those included with the NICHD definition: PCOS would be diagnosed not only in women presenting with hirsutism, hyperandrogenemia, and anovulation, but also in patients presenting with anovulation and polycystic ovaries but no clinical and/or biochemical evidence of hyperandrogenism. Therefore, these revised criteria are unlikely to be of significant advantage over previous ones with respect to molecular genetic studies. And to further complicate the search for PCOS-related genomic abnormalities in family-based studies, the male PCOS phenotype is still uncertain.

Because of the heterogeneous and syndromic nature of PCOS, it would be more helpful for molecular genetic studies to use criteria oriented toward the identification of specific clinical, reproductive, and metabolic traits associated with hyperandrogenism. This would require an important effort to identify and especially to standardize the methods used to identify these traits in large populations such as those needed for family-based or case-control designs.

Instead of trying to reach a consensus on how to diagnose precisely a disorder that is heterogeneous by definition, the practical issue would be to standardize the definitions and methods used to identify specific traits such as insulin resistance, overweight, visceral adiposity, dyslipidemia, hirsutism, acne, oligoovulation, and many others that characterize or are frequently found in hyperandrogenic women.

Given the apparently multigenic etiology for functional hyperandrogenism and PCOS, this approach would permit a more precise definition of the kind of hyperandrogenic patients included in the different molecular genetic studies. It would facilitate well-sized multicollaborative studies and thereby increase the probability of success in identifying genomic variants and abnormalities related to these particular traits that might be used as diagnostic and/or therapeutic targets in the future. It is hoped that scientific societies that address the study of hyperandrogenism, such as the recently created Androgen Excess Society (<http://www.androgenexcesssociety.org>), will serve as an adequate forum where these efforts in standardization could be made.

In addition to the problems of defining the PCOS phenotype, sampling issues also should be considered. For family-based studies, a common sampling procedure is to collect from an affected proband with at least one or two affected relatives, instead of the ideal, but rarely performed, procedure of selecting families from the population at random (340). Nonrandom ascertainment makes it more likely that families with multiple PCOS members enter the study than families with no affected relative, resulting in biased heritability estimates (340, 341). Another common source of error is that the affected status in relatives of the proband is typically determined on the basis of his or her report because of constraints in time and resources (340). Moreover, affected subjects may be more likely to be aware of the diagnosis in their relatives than nonaffected subjects (340), or more likely

to misinterpret the symptoms of their relatives (340), such as considering the presence or absence of hirsutism as the equivalent of having or not having PCOS.

B. Involvement of environmental factors

The interactions between genetic and environmental factors are essential for the comprehension of the pathogenesis of common complex disorders (342). The precise knowledge of these interactions requires long-term studies analyzing the impact of different environmental factors in specific subgroups of patients, because controlling all the confounding environmental variables is extremely difficult (342).

Environmental factors such as weight gain may trigger the development of PCOS in predisposed women, as occurs in other complex metabolic disorders in which insulin resistance plays a major role. The identification and precise delimitation of the contribution of the environmental influences triggering the development of functional hyperandrogenism and PCOS may direct the search for the specific proteins and/or genomic variants involved to the metabolic pathways influenced by these environmental factors.

However, the environmental factors contributing to complex metabolic disorders may change depending on the population studied, because diet, exercise, and lifestyle have wide ethnic variations. Therefore, it should not be surprising that the genomic abnormalities contributing to these disorders may also change depending on the environmental conditions (*i.e.*, the genes contributing to PCOS in obese sedentary women from a Western country are probably different from those involved in the PCOS phenotype of lean women from the Mediterranean area or from Asia). Finally, to further complicate the study of complex metabolic disorders, the phenotype changes during the life of the affected subjects as age advances. Therefore, different phenotypic traits may not be present when these women were phenotyped, but became apparent later in life, constituting one more confounding factor that is especially difficult to control in molecular genetic studies.

C. Possible polygenic etiology for functional hyperandrogenism and PCOS

It has been suggested that the phenotypic heterogeneity observed in PCOS patients, even within the same family, could be attributed to the interaction of a small number of genes with one another and with environmental factors (18, 22, 33). Furthermore, given the large number of genomic variants found associated with functional hyperandrogenism and PCOS to date, the emerging picture may be that of a complex metabolic disorder resulting from small predisposing or protecting effects arising from the interaction of multiple genomic variants and several environmental factors.

Even if a more precise definition for hyperandrogenic phenotypes was used, and that has not been the case, the classic requisite of replication of linkage or association of a genomic abnormality with monogenic diseases may not be applicable for complex disorders because the functional consequences of the genomic variant may be only apparent in certain pop-

ulations or when a particular environmental factor is present (339). However, it is important that internal replication of findings is provided in larger series, because this might reveal false-positive associations reported in preliminary studies when limited sample sizes were studied.

Nowadays, it is technically feasible to genotype large series of individuals for multiple genomic variants, allowing whole-genome scans and high-throughput candidate gene analysis. These approaches will disclose reliable information of the relative contribution of these genomic variants to functional hyperandrogenism and PCOS and will facilitate the study of gene to gene and gene-environment interactions that probably contribute to the development of these prevalent disorders.

Finally, to avoid spurious associations from being considered causative of any disease-associated trait, every effort should be made to demonstrate *in vivo* or *in vitro* a functional consequence of the associated genomic variant that might reasonably account for the contribution of the variant to the disorder or its associated traits.

D. Limitations of the genetic techniques used to date

As discussed previously, the molecular genetic studies regarding PCOS and functional hyperandrogenism conducted to date had important limitations, especially because adequately sized whole-genome scans and large case-control association studies are still lacking, and therefore associations with genomic variants that have small effects on hyperandrogenism might have been missed by these studies.

Another source of confusion is the fact that quality control of genetic data has not been as strict as that applied to other methods used in clinical research or even in routine clinical practice. Genetic data are usually obtained from a single measure, and reliability and reproducibility of these analyses might be a problem, because genotyping errors may severely bias the estimates of genetic studies (339, 343). Although departure from the Hardy-Weinberg equilibrium may be useful for the detection of these genotyping errors (344), and although modern methods incorporate models of typing error (343, 345), efforts in standardization of these techniques should be made in the future (339).

VIII. Future Perspective: Functional Hyperandrogenism and PCOS in the Age of “Omics”

The suffix “omics” is being applied to recent technologies that are exponentially increasing our knowledge of human biology. Perhaps at present the most developed one is genomics.

Genomics aims to map, sequence, and analyze all the genes and their products in the genome, with the final intention of providing the complete and accurate DNA sequence of an organism (56, 346). The number of genes in the human genome is in the order of 35,000, and because of exon shuffling, alternative splicing, and posttranslational modifications, as many as 100,000 different proteins may be encoded in the human genome. Therefore, identification of all the genes and proteins of the human organism and their interactions requires an enormous effort.

Genomics is in constant evolution, and more specific subspecialties are being developed, such as functional genomics. Its aim is the identification of the biological functions of genes and their products, and how they interact with the environment in health and disease (347). To date, functional genomics has contributed to unravel the mechanisms of many diseases (348–350), and the genomic approach might be especially adequate for the study for complex polygenic disorders, given that traditional molecular genetic approaches have not been successful to date (351).

Genomic techniques, such as differential gene expression analyzed by DNA microarrays, allow the identification of genes that are differentially overexpressed or suppressed in patients compared with controls. This approach has the advantage over molecular genetic analyses in that the result integrates the presence of molecular genetic abnormalities with both gene-gene and gene-environment interactions. Therefore, the genes identified can be considered potential candidates to explain the disorder and also potential diagnostic and therapeutic targets. Recently, comparison of gene expression in cultured theca cells from PCOS patients and controls using DNA microarrays identified the genes encoding aldehyde dehydrogenase 6 and retinol dehydrogenase 2 as candidate genes for PCOS (352). These factors play a role in all-trans-retinoic acid biosynthesis and the transcription factor GATA6, which increase the expression of 17 α -hydroxylase (352), a characteristic of PCOS theca cells (137). In the near future, undergoing studies using DNA microarrays to compare the expression profiles of tissues such as adipose tissue and muscle, which are essential for the development of insulin resistance, will undoubtedly contribute to the identification of candidate genes in hyperandrogenic women.

But given that gene expression and protein concentration and activity are poorly correlated (353), modern techniques have been developed to study the “proteome” of a cell, tissue, or organism. Proteomics allows large-scale analysis of proteins, including their relative abundance, distribution, post-translational modifications, functions, and interactions with other molecules (347). For example, it is possible to examine the expression of more than 1000 proteins by coupling mass spectrometry technology with several separation methods. Proteomic analysis of tissues involved in the pathogenesis of functional hyperandrogenism and PCOS, such as ovarian theca and granulosa cells, adrenal cortex, sc and omental adipose tissue, and muscle, are essential for our understanding of the complex interactions between the genome and the environment that underlie these disorders.

Ultimately, the identification of genes and proteins related to functional hyperandrogenism and PCOS, and their interactions with the environment, will be an essential step for the development of more precise diagnostic techniques, the identification of new therapeutic targets, and the identification of particular individuals that, because of their genetic background, may be predisposed to certain complications of the syndrome or respond differently to available treatments.

IX. Summary

Functional hyperandrogenism and PCOS appear to be complex multigenic disorders, arising from the interaction of

predisposing and protective genetic variants that might have been selected during evolution because of a previous survival advantage, with environmental influences that play an important role in the expression of the hyperandrogenic phenotype.

Among others, genomic variants in genes pertaining to the regulation of androgen biosynthesis, insulin resistance, metabolic syndrome, and proinflammatory genotypes are involved in the genetic predisposition to functional hyperandrogenism and PCOS. Progress in this area requires adequately sized multicenter collaborative studies in which modifying environmental factors such as ethnicity, diet, and lifestyle are identified with precision.

In the future, classic molecular genetic techniques such as linkage analysis in the form of a whole-genome scan and large case-control studies, as well as modern genomic and proteomic approaches, will hopefully provide new insights into the pathogenesis of functional hyperandrogenism and PCOS, with the ultimate aim of improving the prevention, diagnosis, and treatment of these prevalent disorders.

Acknowledgments

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The effectiveness of lifestyle training program promoting adolescent health with polycystic ovarian syndrome: A study protocol for a randomized controlled study

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Abstract:

BACKGROUND: Lifestyle training is of a key important in adolescent age for better life in the future. Healthy lifestyle in adolescents can management of any disease such as diabetes and polycystic ovarian syndrome (PCOS). Schools can provide an important environment to identify and change the lifestyle of students. The aim of this protocol is designing and evaluating the effectiveness of school-based lifestyle training program improving the PCOS of adolescents.

MATERIALS AND METHODS: A cluster-randomized controlled trial will be conducted to examine the effectiveness of school-based lifestyle training program in 16 to 18 years old adolescent girls. The healthy lifestyle program will be designed by modification of behavioral habit, dietary intake, and physical activity and educated in eight sessions for adolescents and one session for parents in the intervention groups with sixty participants.

RESULTS: Changes in primary and secondary outcomes in PCOS and healthy adolescents before and after intervention in the intervention and control groups will be analyzed for evaluation effectiveness by one-way ANOVA or other nonparametric equivalents.

CONCLUSION: The current study will provide information on the effectiveness of school-based lifestyle training programs for adolescents. With increasing numbers of PCOS at risk for long-term and/or late effects of treatment and other chronic diseases, efforts for promoting the healthy lifestyle of this important group are urgently needed. This lifestyle program may provide valuable information relating to the development of other healthy lifestyle interventions for PCOS and result in appropriate behavior change and self-management strategies.

Keywords:

Adolescence, education, lifestyle, polycystic ovarian syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is a long-term recognized, and complex, heterogeneous familial disorder.^[1] Some clinical symptoms of this multifactorial syndrome, including hyperandrogenism and chronic anovulation initially appears

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in puberty^[2]. Insulin resistance seemed inherent in PCOS independent of obesity;^[3] regardless of weight, PCOS can present in each girl with family history.^[4] Researchers in an international consortium update in PCOS adolescents reported that lifestyle modification is a first step PCOS treatment in adolescents.^[5]

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Lifestyle modification based on weight loss and increased activity is useful, especially in obese and overweight girls with PCOS.^[6] Even 5%–10% weight loss in obese patients has been beneficial effects. The benefits of lifestyle education for PCOS patients include improved clinical, hormonal, metabolic parameters of PCOS, improved mood and quality of life, body composition, sleep, self-esteem, depression, anxiety, and tiredness in PCOS patients.^[7] Although healthy lifestyle has positive effects on PCOS girls with obesity and overweight, these effects in normal weight or underweight adolescents are not proven.^[8]

Several studies in some countries investigated lifestyle education for PCOS management in adolescent girls with different significant outcomes.^[9-11] Parent role in achieving a healthy lifestyle by their adolescent is very important, and for this participant, facilitator and barrier should be considered.^[12] Next to the parents, schools are the major center for providing the guideline that prepares adolescents for their healthy lifestyle.^[13-15] The lifestyle intervention in PCOS including dietary, physical activity, and behavioral habits strategies need at least 6–12 months to be effective.^[16]

A variety of balance dietary approaches could be recommended to reduce dietary energy intake and induce weight loss in obese and/or overweight women with PCOS.^[17] Moreover, an energy deficit of 30% or 500–750 kcal/day could be suggested for PCOS women.^[18] Since there has been no evidence for specific diet in PCOS patients, a healthy dietary intake with energy balance for PCOS adolescents is recommended.^[19] Usage by taking some herbal medicines in Iranian women can help improving the symptoms for short time.^[20]

According to the World Health Organization, an adequate daily physical activity from 60 to 90 min is recommended. In particular, all young people should be active for at least 60 min each day (including at least 3 days a week and 30 min of structured physical activity or around 3000 steps).^[16] The presence of lifestyle guideline for adolescents based on indigenous culture and native language in each country can be an important step in the effectiveness of this type of intervention,^[21] however, the information alone is not sufficient to create changes in health behaviors. Information and awareness are the first step of healthy lifestyle training but not the final step toward behavior change.^[22]

Applying behavioral strategies, such as life skills reinforcement (self-monitoring, problem-solving, and coping with stress) can be effective in the elimination of bad habits during adolescents.^[23] The individual must be motivated and prepared to make health behavior

change.^[24] Without motivation and preparation for change, health behavior changes cannot be maintained over time.^[25] Motivational interviewing may be a good strategy to support adolescents in making decisions that will help them appropriately to manage their weight.^[26]

Although some studies stated that lifestyle along with weight loss can be effective in improving PCOS problems in adolescents^[9,10,27] but in another articles the effectiveness of this treatment was not confirmed.^[28,29] The researchers decided to design and evaluate school-based lifestyle training program in Iranian adolescents for managing of PCOS.

Objectives

- Design of a school-based lifestyle training program in adolescents for PCOS management
- Education of school-based lifestyle training program in intervention groups
- Evaluation of the primary outcomes before and after school-based lifestyle training program
- Evaluation of the secondary outcomes before and after school-based lifestyle training program.

Materials and Methods

Study design and setting

The methodological approach for lifestyle training in adolescents is a cluster-randomized clinical trials study. The design, conduct, and reporting of this study will adhere to the Consolidated Standards of Reporting Trials guidelines.

This study will be carried out in three phases: (1) design of a school-based lifestyle training program, (2) education of this program, and (3) evaluation of this program by comparison of clinical assessment 6 and 12 months after intervention [Figure 1]. This study will be done on high school girls in Tehran, Iran.

Study participants and sampling

Single girls between the range of 16 and 18 years old

Procedure

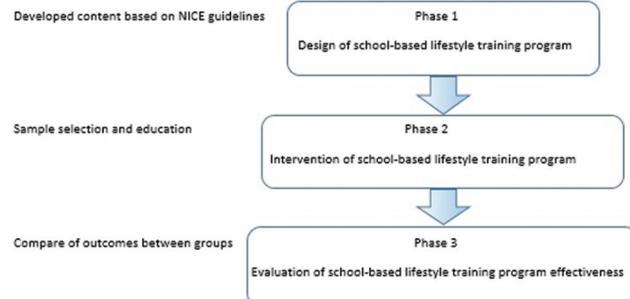


Figure 1: Study visual design

without sexual relation that at least 2 years has passed from their juvenile menarche and been healthy in terms of all diseases, including liver, kidney, thyroid, mental, heart, and skeletal diseases, are included in this study. They no use any drug, smoke, and alcohol. They should not exercise professionally or attend sporting teams, or have a specific diet. PCOS adolescents based on the American Society for Reproductive Medicine criteria will be diagnosed and included in the study. Finally, healthy and PCOS adolescents, regardless body mass index, will be included in the study.

Adolescents who for any reason will fail to attend a one-third of the classes hold at the school or will be affected by a specific illness or need to take a particular drug after entering the plan are excluded from the study.

Participants will be recruited via school screening methods, including referrals by health professionals to Endocrine Sciences Laboratory Center at Shahid Beheshti University of Medical Sciences for assessment. Our strategies for achieving adequate participant enrollment to study are using student medical history that has been saved by school health educators.

Allocation will be done by stratified randomization by cluster method. In this study, the unit of randomization will be a school group in four geographical directions (west, east, south, and north) of Tehran, Iran. The researcher will use a random number table to allocate consenting school to intervention or control group, stratified by girls' high school code. Two schools will be selected in each direction (one school for the intervention and one school for the control). Finally, eight high schools will be enrolled in this study. Girls and their parents will be asked to read and sign an informed consent form before attending the project. After participants enrolled in the study, they will be referred for tests: blood tests and ultrasounds. They should also submit anthropometric indices, physical activity status, and dietary intake status information.

We will recruit 60 healthy adolescent girls and 60 PCOS adolescent girls, which will be divided into four groups: intervention groups (30 PCOS + 30 healthy) and control groups (30 PCOS + 30 healthy) [Figure 2]. One researcher (S.A) will generate the allocation sequence, another researcher (F.R.T) in endocrine research will enroll participants and will assign participants to interventions, and finally, S.A will hold a school-based lifestyle training program. In this study, the data analyzer will be blinded only after the assignment to interventions. All students in four groups are coded by ID number.

Adolescent girls in the intervention group will be school-based trained and control groups will receive only

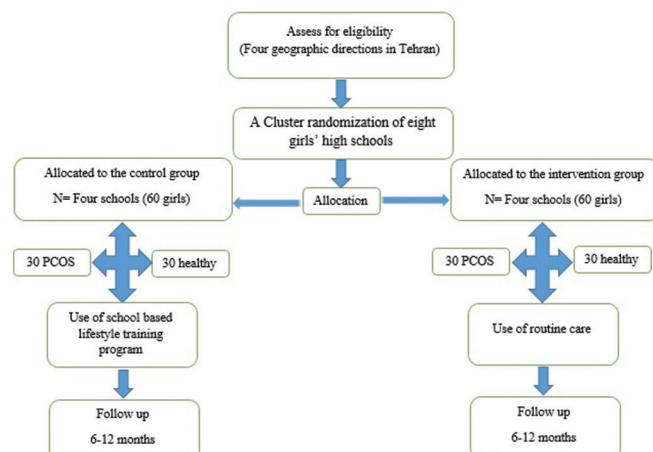


Figure 2: Consort diagram of study

routine care. The draft content of the healthy lifestyle program will be prepared in the first phase of the study. The content of lifestyle in intervention adolescents for PCOS management will be developed based on the National Institute for Health and Care Excellence guideline [Figure 3] and literature review. The program will be developed by a group of experts (reproductive health specialist, gynecologist, midwife, health psychologist, and nutritionist). The three main goals of the intervention are to increase physical activity, healthy diet, and change of behavior habit. The design of physical activity content was based on minimum facility and equipment availability at school or community. Each standard aerobic exercise is explained in terms of duration, repetition, and intensity. Traditional sports are also considered. The healthy diet regime is based on the consumption of essential nutrients, such as fluid, macronutrients, micronutrients, and adequate calories including five main food groups. The usage of supplements and herbal drugs will be considered. Change of behavior habit designed is based on life skill and motivational reinforcement in adolescents for daily energy balance.

Lifestyle training in high school will be conducted face to face, teaching in 45-min sessions of lecture and question-answer for eight training classes every week. The educator is obliged to teach the educational content based on the behavioral goals set for each session by the use of movie, PowerPoint, speech, and peer review of teaching.

A pamphlet for adolescents and their parents will be prepared and provided to them. Motivational interviewing strategy will be used for lifestyle training in school, thus asking open-ended questions, reflection statement, affirming response, and summaries. An educational session is also held for parents to participate in home to accompany the adolescent in maintaining a healthy lifestyle.

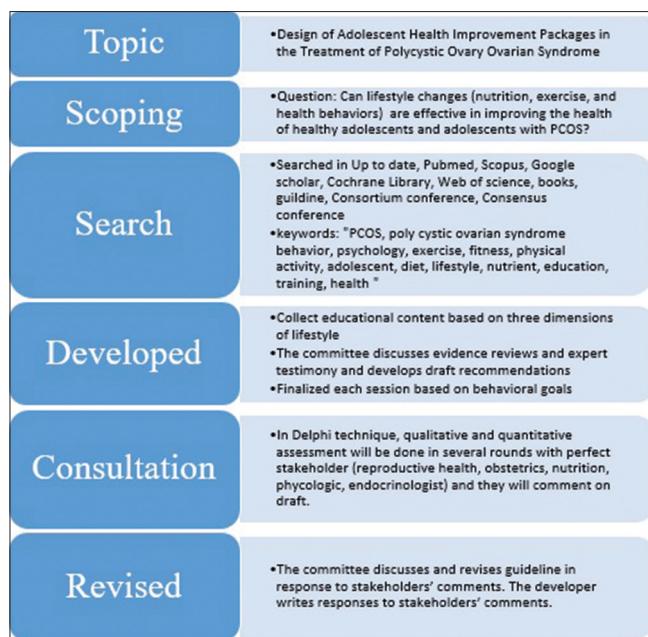


Figure 3: Stage of developed content of school-based lifestyle training program based on NICE guideline

Participant evaluation of the educational program and sessions will be measured via a participant program evaluation form (to be completed by participants at the final educational session). The program evaluation form will consist of nine questions from the course evaluation module of the Health Education Impact Questionnaire.^[30] Participants in the intervention and control groups were required to take hormonal medications at any time during the study, they could be excluded from the study, and there was no interference with their treatment.

Data collection tool and technique

In this study for evaluation of program effectiveness, primary outcomes (anthropometric indices, clinical symptom, physical activity status, and dietary intake status) will be compared at baseline, 6, and 12 months after intervention and secondary outcomes (blood biomarkers and Sonography factors): will be compared at baseline and 12 months after intervention.

In anthropometric index measurement, weight, height, waist, and hip circumstance will be submitted. Participants will be relaxed for 15 min before the measurements are taken. Body weight (to nearest 0.1 kg) and height (to nearest 0.01 m) will be measured while subjects had light clothing and stood barefoot, with eyes directed straight ahead.^[31] The waist circumstance will be obtained by inelastic tape measure, with an accuracy of 0.1 cm, directly on the skin at the umbilicus level.^[32] Hip circumference will be measured at the point yielding the maximum circumference over the buttocks using a tape measure to measure to the nearest 1 cm at the widest part of the hips.^[33]

In clinical symptom measurement, menstrual cycle regularity, hirsutism status will be submitted. Participants who are 1–3 years postmenarche and their menstrual cycles are <21 days or more than 45 days will be considered an irregular menstrual cycle. Furthermore, more than 3 years postmenarche adolescents whose menstrual cycles are <21 or more than 35 days or have <8 cycles per year will be considered irregular.^[34] The Ferriman–Gallwey scale will be used for hirsutism status; a score of 1–4 is given for nine areas of the body. A total score <9 is considered normal, a score of 9–15 indicates mild hirsutism, and a score >15 indicates moderate or severe hirsutism.^[35]

Physical activity will be measured using the International Physical Activity Questionnaire (IPAQ). IPAQ has undergone extensive reliability and validity testing in 12 countries.^[36] This instrument has acceptable measurement properties for use in many settings and is specifically designed for population-based prevalence studies of physical activity. Dietary intake will be measured using a 24-h recall questionnaire.

Blood biomarkers (prolactin, testosterone, dehydroepiandrosterone sulfate, luteinizing hormone, follicle-stimulating hormone, sex hormone-binding globulin, thyroid-stimulating hormone, T4, triglyceride, low-density lipoprotein, high-density lipoprotein, anti-Mullerian hormone, and fasting blood sugar) will be measured in the Research Institute for Endocrine Sciences Laboratory Center at Shahid Beheshti University of Medical Sciences with blood sample before and after 12 months after intervention. Participants without oligomenorrhea will be referred to laboratory test in the follicular phase of menstrual cycle with 8 h fasting.

Sonography factors will be measured by one sonographer via transabdominal ultrasound, the usage of probes with 8 MHz, in Research Institute for Endocrine Sciences Laboratory Center at Shahid Beheshti University of Medical Sciences. Participants without oligomenorrhea will be referred to this center in the follicular phase of menstrual cycle. Sonography factors will include three dimensions and volume of each ovary and endometrial thickness.

It should be noted that all clinical tests have been performed at the Endocrine Research Institute of Shahid Beheshti University of Medical Sciences and no cost will be imposed on students.

The sample size was calculated in order to detect, with at least 90% power, and 95% certainty, and 0.05 level of statistical significance. Based on this formula, sample size was calculated to be 56 for intervention and 56 for control. Due to the follow-up duration time (12 months),

and considering the 20% attrition of sample, finally 60 samples will be assumed for each group. Data will be entered into IBM SPSS Statistics 25 (Chicago, IL, USA).

Ethical consideration

Ethical approval was obtained from the Ethics Committee of Shahid Beheshti University of Medical Sciences (reference number IR.SBMU.PHARMACY. REC.1397.100). Students and parents gave written active informed consent for participation of the student.

Results

Changes in primary and secondary outcomes in PCOS and healthy adolescents before and after intervention in the intervention and control groups will be analyzed for evaluation effectiveness by one-way ANOVA or other nonparametric equivalents.

Discussion

The current protocol describes a study that will investigate the design and effectiveness of school-based lifestyle training program targeting healthy lifestyle to deal with improving behavioral habit promoting dietary intake and physical activity in adolescents for PCOS management. The healthy lifestyle program meets a current gap in the provision of care to PCOS women during the adolescent phase of life. A healthy lifestyle is not only beneficial for obese or overweight adolescents but also protects normal or underweight adolescents against inherited diseases such as PCOS, diabetes, and cardiovascular disease in the future,^[37] and prevention is a cost-effective strategy for adolescents and its benefits are long-lasting.

It is of crucial importance that the school environment can provide students with competition and motivation interventions to help them for maintaining a healthy lifestyle. Lifestyle education at school makes school staff more sensitive to the health of adolescents and, as a result, oversees the school's food environment.^[38]

Training of lifestyle program focuses on important behavior strategy via motivational interviews that have the potential to address long-term and late effects. It is important that the educators have a good understanding of the interviewee's stage of readiness to make a change in behavior.^[24] Although the benefits of a healthy lifestyle intervention have been documented in many studies and suggested as a scientific fact for the treatment and prevention of PCOS,^[39] There are still many challenges regarding treatment of PCOS, especially in lean or normal weight adolescents. The best training time, the best training style, and the best training place which will be most effective on lifestyle change are challenging in other scientific studies.^[40,41]

If this study program works, it can become one of the lifestyle education guidelines for improving health in adolescent girls with PCOS.

Limitation and recommendation

Limitations of the study include the reliance on self-report data on adolescents in terms of physical activity and dietary behavior. A novel approach of the program is the emphasis on self-management constructs and training in socioeconomic variations in one metropolis and comparison of clinical assessment in health and PCOS women into four groups for control of several confounders. There is further potential for this program to be done school based. If this lifestyle program works, it can become one of the lifestyle education guidelines for improving health in Iranian adolescent girls with PCOS.

Conclusion

The current study will provide information on the effectiveness of school-based lifestyle training programs for adolescents. With increasing numbers of PCOS at risk for long-term and/or late effects of treatment and other chronic diseases, efforts for promoting the healthy lifestyle of this important group are urgently needed. This lifestyle program may provide valuable information relating to the development of other healthy lifestyle interventions for PCOS and result in appropriate behavior change and self-management strategies.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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The Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (PCOSQ): a validation

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BACKGROUND: We wished to evaluate the psychometric properties of the Polycystic Ovary Syndrome Questionnaire (PCOSQ), a questionnaire developed to measure the health-related quality of life (HRQoL) of women with polycystic ovary syndrome. **METHOD:** To assess reliability and validity, women recruited from an outpatient gynaecology clinic at the Jessop Wing, Royal Hallamshire Hospital, Sheffield completed two copies of the PCOSQ and the Short Form-36 (SF-36). Secondary factor analysis was carried out to verify the composition of the dimensions. Semi-structured interviews were conducted to assess face validity. **RESULTS:** Of the 92 women who consented, 82 women (89%) returned questionnaires at time 1, and 69 women (75%) returned questionnaires at time 2. All five PCOSQ dimensions were internally reliable with Cronbach's α scores ranging from 0.70 to 0.97. Intra-class correlation coefficients to evaluate test-retest reliability were high (range 0.89–0.95, $P < 0.001$). Construct validity was demonstrated by high correlations for all comparisons of similar scales of the SF-36 and PCOSQ (0.49 and 0.54). Acne was identified as an important area of HRQoL missing from the questionnaire. **CONCLUSIONS:** The PCOSQ is a reliable instrument for measuring the HRQoL in women with PCOS. However, the validity of the questionnaire needs to be improved by incorporating a dimension on acne into the instrument.

Key words: health-related quality of life/health status/polycystic ovary syndrome/psychometric properties/questionnaires

Introduction

Polycystic ovary syndrome (PCOS) affects 5–10% of women in the developed world, making it the most common endocrine disorder among women of reproductive age (for review see Franks, 1995; Solomon, 1999). It is typically defined as the association of hyperandrogenism with chronic anovulation in women without specific underlying disease of the adrenal or pituitary glands (Franks, 1995). PCOS is diagnosed on the clinical picture, supported in some women by biochemical abnormalities and/or polycystic ovaries on ultrasonography (Zawadski and Dunaif, 1992).

The symptoms typically associated with PCOS—amenorrhoea, oligomenorrhoea, hirsutism, obesity, subfertility, anovulation and acne—can lead to a significant reduction in quality of life. For example, hirsutism has been shown to cause marked psychological stress (Sonino *et al.*, 1993) and infertility issues can cause tensions within the family, altered self-perception, and problems at work (Paulson *et al.*, 1988; Downey *et al.*, 1989). Despite this, a recent systematic review revealed that limited research had been carried out to assess the impact that the symptoms and associated treatments for PCOS

have upon the quality of life of women with the condition (Jones *et al.*, 2002).

Health-Related Quality of Life (HRQoL) is a multidimensional, dynamic concept that encompasses physical, psychological and social aspects that are associated with a particular disease or its treatment (Naughton and McBee, 1997; Colwell *et al.*, 1998). Although HRQoL measurement has an important role in evaluative research, the reliable assessment of quality of life depends upon the psychometric properties of the questionnaire (i.e. the tests underlying the construction and evaluation of the questionnaire) and the statistical methods employed to analyse and interpret the data (Fayers and Machin, 2000). It is important therefore that any HRQoL questionnaire to be used is based upon these psychometric properties. Although there are many tests which can be performed to evaluate these properties, the general consensus is that they should be reliable, valid and sensitive to change (Nunally, 1978).

At present, one reason for the limited research on the impact of PCOS upon quality of life may be because no validated health outcome measure exists to measure the health status of

women with the condition. One disease specific questionnaire has been developed, the Polycystic Ovary Syndrome Questionnaire (PCOSQ) (Cronin *et al.*, 1998). It contains 26 items, measuring the following five areas of HRQoL: emotions (eight items, e.g. moody as a result of having PCOS?), body hair (five items, e.g. growth of visible hair on chin?), weight (five items e.g. had trouble dealing with your weight?), infertility problems (four items, e.g. concerned with infertility problems?) and menstrual problems (four items, e.g. irregular menstrual periods?). However, only the content validity of the instrument had been evaluated, thus preventing its use in clinical settings and limiting the research that can be carried out to evaluate the impact of PCOS-associated symptoms and their treatment upon quality of life. While generic questionnaires exist to measure HRQoL, such as the SF-36, they may not be sensitive enough to measure changes in specific illnesses as they were designed to measure health status across a wide variety of diseases (Streiner and Norman, 2000).

Consequently, the aim of this study was to evaluate the other psychometric properties of the PCOSQ, in particular the reliability, validity and factor structure of the domains when assessing the HRQoL in women with PCOS.

Materials and methods

Ethical approval for this study was obtained from the South Sheffield Research Ethics Committee.

A total of 186 women of reproductive age with PCOS was recruited from a gynaecology clinic at the Jessop Wing, Royal Hallamshire Hospital, Sheffield. We defined the inclusion criteria as two out of three of the following: a physical symptom, a biochemical abnormality or polycystic ovaries visualized on ultrasound scan (Lewis, 2001). Physical symptoms included hirsutism, oligo/amenorrhoea, infertility, body mass index $>28 \text{ kg/m}^2$ or acne (Heineman, 1997). Biochemical abnormalities included an LH/FSH ratio >1.5 , a testosterone level >2.0 or sex hormone binding globin <30 (Balen, 1999). Women were excluded from the study if they had another major illness that substantially influenced their quality of life or another cause of androgen excess, e.g. congenital adrenal hyperplasia. The patients' notes were reviewed to identify those who met the study inclusion criteria, from which 172 women were eligible. These women were sent a consent form and a letter inviting them to participate, to which 92 (53.5%) responded.

The PCOSQ was then administered by postal survey to the 92 women who had consented (time 1). Included with the questionnaire was the SF-36 (Ware *et al.*, 1992). The SF-36 was used for two reasons. First, it has been argued that different health status measures (ideally generic and disease-specific health questionnaires) should be used in studies concerned with quality of life measurement (Fitzpatrick *et al.*, 1993). Second, it was necessary to include another instrument to evaluate the construct validity of the PCOSQ.

Construct validity is a powerful measure of evaluating the validity of an instrument (Kline, 1986). It is usually evaluated by testing the instrument against hypotheses concerning the scores in the test (Kline, 1986). The test is said to have demonstrated construct validity if the hypothesis is supported but poor construct validity if it is rejected (Kline, 2000). In the absence of another disease-specific PCOS questionnaire, the SF-36 was chosen. It is a well-validated generic questionnaire (Kosinski *et al.*, 1999) and contained two scales which could be used to help evaluate the construct validity of the PCOSQ.

A second copy of the PCOSQ and SF-36 was also included in a sealed envelope and respondents were requested to complete the second copies 3–6 days after they had completed and returned the first (time 2). This was to evaluate the test-retest reliability of the questionnaire. Test-retest reliability (i.e. how stable the questionnaire is over time) is fundamental if the purpose of the instrument is to measure outcome (McDowell and Newell, 1996). Usually a test is administered to a set of subjects on two occasions (given that there has been no change during this time) and then the scores obtained from the test and the retest are correlated (Kline, 1986). A 'change' letter was also included in the sealed envelope for the respondent to report any important changes in their health status. This was because test-retest reliability would only be analysed on those patients who reported 'no change' to their health status during that time.

Face validity is concerned with how appropriate, relevant and understandable items on a questionnaire are to the focus or aim of the questionnaire (Jenkinson and McGee, 1998). Although on its own, face validity does not ascertain the true validity of a questionnaire, it is important to establish as it can improve the co-operation of respondents completing a questionnaire (Kline, 2000), identify any ambiguities in the wording of items (Jenkinson and McGee, 1998) and identify any irrelevant or missed-out items.

To check the face validity of the PCOSQ, individual interviews with 12 women with PCOS recruited from an outpatient gynaecology clinic at the Jessop Wing Hospital, Sheffield were carried out. These explored whether the PCOSQ was addressing the relevant issues regarding the impact of PCOS upon the health status of women suffering from the condition. This sample size was determined at the point where no new issues emerged regarding the face validity of the questionnaire (Peto *et al.*, 1998).

Analysis

The PCOSQ consists of five domains, each relating to a common symptom of PCOS; body hair, emotions, infertility, menstrual problems and infertility. Each question on the PCOSQ is associated with a 7-point scale in which 7 represents optimal function and 1 the poorest function. In order to compare it with the SF-36, each question was re-coded from 0 to 6 in which 6 represents optimal function and 0 the poorest. Each scale was then transformed on a range from 0 (indicating worst health status) to 100 (best health status) enabling the extent of ill health to be measured (scale score = total of raw scores for each item in the scale/maximum possible raw score $\times 100$). This was repeated for time 2 responses. Similar tables were constructed for the SF-36.

To verify the factor structure and compositions of the PCOSQ dimensions, secondary factor analysis was used. Factor analysis is a statistical procedure which enables the underlying dimensions (or scales) of a questionnaire to be determined (Kline, 2000). The data from the questionnaires returned at time 1 were analysed using principal component analysis (varimax rotation) as used in the development of the original questionnaire (Cronin *et al.*, 1998). To reduce statistical error, it has been postulated that ≥ 100 subjects are needed for factor analysis or a $\geq 2:1$ ratio of subjects to items (Kline, 2000).

To measure the internal consistency reliability of the questionnaire, Cronbach's α statistic was used. Internal consistency reliability is an indication of how well the items within a scale are associated with each other or their 'homogeneity' (Velikova *et al.*, 1999) and Cronbach's α is the measure which is most frequently used for establishing this. Scores >0.7 usually indicate that scale items are measuring related constructs (Cronbach, 1951). Item-total consistency was also calculated to check the internal reliability of a dimension. This is the extent to which there is a linear relationship between an

item and its scale score, which has been corrected for overlap (Gandek *et al.*, 1998). To correct for overlap, the item which is to be correlated with the scale is omitted from the scale total. A correlation coefficient of ≥ 0.40 indicates satisfactory item-total consistency (Ware *et al.*, 1980).

To analyse test-retest reliability, the Wilcoxon signed rank test (nonparametric) was used to calculate if there were any statistical differences between the scores at times 1 and 2 on those patients who had reported 'no change' to their health status during that time. The intra-class correlation coefficient was calculated to examine the

relationship between the scale scores at time 1 and 2. The results were taken to be significant if $P < 0.05$.

To assess construct validity, we hypothesized a significant correlation (Spearman's ρ non-parametric coefficient) would be found between scales with a similar content on the PCOSQ and SF-36 (the 'emotions' scale of the PCOSQ with the domains 'mental health' and 'role-emotional' of the SF-36). We also hypothesized that these two domains of the SF-36 would correlate more strongly with the 'emotions' domain of the PCOSQ than any of its other four scales. All statistical analyses were performed using SPSS v 11.5.

Table I. Clinical features of the patient sample

Clinical features	No. of total data set affected (%) (n = 186)	No. of sample set affected (%) (n = 92)
Symptoms		
Excessive body hair	94 (50.6)	46 (50.0)
BMI >28 kg/m ²	100 (53.8)	48 (52.2)
Acne	54 (29.0)	31 (33.7)
Infertility	120 (64.5)	59 (64.1)
Oligo/amenorrhoea	160 (86.0)	80 (87.0)
Biochemical abnormalities		
LH/FSH ratio > 1.5	89 (47.8)	50 (54.3)
Testosterone > 2.0	43 (23.1)	40 (43.5)
SHBG < 30	19 (10.2)	28 (30.4)
PCO diagnosed on ultrasound	133 (71.5)	75 (81.5)

BMI = body mass index; SHBG = sex hormone-binding globulin; PCO = polycystic ovaries.

Results

Of the 92 women who agreed to take part in the study, 82 returned questionnaires at time 1 (89.1%) and 69 at time 2 (75.0%). The mean age of the sample was 29.4 ± 5.7 (range 20–41). Ethnicity was also recorded; 78 (84.9 %) of the respondents were white, five (5.4%) were Pakistani, 1 (1.1%) was Chinese, and no ethnicity data were provided for seven (7.6%) respondents. The clinical features of the sample are reported in Table I.

Secondary factor analysis was carried out on the 82 questionnaires returned at time 1, producing a ratio of 3:1 items to subjects. The results from the secondary factor analysis (principal component analysis, varimax rotation) are shown in Table II. Initially, only factors which gained an eigenvalue (raw sum of the squares) of ≥ 1 were retained. This procedure identified six factors which accounted for 78.8% of

Table II. Secondary factor analysis on the Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (PCOSQ)

Items	Rotated component matrix mactors					
	1	2	3	4	5	6
W3. Concerned about being overweight	0.841					
W10. Had trouble dealing with weight	0.851					
W12. Felt frustration trying to lose weight	0.877					
W22. Feel not sexy because overweight	0.704					
W24. Difficulties staying at ideal weight	0.847					
BH1. Growth of visible hair on chin		0.823				
BH9. Growth of visible hair on upper lip		0.793				
BH15. Growth of visible hair on face		0.873				
BH16. Embarrassment of excess body hair		0.898				
BH26. Growth of visible body hair		0.881				
EM2. Depressed having PCOS			0.756			
EM4. Easily tired			0.345			
EM6. Moody as a result of having PCOS			0.567			
EM17. Worried about having PCOS			0.765			
EM18. Self-conscious having PCOS			0.744			
EM11. Had low self-esteem having PCOS			0.801			
INF23. Feel a lack of control over PCOS			0.652			
EM14. Felt frightened of getting cancer				0.497		
INF5. Concerned with infertility problems				0.914		
INF13. Felt afraid of not having children				0.823		
INF25. Feel sad because of infertility				0.902		
MEN7. Headaches					0.757	
MEN19. Abdominal bloating					0.722	
MEN21. Menstrual cramps					0.682	
EM20. Late menstrual period						0.797
MEN8. Irregular menstrual periods						0.789

Extraction method: principal component analysis; rotation method: varimax with Kaiser normalization.

A factor indicates the relationships between a set of items. A factor is therefore defined by the items which load on it or the factor loadings. Loadings > 0.5 are considered satisfactory.

Bold type indicates the items which loaded on original factors as determined by Cronin *et al.* (1998).

W = items from weight domain; BH = body hair; EM = emotions; INF = infertility; MEN = menstrual; PCOS = polycystic ovary syndrome.

Table III. Distribution of the scale scores for the Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (PCOSQ) and Short Form-36 (SF-36) from the questionnaires returned at time 1

Scale	<i>n</i>	Mean	SD	Range of scores	% scoring minimum (floor)	% scoring maximum (ceiling)
PCOSQ						
Body hair	81	55.6	34.1	0–100	3.7	18.5
Emotions	78	49.8	30.0	8–100	2.6	2.6
Infertility	81	39.3	31.4	0–100	13.6	4.9
Menstrual problems	81	44.3	24.7	0–100	3.7	2.5
Weight	82	32.4	33.1	0–100	22.0	4.9
SF-36						
Bodily pain	82	69.7	22.7	27–100	4.9	20.7
Energy and vitality	82	51.5	16.7	17–100	2.4	1.2
General health	80	64.4	18.3	30–100	1.3	5.0
Mental health	82	63.4	16.3	23–100	1.2	2.4
Physical functioning	80	89.8	11.0	47–100	1.3	23.8
Role limit/emotion	82	50.4	40.3	0–100	29.3	30.5
Role limit/physical	82	69.5	36.7	0–100	12.2	50.0
Social functioning	82	67.4	23.4	20–100	1.2	23.2
Change in health	82	60.0	17.3	20–100	3.7	6.1

The scales run from 0 (poor health) through to 100 (good health).

Table IV. Internal reliability and test-retest reliability correlation of scales generated from time 1 and time 2 on the Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (PCOSQ) and the Short Form-36 (SF-36)

Scale	Internal reliability, time 1 ^a α (<i>n</i>)	Internal reliability, time 2 ^b α (<i>n</i>)	Differences between time 1 and time 2 ^c Wilcoxon signed rank test (Z)*	Test-retest reliability ^c Intra-class correlation**
PCOSQ				
Body hair	0.95 (81)	0.97 (69)	-1.44	0.95 (60)
Emotions	0.88 (78)	0.91 (67)	-0.86	0.93 (56)
Infertility	0.87 (81)	0.91 (68)	-1.82	0.92 (59)
Menstrual problems	0.70 (81)	0.73 (67)	-1.35	0.89 (56)
Weight	0.96 (82)	0.95 (68)	-1.48	0.95 (54)
SF-36				
Bodily pain	0.91 (82)	0.90 (68)	-0.29	0.67 (61)
Energy and vitality	0.79 (82)	0.83 (68)	-0.97	0.79 (61)
General health	0.81 (80)	0.83 (68)	-0.20	0.88 (59)
Mental health	0.77 (82)	0.79 (66)	-1.46	0.80 (59)
Physical functioning	0.85 (80)	0.83 (67)	-1.63	0.84 (59)
Role limit/emotion	0.74 (82)	0.88 (68)	-0.19	0.89 (61)
Role limit/physical	0.82 (82)	0.85 (68)	-1.42	0.75 (61)
Social functioning	0.83 (82)	0.85 (68)	-1.27	0.81 (60)

Values in parentheses are numbers (*n*).

Cronbach's α -values indicate how well the items within a scale are associated with each other and are used to establish internal reliability; α -values >0.7 are usually considered satisfactory.

^aEveryone who completed questionnaires from the survey at time 1.

^bEveryone who completed questionnaires from the survey at time 2.

^cEveryone who completed questionnaires at time 1 and time 2 and reported no significant change in their health/life during that period.

* $P > 0.05$ for all values.

** $P < 0.001$ for all values.

the variance. Only those questions which obtained a value of ≥ 0.50 on any of the factors were initially retained and any factors which scored less than this were omitted.

From this analysis, two dimensions (weight and body hair) were identical to the initial composition of the scales on the PCOSQ, with the same items loading on each factor.

The infertility scale was identical except that item 23, 'feel a lack of control over the situation with PCOS', loaded on the emotions scale instead. The remaining two scales were the same except that two original items (frightened of getting cancer, and late menstrual period) did not load on the emotions

scale and one item (irregular menstrual periods) did not load on the menstrual problems domain. Only one item failed to obtain a value of 0.50 which was originally in the emotions scale (easily tired) but this was close at 0.40.

The distribution of the scale scores for the five domains on the PCOSQ and SF-36 are shown in Table III. The mean scale scores for the PCOSQ showed that 'weight' (32.4) and 'infertility' (39.3) scored the lowest, indicating worst health in these dimensions. This was in comparison to the body hair domain which had the highest mean score (55.6) suggesting that this symptom was causing the least negative impact upon

quality of life. The SF-36 questionnaire results indicated that the 'role limitation-emotional' and 'energy and vitality' domains were the areas of poorest health with mean scores of 50.4 and 51.5 respectively. The highest mean score was evident for physical functioning (89.8), indicating the best area of health as measured on the SF-36.

The internal reliability consistency of the scales was assessed using Cronbach's α . As shown in Table IV, all the scales on the PCOSQ reached the required 0.7 at both time 1 (range 0.70–0.96) and time 2 (range 0.73–0.97). All the item-total correlations of the individual items exceeded the minimum value of 0.40 except for item 14 at time 1 on the emotions scale (felt frightened of getting cancer). However, this was close at 0.39. At time 2, both item 17 (worried about having PCOS) and item 8 (irregular menstrual periods) achieved an item correlation <0.40 with the scores reaching 0.13 and 0.37 respectively.

The SF-36 was tested in the same way. The Cronbach's α value results are shown in Table IV. At both times 1 and 2, all of the domains showed internal reliability with Cronbach's α scores >0.7 (range 0.74–0.91). The item-total correlation scores were >0.40 for all individual questions, except for three items in the physical functioning domain which achieved item-total correlations of 0.39 ('vigorous activities', time 1), 0.31 ('lifting or carrying groceries', time 2) and 0.12 ('bathing or dressing', time 2).

Sixty-nine women (75.0%) returned the questionnaires at time 1 and 2. Of these, 57 (82.61%) women reported no change in their health status during this time. No significant differences (Wilcoxon signed rank test) between the scores at times 1 and 2 were found on the five scales of the PCOSQ or SF-36 (Table IV).

The intra-class correlation coefficients to evaluate the test-retest reliability of the PCOSQ were high for all domains. As shown in Table IV, they ranged from 0.89 to 0.95 ($P < 0.001$). The SF-36 was less well correlated (0.67–0.89) with a greater P -value for some domains, showing less significance (Table IV).

Construct validity was assessed by correlating the 'emotions' scale of the PCOSQ with the 'mental health' and 'role-emotional' scales of the SF-36. As hypothesized, a good positive correlation was found for both analyses. Emotions (PCOSQ) correlated with role-emotional (SF-36) ($r = 0.49$, $P < 0.01$, $n = 55$). This correlation was greater than with the weight domain ($r = 0.37$, $P < 0.05$, $n = 47$), the infertility domain ($r = 0.37$, $P > 0.05$, $n = 58$) and the body hair domain ($r = 0.41$, $P > 0.05$, $n = 60$), but not for the menstrual domain ($r = 0.50$, $P < 0.01$, $n = 56$). Emotions (PCOSQ) correlated with mental health (SF-36) ($r = 0.62$, $P < 0.01$, $n = 54$) and this was more strongly correlated than with the other four scales of the PCOSQ, including infertility ($r = 0.43$, $P < 0.01$, $n = 53$), body hair ($r = 0.22$, $P > 0.05$, $n = 50$), weight ($r = 0.34$, $P < 0.05$, $n = 47$) and menstrual problems ($r = 0.59$, $P < 0.01$, $n = 50$).

Face validity

Of the 12 women interviewed to assess face validity, 11 felt that overall the questionnaire did address the areas of HRQoL

negatively affected as a result of PCOS. However, some limitations with the instrument were reported.

Three women (25%) mentioned that questions relating to their symptom of acne were missing from the questionnaire. Three women (25%) were worried by the question that asked 'during the past two weeks, have you felt frightened of getting cancer?' (no. 16). One woman (8%) expressed concern that the wording of the questionnaire implied that PCOS was a short-term condition. Two women (17%) felt the questionnaire did not address their feelings of frustration about the lack of available information on PCOS. One woman (8%) mentioned the omission of a question about weight-related prejudice from infertility services.

Discussion

At present, no validated health outcome measure exists to measure the quality of life of women with PCOS. Although a disease-specific questionnaire has been developed, only the content validity of the instrument has been established, therefore preventing its use in clinical and research settings. While generic questionnaires exist to measure HRQoL, such as the SF-36, they do not collect information on all the areas of well-being and functioning that may be important to women with PCOS. For example, infertility and hirsutism can place a considerable strain on the emotional well-being and personal relationships of women with this disease. However, this information is not collected on the SF-36 generic health measure.

The mean scale scores on the PCOSQ reflect the negative impact PCOS can have upon the quality of life of women with the condition. Perhaps not surprisingly, weight and infertility appeared to be the most significant aspects of the illness. Other studies have reported the negative impact infertility can have upon women and their personal relationships (Epstein and Rosenberg, 1997; Leiblum and Greenfeld, 1997). The finding that weight caused the most negative impact on quality of life has implications for the management of the condition, especially as it has been estimated that ~50% of women with PCOS suffer from obesity or are overweight (Gambineri *et al.*, 2002), yet the best way to manage and aid weight loss in this group of women is unclear (Moran and Norman, 2002).

The secondary factor analysis carried out in this new data set would suggest that overall the structure of the PCOSQ domains are verified, especially for weight, body hair, menstrual problems and infertility. The composition of the emotions scale was less supported. Two original items failed to load on this scale, and an item originally from the infertility scale (lack of control over PCOS) did, suggesting that there may be limitations with this scale. In addition, the item 'felt frightened of getting cancer' loaded on the infertility domain. This was consistent with the original factor analysis carried out by Cronin *et al.* (1998), although the authors subsequently moved this item to the emotions scale as they felt it to be more appropriate to that domain.

One limitation with the results produced from our factor analysis may be that the ratio of respondents to items was not large enough. Although it has been shown that a ratio of 2:1 of

respondents to variables is satisfactory and can produce similar results to a larger ratio (Kline, 2000), it has been argued that the ratio of the number of subjects to the number of items on the instrument should be $\geq 5:1$ (McDowell and Newell, 1996). A study containing such a ratio of respondents to items would be recommended for the future before amending the composition of the emotions scales on the PCOSQ.

The internal reliability of the PCOSQ was found to be high, with all the scales exceeding the accepted α value of 0.70, although the menstrual problems scale was weaker than the other domains with an α of just 0.7. This indicates that this scale may benefit from further analysis. This is further supported as item 20 (late menstrual period) and item 8 (irregular menstrual period) loaded on a new factor, suggesting that a new scale referring to menstrual periods specifically may be required.

The test-retest reliability of the PCOSQ was found to be high. All scales achieved high intra-class correlations >0.8 and were overall higher than for the SF-36. This indicates that the questionnaire produces consistent results from subjects at different times, when no evidence of change in health status exists.

The small sample size, and the absence of another questionnaire which contained similar domains to the PCOSQ, limited the testing of construct validity in this study. However, because scales on the PCOSQ correlated significantly with similar scales on the SF-36 as hypothesized and overall less with the other scales on the questionnaire, it suggests that the construct validity of the instrument is supported. Further analysis on the construct validity of the questionnaire needs to be carried out to verify this further.

In terms of face validity, the women interviewed felt that, on the whole, the questionnaire was addressing the relevant issues to women with PCOS. However, the lack of questions about acne was raised as a serious omission. Acne is recognized as a common symptom of the condition. The finding that 34% of respondents in the study suffered from acne would support this and suggest that the addition of a new acne domain to the PCOSQ would be important if the instrument is to be used in a clinical setting.

One explanation for the omission of an acne domain may be due to the item selection phase of the PCOSQ. During this phase, only 10 PCOS patients were interviewed. Although it was reported that these women had the full range of complaints, it is not known exactly what the symptom profile or presenting symptoms of these patients were. This small number was justified by the fact that no further items were generated after the first five interviews (Cronin *et al.*, 1998). Although this may have been an acceptable number, other studies have interviewed more subjects to generate items for disease-specific questionnaires (Jenkinson *et al.*, 1998; Jones *et al.*, 2001).

There are two methodological issues which are important to discuss. First, the definition of PCOS used in our study differed from that in the original paper by Cronin *et al.* (1998). For this validation study, a definition of the syndrome commonly used in Europe and the UK was used (Balen *et al.*, 1999; Lewis *et al.*, 2001) instead of the National Institutes of Health (NIH)

definition as used in the development of the PCOSQ. The aim of our study was to validate the use of the questionnaire in UK practice and we therefore have applied it to a group of women who have PCOS using the definition currently accepted in this country. For this reason, it was felt that using the NIH definition to recruit patients would not help ascertain the validity of the PCOSQ for measuring the HRQoL of PCOS patients within Europe and the UK.

Another potential limitation to the study is that patients were recruited from a gynaecology clinic. Consequently, it could be argued that there was a bias towards PCOS patients with menstrual disturbance and infertility and not those presenting with other PCOS-related conditions (i.e. weight increase and acne) that are often referred to endocrinology and dermatology clinics. However, it was felt that sufficient patients with complaints of a dermatological or endocrinological nature to allow us to validate the PCOSQ were seen in the gynaecology clinics. For example, in our group of patients 50.6% of the population had hirsutism and 29% of the population had acne. The findings are therefore of interest to dermatologists and endocrinologists and the validation of the questionnaire seems relevant to women with PCOS, notwithstanding which subspecialist sees them. Furthermore, our finding that a domain on acne needs to be included was generated by the composition of our group of patients, which, in distinction from the patients selected to develop the instrument, did include a large number of women with acne and is therefore more representative of the PCOS population than used to develop the initial questionnaire.

In conclusion, the PCOSQ is a promising tool for measuring the HRQoL of women with PCOS. The next phase of our research is to develop and incorporate an acne domain into the PCOSQ. The amended PCOSQ will be tested by the same criteria on a new sample of PCOS patients, along with the 'sensitivity to change' of the new instrument. This is the ability of a questionnaire to detect and describe changes in patients' health status over time and whether these changes are clinically relevant (Kazis *et al.*, 1989). An improved questionnaire could potentially be used to assess the full impact of treatment regimes, for example, in randomized controlled trials for patients with PCOS and be used to generate more understanding into the impact that symptoms and treatments for this condition have upon HRQoL.

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Mini-Review

Update on PCOS: Consequences, Challenges, and Guiding Treatment

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Abbreviations: AMH, anti-Müllerian hormone; COC, combined oral contraceptive; CVD, cardiovascular disease; DM, diabetes mellitus; FNPO, follicle number per ovary; GnRH, gonadotropin-releasing hormone; mFG, modified Ferriman-Gallwey; PCOM, polycystic ovary morphology; PCOS, polycystic ovary syndrome.

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common reproductive endocrine disorders in women and despite this, diagnostic challenges, delayed diagnosis, and less-than-optimal treatment regimens plague the condition. The International PCOS network, consisting of geographically diverse international experts in PCOS as well as consumers, engaged in a multi-year international evidence-based guideline development process that was jointly sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM). The guideline was published in 2018 and endorsed by more than 40 international societies involved in PCOS. Translation of this evidence-based guideline to medical practice and consumer groups remains a priority. However, there remain many challenges to both understanding the diagnosis and treatment of PCOS. Evidence suggests that both clinicians and consumers are not satisfied with the timeliness of diagnosis and treatment options. This review summarizes the important findings for diagnosis and treatment from the guidelines and expands on recent developments in the literature since its publication. Special attention to diagnosis at the ends of the reproductive spectrum are discussed and remaining areas of controversy are noted. Additionally, the review highlights some of the remaining challenges in the understanding and management of PCOS to help guide clinicians and investigators in this perplexing condition.

Key Words: PCOS, pathophysiology, diagnostic criteria, metabolic disease, lifestyle intervention

Polycystic ovary syndrome (PCOS) is the most common endocrinologic condition in women, affecting from 8% to 13% of reproductive-aged women ([1](#), [2](#)). It is an enigmatic

condition that, while extremely common, creates challenges in its diagnosis and management, as leading symptoms may vary with age, and treatment may be tailored

to specific requirements of individual need. The vast array of possible diagnostic schemes, treatment offerings, and often conflicting recommendations, led to the formation of a large international consortium to examine the evidence in a rigorous way and produce evidence-based guidelines on diagnosis and management published in 2018 (3, 4). What was clear, however, in this published guideline is that there remain many challenges in the diagnosis and treatment of PCOS. Additionally, research has exposed the still-large gap between the available evidence and its translation to improved diagnostic timing and evidence-based treatments (5, 6). There are still knowledge gaps in different disciplines of medicine (e.g., Obstetrics and Gynecology (OBGYN), Medicine, Pediatrics, Dermatology) regarding the diagnosis and treatment of PCOS, and women with PCOS report significant delays in the diagnosis (7), dissatisfaction with the treatment and recommendations they receive (8), and a lack of satisfactory treatment options. This gap is not limited to practicing physicians who completed training before the international guidelines were published, but recent assessment of OBGYN residents in training identified significant deficiencies in the knowledge of the diagnostic criteria for PCOS. In one recent survey of US-based OBGYN residents, 85.4% of 347 trainees completing the survey reported using Rotterdam criteria to diagnose PCOS. However, only 55% correctly identified the 3 main criteria used in the diagnosis (9).

This paper will review the diagnostic criteria and the challenges that continue to present for clear diagnosis. PCOS impacts all aspects of the reproductive hormone physiology; however, the precise pathophysiology remains incompletely elucidated. The current evidence for leading pathophysiologic disturbance in PCOS will be reviewed, as well as the best evidence of reproductive, psychological, and metabolic consequences. Finally, an update on the best evidence-based treatments for PCOS will be reviewed. This review will highlight the challenges that remain in the diagnosis and treatment of PCOS and bring forth the most recent evidence to support the recommendations.

Search Strategies

This mini-review is a limited qualitative narrative review of the literature in PCOS, intended to inform clinical guidance in PCOS and summarizing and building on the International Evidence-Based Guidelines published in 2018 (3). In addition to the literature reviewed by the international guidelines (3), PubMed was searched with the MeSH term of *Polycystic Ovary Syndrome*, combined with the subcategories of *clinical trials, meta-analysis, systematic reviews* for the period from June 2017 to June

2020. Articles were excluded from the review if they were pilot trials, only included animal data, limited in population scope, or the focus was not on PCOS. Articles from the international guidelines were referenced (15 references from this guideline cited here) if there was specific quality without substantive change or additional guidance in more recent literature.

Pathophysiology

The pathogenesis of PCOS is complex and multifactorial, including genetic, environmental, and transgenerational components. These sources drive the underpinnings of unbalanced hypothalamus-pituitary-ovarian axis signaling, promoting ovarian and adrenal hyperandrogenism. The syndrome is also burdened with insulin resistance that is worsened by hyperandrogenism-related adipose tissue accumulation and dysfunction with lipotoxicity and oxidative stress (10). Thus, the full clinical spectrum of the syndrome involves metabolic, reproductive, and psychological impairments. In addition to genetic factors, environmental factors likely also play a role. The link between obesity and the prevalence of PCOS is highly correlated; among women with body mass index (BMI) $<25 \text{ kg/m}^2$, the prevalence is 4.3%, and in women with BMI $>30\text{kg/m}^2$ it is 14%, although selection bias may play a role in assessment (11).

Neuroendocrine link to PCOS

Women with PCOS present with gonadotropin-releasing hormone (GnRH) neuronal network dysfunction and increased pulse amplitude for pituitary activity, shown as high serum luteinizing hormone levels and high ovarian androgen response, most likely relating to decreased responsiveness to steroid hormone negative feedback (12). Different animal models have successfully been able to recapitulate the hyperandrogenism driven neuroendocrine pathology of PCOS and other central mechanisms involved (13). Recently, aberrant neuroendocrine signaling was linked with adipose tissue dysfunction in a murine model (14), whereas other studies have proposed high anti-Müllerian hormone (AMH) promoting GnRH neuron activation and PCOS onset (15). Given the central role of hyperandrogenism and obesity in the impairments in neuronal circuitry and the high prevalence of psychological distress among women with PCOS, the central dysfunction most likely involves larger and more complex neuronal networks than previously recognized (16, 17).

Genetic factors

The genetic factors and familial clustering are described in the early PCOS literature (18); however, as more genetic data has started to accumulate, it has become obvious that the syndrome harbors multigenetic background. Indeed, the genome-wide association studies have identified a total of 19 risk gene loci for PCOS located in the neuroendocrine, metabolic, and reproductive pathways (19), with the reproductive and metabolic populations segregating in a recent unsupervised clustering analysis (20). In line with this, Mendelian randomization analyses suggest a causal link between PCOS and variants associated with BMI, fasting insulin, menopause timing, depression, and male-pattern balding (21). From all genes of interest, the gene loci with the most potential, namely *THADA*, *FSHR*, *INS-VNTR*, and *DENND1A*, would require validation in the future. Interestingly, the clinically validated PCOS cases have similar genetic profile to the self-reported ones, allowing data generation in the future also through less burdensome and more inexpensive means (21). Known genetic risk alleles account for less than 10% of PCOS heritability; therefore, other etiological factors also have to be considered.

Transgenerational transmission of PCOS

Animal studies and human data show the syndrome having transgenerational origins, with a 5-fold higher risk for daughters born to mothers with PCOS for inheriting the syndrome (13, 22). In a murine model, prenatal androgen excess alone can predispose to transgenerational transmission of PCOS. Early androgen exposure may increase susceptibility to the syndrome. Longer anogenital distance (AGD) has been shown in infant girls born to PCOS mothers, and daughters of PCOS mothers have higher metabolic and androgenic risk (22, 23). Maternal testosterone in women with PCOS was found to be a predictor of infant AGD (24). The mechanism through which the daughters are exposed to hyperandrogenism remains elusive, although AMH could be one of the players. Interestingly, a recent study showed that mice subjected to high levels of AMH at late pregnancy produced PCOS offspring with high luteinizing hormone pulsatility and increased androgen levels (25). The mechanism was thought to transit via AMH effect on aromatase activity in the placenta, promoting hyperandrogenism. Even though AMH levels have been reported to be high in the second and third trimesters in women with PCOS (25, 26), the role of AMH on transgenerational transmission in humans warrants further studies.

Diagnosis

Criteria for diagnosis

There is no specific diagnostic test that unequivocally identifies PCOS, but rather the diagnosis is based on the varying presence of 3 specific elements, namely oligo-anovulation, androgen excess, either clinical or biochemical, and the ultrasound assessment of ovarian morphology. The International Evidence-Based Guideline (3) endorsed the use of the Rotterdam criteria (27) that requires 2 of the 3 diagnostic criteria be present for the diagnosis in adult women. Exclusion of thyroid disease (thyroid stimulating hormone, TSH), hyperprolactinemia (prolactin), and nonclassic congenital adrenal hyperplasia (screening with 17-hydroxy progesterone) is recommended. Further evaluation is recommended in those with amenorrhea and more atypical features, with consideration to assess for hypogonadotropic hypogonadism or Cushing disease, and where there is a more severe androgenic picture, consideration for evaluation for androgen-producing tumors. Severe androgenic profiles are present if serum androgen measures are elevated more than 2-fold the upper limits of normal for the local clinical assay standard. The guidelines also endorse the use of phenotype descriptions when diagnosing PCOS and present 4 phenotypes (A-D) based on the presence or absence of the 3 diagnostic criteria (see Table 1). The specific clinical implications or natural history of each of the phenotypes remains unclear at this time, although recent study has found, using unsupervised phenotypic clustering analysis, reproductive and metabolic phenotypes segregating by novel genetic findings (20). Moreover, a review of metabolic features and phenotypes noted that while androgenic phenotypes were more often associated with more severe metabolic dysfunction, this was confounded in most studies by the presence of adiposity, with increased adiposity leading to more severe complications and not all studies controlled for BMI (28, 29). Diagnostic features of the condition also vary across the lifespan and by ethnicity, which complicates the categorization and natural history.

Table 1. Phenotypes of PCOS Based on Rotterdam Criteria

Phenotype	Androgen excess	Ovulatory dysfunction	PCOM on ultrasound
A	✓	✓	✓
B	✓	✓	
C	✓		✓
D		✓	✓

Abbreviations: PCOM, polycystic ovary morphology; PCOS, polycystic ovary syndrome.

The recommendations for the diagnostic criteria from the international guidelines are noted in Table 2. Androgenic status can be assessed by either biochemical measures or clinical measures. The presence of androgenic excess is clinically indicated by cutaneous manifestations such as the presence of hirsutism (indicated by modified Ferriman-Gallwey (mFG) score) (30), acne, or alopecia. There is significant ethnic variation in clinical androgenic expression and examination is often limited by self-treatment of hirsutism. There are limited data from diverse populations, making the interpretation of the mFG score challenging. Current recommendations in the guidelines are based on limited controlled data, with an overall reduction in mFG score threshold required to be consistent with hyperandrogenism. Ovulatory dysfunction is signaled by oligo-anovulation, with irregular menses as the marker based on published data as noted in Table 2. If irregular menses is present along with hyperandrogenism, biochemical or clinical, then the use of pelvic ultrasound is not required for diagnosis. Although assignment of the full phenotype is limited without this measure, clinical diagnosis is possible without ultrasound.

Challenges for the ultrasound diagnostic criteria and role of AMH

Ultrasound morphology is the most challenging of the criteria, as there has been variation in the standards in the reporting of the follicle count cutoffs. As technology has improved, the ability to see more follicles increases, so the cutoffs previously published were not based on current technology (31) and are no longer valid to distinguish populations. The Androgen Excess and Polycystic Ovary Syndrome Society published guidelines in 2014 (32). Reviewing the available literature, the guideline recommended using follicle number per ovary (FNPO) for the definition of polycystic ovary morphology (PCOM) and recommended the threshold be set at ≥ 25 , but only when using newer technology that affords maximal resolution of ovarian follicles (ie, transducer frequency ≥ 8 MHz). The guidelines recommend the use of ovarian volume for diagnosis of PCOM if such technology was not available for routine daily practice. When using ultrasound in PCOS research, use of newer technology to adequately characterize follicle count is suggested. The International Evidence-Based Guideline (3) included a systematic review (11 studies with 2961 adult participants) of ultrasound for FNPO criteria in the diagnosis of PCOM and concluded that the optimal sensitivity and specificity for FNPO was ≥ 20 follicles per ovary in at least one ovary. The available ovarian volume data did not indicate a recommended change in the ovarian volume criteria for PCOM at ≥ 10 mL.

Table 2. Definitions of Features of PCOS for Diagnosis

Feature	Definition
Irregular menses	<ul style="list-style-type: none"> • > 1 year and < 3 years post menarche: < 21 or > 45 days • > 3 years post menarche: < 21 or > 35 days • > 1 year post menarche: any cycle > 90 days • Primary amenorrhea at age 15 or > 3 years post thelarche
Biochemical hyperandrogenism	<ul style="list-style-type: none"> • Calculated free testosterone or free androgen index • Calculated bioavailable testosterone • Liquid chromatography/mass spectrometer with extraction is the preferred method of assay measure; reference range upper limits of normal free testosterone 1.06 ng/dL, total testosterone 60 ng/dL • Can consider androstenedione or DHEAS if testosterone is normal and high index of suspicion for hyperandrogenism
Clinical hyperandrogenism	<ul style="list-style-type: none"> • Examination specifically for acne, alopecia, and hirsutism • For adolescents use severe acne and hirsutism • Use standardized visual scale of mFG $\geq 4-6$ recognizing there are ethnic variations that are not well defined
Ultrasound criteria	<ul style="list-style-type: none"> • Ultrasound should be transvaginal and using high resolution • In this setting follicle count per ovary should be ≥ 20 or ovarian volume ≥ 10 mL • Ultrasound should not be used in those < 8 years post menarche

Adapted from the International Evidence-Based Guideline for the diagnosis and management of Polycystic Ovary Syndrome 2018 https://www.monash.edu/_data/assets/pdf_file/0004/1412644/PCOS_Evidence-Based-Guidelines_20181009.pdf

Abbreviations: DHEAS, dehydroepiandrosterone sulfate; mFG, modified Ferriman-Gallwey.

AMH levels have been considered as a surrogate marker or as an alternative to ultrasound FNPO count for the diagnosis of PCOM or as an independent marker of PCOS. Overall serum AMH levels are 2- to 3-fold higher in women with a diagnosis of PCOS than in women with normal reproductive function and the levels correlate with FNPO ultrasound measures. The assays utilized vary significantly between reports, with PCOS median AMH levels ranging from 20 to 81.6 pmol/L and normal control medians from 16.7 to 33.5 pmol/L (33-36). There are recognized challenges in the AMH measurement (37), such as proteolysis,

changes in the AMH dimer, or interfering substances that lead to poor performance of the assay in predictive models. Additionally, there are variations across the reproductive lifespan in AMH ranges, making it difficult to distinguish cases from controls on this criterion (38). Recent study also showed overlap between PCOS and hypogonadotropic hypogonadism as for AMH measure, warranting awareness and in some cases also further serum assessments to discriminate between these 2 phenotypes (39). Given all this and the limitations of AMH measurement, AMH alone is not sufficient to establish the diagnosis. A recent systematic review of the use of AMH in replacing ultrasound in PCOS diagnosis identified the research gaps that remain before AMH can be considered in the diagnostic algorithm (40).

Special age-group considerations

Adolescence, the period of time between 10 and 19 years of age and the time of pubertal maturation, represents a distinct dilemma in the diagnosis of PCOS. The diagnosis in adolescence is challenged by the overlap of normal pubertal physiology changes and those that mimic adult diagnostic criteria for PCOS, namely irregular menstrual cycles and multifollicular ovaries. Additionally, the time from menarche to full maturation of the reproductive axis (41-43) can be variable post menarche, which may bridge young adulthood (44). Since there is evidence for the underpinnings of PCOS presenting in adolescence and the normal pubertal overlap, there is the risk of both underdiagnosis (7) and that of overdiagnosis, without adequate support for disease. As such, it is recommended that the diagnosis of PCOS not be made early in the post menarchal timeframe. The recommendation for diagnosis in adolescence cannot depend on pelvic ultrasound findings given the increased overlap with normal ovarian findings in this age group and instead is based on irregular menses and hyperandrogenism. Care should be taken when using biochemical evidence of hyperandrogenism to establish a normative range for the assay used in this population. AMH is also unhelpful in distinguishing PCOS in this age group. In adolescents, levels are high and overlap considerably between adolescents with and without diagnostic features of PCOS (38). Menstrual cycles may not establish a regular pattern until >2 years post menarche (45). In a recent study of 317 Danish 16-year old adolescents, the majority had regular cycles within 3 years post menarche (46). Therefore, the diagnosis should not be made within 2 years of menarche to allow for this maturation. There is a recommendation regarding adolescents who are not yet at the developmental stage for full endorsement of a PCOS diagnosis, but who demonstrate concerning features like persistent irregular menses or clinical androgen

concerns requiring clinical intervention, that they be considered “at risk for PCOS.” There may therefore be utility in reinvestigating the possibility of PCOS in the future. It is then recommended that further evaluation of androgens and consideration for ultrasound at the appropriate gynecologic age be completed to fully assess the diagnosis (47). On the other end of the reproductive spectrum, there are challenges to diagnosis in women in the peri- and postmenopausal reproductive spectrum. The average age of menopause is 51 years, but menstrual changes occur much earlier than this in normal aging (48), so ovulatory dysfunction is unreliable as a diagnostic criterion. In fact, there is evidence of increase in regular menstruation in women diagnosed with PCOS as they approach perimenopause (49-51). Also, ovarian volumes and follicle counts decline with age. Ovarian androgen production may decline in both groups, but clinical hyperandrogenism may be more prevalent due to decline in estrogen levels in menopause (52). At this point, there is insufficient evidence about natural history to specifically distinguish the phenotype in menopausal women. The Guidelines suggest that a diagnosis of PCOS could be considered if there is a past diagnosis of PCOS, a long-term history of irregular menstrual cycles, and hyperandrogenism, and/or PCOM, during the reproductive years, but they do not endorse specific diagnostic criteria separately (53).

Consequences

What is known

Metabolic/obesity

PCOS is associated with an increased risk of metabolic complications starting from a young age. These comorbidities include traditional cardiovascular disease (CVD) risk factors such as obesity, impaired glucose tolerance, type 2 diabetes (DM), dyslipidemia, and hypertension. Obesity is one of the most common concerns expressed in surveys of patients with PCOS (7). Depending on the ethnicity and study population assessed, the obesity rate varies from 50% to 80%. According to an examination of high-quality studies in a large meta-analysis, the risk of obesity in women with PCOS was reported to be 4-fold higher compared with controls and also higher in white women compared with Asian women (54). Importantly, women with PCOS have been shown to present with long-term overweight or obesity, with the onset of BMI trajectory deviation occurring as early as age 5 (55). Evidence from cross-sectional studies suggests that the risk of overweight/obesity persists beyond the fourth decade of life (56) and a few longitudinal studies also suggest an increase in weight with age (57). The increased preference for abdominal fat deposition, seen primarily in

the hyperandrogenic phenotype, further predisposes this population to other cardiometabolic complications (58). The risk of impaired glucose tolerance is 3-fold higher with PCOS, independent of BMI, and highest in women living in Asia and in North and South America (59). Although the risk of DM is also increased in this reproductive-age population, there are mixed data regarding these findings independent of weight. In women over age 40, a few longitudinal studies and other cross-sectional studies indicate an increased risk of type 2 DM independent of BMI (56). In adolescents with PCOS, there are only a few small studies examining the risk of DM, and these show an overall low prevalence. When examining the differences based on PCOS phenotype, a large cross-sectional study showed a similar risk of DM in all 4 phenotypes (60). Dyslipidemia, reflected by high triglycerides and low high-density lipoprotein cholesterol, is the commonest metabolic abnormality detected in PCOS (61). Some studies have performed deep lipid phenotyping and demonstrate high low-density lipoprotein cholesterol levels, an increase in atherogenic lipoproteins and a decrease in high-density lipoprotein cholesterol efflux capacity, indicating increased CVD risk (62). When examining the risk in different age groups, there are few studies in adolescents and those in older women show a higher prevalence of dyslipidemia in the hyperandrogenic phenotype (63). The association between hypertension and PCOS is mixed. Most studies do not demonstrate a higher risk of hypertension independent of BMI, although longitudinal data demonstrate elevated blood pressure even in lean women with PCOS (64). The few studies in adolescents and older women do not show significant differences compared with control groups (65). Given that most of the data on metabolic risk is derived from cross-sectional studies, the long-term significance of mild to moderately abnormal values for blood pressure measurements and serum lipids is not clear. Another approach is to evaluate the prevalence of metabolic syndrome as it assesses early evidence of dyslipidemia, hypertension, glucose intolerance, and obesity as a composite score and may predict long-term risk of DM and CVD. Reproductive-age women with PCOS have a 2-fold increased risk of metabolic syndrome (66), with a higher risk in the hyperandrogenic phenotype (29). More importantly, in adolescents with PCOS, the risk of metabolic syndrome is at least 2-fold higher than in girls without PCOS (67).

Reproductive/obstetric

Women with PCOS are at an increased risk of endometrial hyperplasia and infertility related to anovulation. Premenopausal women with PCOS may have a 4-fold increased risk of endometrial cancer (68). For women with PCOS who are seeking pregnancy, the ovulation induction

agent letrozole is associated with higher live birth rates compared with clomiphene citrate (69). Use of metformin in conjunction with these medications may improve the ovulation rate in a subpopulation of obese women. Depending on the ethnicity and study population assessed (eg, clinical cohorts vs population-based studies) the obesity rate varies from 50% to 80% (70). Metformin, on the other hand, has not been shown to reduce the risk of gestational diabetes (GDM); thus, its use should be limited to prior to pregnancy for metabolic management and to facilitate weight loss. Once pregnant, women with PCOS are at an increased risk of miscarriage, GDM, pregnancy-induced hypertension, and preeclampsia (71). These complications are increased in the hyperandrogenic phenotypes.

Behavioral/emotional

PCOS is associated with a higher prevalence of psychiatric disorders. Both moderate-to-severe depressive and anxiety symptoms are increased in cross-sectional studies (72), while a few longitudinal studies support an increased risk of incident depression and anxiety (73). However, there is limited data on the persistence of depressive and anxiety symptoms in adolescents and beyond the fourth decade, although recent data implies psychological distress prevailing long-term (74, 75). In addition, women with PCOS have a higher prevalence of disordered eating (76) and body image distress (77). Interestingly, in the latter study various aspects of body image distress predicted anxiety and depressive scores, indicating that improvement in body image could potentially decrease anxiety and depressive symptoms. Both eating disorders and body image distress add to difficulty in losing weight, highlighting the importance of routine screening for these disorders and use of interventions such as cognitive behavioral therapy (72, 78).

Quality of life

PCOS symptoms and comorbidities burden women with PCOS. Women with PCOS report poorer health status than non-PCOS counterparts (79) and indeed, health professionals and women should be aware of the adverse impact of PCOS on health-related quality of life (80, 81), which seems to prevail at least until the late reproductive years (79).

What remains to be clarified

Cardiovascular disease

The risk of dyslipidemia, DM, and metabolic syndrome in older women with PCOS have been compared in fewer studies relative to the outcomes of obesity and impaired glucose tolerance. Most of the available data in perimenopause and beyond is obtained from small cross-sectional

studies that included women with a presumed diagnosis of PCOS, limiting the validity of the findings. In order to adequately counsel patients, the prevalence of traditional CVD biomarkers needs to be assessed in different phenotypes of PCOS. There is some evidence for increased subclinical atherosclerosis in young women with PCOS. Increase in carotid intima media thickness measurements have been described (82), with data suggesting an increased risk for stroke and myocardial infarction (64). Ultimately, we need more longitudinal studies examining the incidence of cardiovascular events in this populations. Although there is some evidence from population-based studies for increased cardiovascular events in late reproductive-age women with PCOS, most studies lack adequate power to evaluate these outcomes and do not include menopausal women with well-defined PCOS. (83)

Perimenopausal disease course

In a large proportion of women, the clinical features of PCOS improve with age, such that by the fourth decade the menstrual cycles become more regular and serum androgen levels normalize (51). High serum levels of AMH and high antral follicle counts suggest increased ovarian reserve in early reproductive years. These biomarkers also decrease with age, and their trajectory suggests that women with PCOS may go through menopause later than controls (84).

Management

The management of comorbidities related to PCOS such as obesity, type 2 DM, and all health impairments related to metabolic syndrome and psychological distress should be treated following the current common guidelines regardless of PCOS diagnosis. What should be noted is that PCOS increases the risk for all these comorbidities at least 2- to 3-fold (mental distress even up to 5-fold), with the onset occurring several years earlier than in other women. This should be considered when screening and testing for these comorbidities.

The new international PCOS guideline recommends assessing weight and measuring waist circumference during every visit and otherwise every 6 to 12 months also giving high importance for weight gain prevention and pre-pregnancy weight management (3). Given that even lean women with PCOS are insulin resistant, all women should be tested for glycated hemoglobin A1c (HbA1c) levels every 3 years and administered an oral glucose tolerance test every 1 to 3 years if any known risk factors for type 2 DM. During pregnancy, an oral glucose tolerance test should initially be performed in the first trimester and repeated in the second, in gestational weeks 24 to 28, if normal in the first

trimester. Obesity has been shown to be a high-risk factor for GDM also in PCOS, although PCOS also presents as an independent risk factor (85).

Hypertension should be screened annually, whereas dyslipidemia should be considered and tested for in overweight and obese women at diagnosis, although according to a recent Nordic study among women <35 years, only a minority have values warranting statin medication (86). Considering the different PCOS phenotypes and risk profiles for different comorbidities, future studies should target building algorithms or tools facilitating targeted screening for women with PCOS with high metabolic risk.

Mental disorders should be tested and treated similarly to common guidelines for the general population. However, psychological distress should be systematically screened in all women with PCOS by using the common tools and short questionnaires and further assessed and/or referred for assessment if needed. Regarding adolescents, similar increases in emotional disturbance are noted; thus, there is a need to address the management of mental distress in this population, as well.

Lifestyle interventions

Obesity worsens the presentation of the symptoms of PCOS and weight management has been proposed as an initial treatment strategy (3). Lifestyle intervention consists of changes in diet, exercise, and behavioral interventions designed to improve weight. Women with and without PCOS have similar diet and physical activity levels (87), suggesting that interventions can focus on general healthy principles. However, interventions have been studied in only small populations in PCOS and the evidence is of low quality. Meta-analysis of lifestyle interventions (88) demonstrated improvement in weight, free androgen index, and BMI with weight reduction from lifestyle interventions (low-quality evidence). However, there was no specific impact on livebirth or menstrual regularity. An additional randomized trial of behavioral modification in PCOS with a primary outcome of menstrual regularity was reported in 2019 (89). A 4-month intervention resulted in significant weight reduction (-2.1%) and improved menstrual irregularity but did not show improvements in ovulation (89). The majority of women in the trial had moderate-to-severe distress in a global index of psychological wellbeing. There was evidence of improved anxiety, reduced depressed mood, and overall higher general health in the intervention group with no change in the minimal intervention group (90). Exercise alone as intervention in PCOS has been studied (91). Most studies of exercise intervention are small and involved varying exercise interventions— aerobic, resistance,

and combined exercise. There was little evidence of impact on exercise alone on reproductive or hormonal outcomes but evidence for reduction in BMI was moderate.

Adherence to diet and physical activity recommendations for lifestyle intervention is challenging. Critically, such adherence is important to achieve goals, and therefore real-world outcomes of lifestyle interventions may be significantly less over time (92). A review of studies in PCOS involving lifestyle intervention did not provide significant data on adherence to the programs in the majority of trials (93). A detailed look at 4 randomized trials of lifestyle intervention in PCOS involving a total of 221 women showed that attrition from the programs was 47.1%. However, weight loss of $\geq 5\%$ occurred in 63% of the women. Women who were more likely to experience attrition had higher depressive indices at baseline and those who had better appointment attendance had lower attrition and greater weight reduction (94). It is likely that many genetic, psychosocial, sociodemographic, and physiological factors impact the success of a lifestyle/weight loss intervention. The inclusion of behavioral support in these interventions is suggested based on psychological factors that are present with higher attrition from these programs. Overall available evidence suggests that lifestyle intervention involving weight reduction has a positive effect on hyperandrogenism and metabolic features of PCOS as well as on quality of life, however there is less support for improvements in reproductive and fertility outcomes.

Medical interventions

PCOS symptoms

The International PCOS guideline set recommendations for treating PCOS-related symptoms that are core to diagnosis, namely, irregular cycles, hirsutism, and anovulation. As hyperinsulinemia promotes hyperandrogenism, medical treatment is recommended only as second-line therapy after lifestyle modification. For medical interventions, combined contraceptives (COCs) are effective in treating irregular cycles and they are also superior for the treatment of hirsutism and acne compared with progestin-only preparations. Given that there are no data showing superiority for any particular estrogen-progestin combination, the choice for COC can be done according to administration preference and minimizing the side effect profile to ensure compliance (3). Of note, as recommended by the World Health Organization, 35 µg estrogen in combination with cyproterone acetate should only be used as a second-line choice for persistent acne or hirsutism, given the increased risk for vascular thromboembolism related to these preparations.

Metformin-only therapy exerts only mild-to-moderate changes on cycle regularity and hyperandrogenism and has

been reported to be inferior to COC treatment. However, as a novel approach, the new guideline encourages combining metformin with COCs, especially in overweight or obese women with PCOS. This recommendation also applies to adolescents. The data regarding antiandrogen medication were limited due to a lack of high-quality studies, and the already existing data did not show antiandrogens having major advantages when combined with COCs. A recent placebo-controlled randomized controlled trial also confirmed this, as only minimal additional benefit was shown when combining bicalutamide, an androgen receptor antagonist, with COC treatment for 12 months (95). In clinical practice, when treating reproductive-aged women, the risk of virilization of the male offspring in case of pregnancy should be noted, warranting effective contraception when prescribing antiandrogens.

Metabolic outcomes

Metformin, especially in combination with lifestyle modifications, has the most data on improving menstrual cycles, glucose levels, and adiposity in PCOS; mild-to-moderate alleviation of insulin resistance and minimal-to-moderate effect on improving lipid profile (96). Low cost, availability, and the low adverse event profile of metformin supports its use. The most common side effects related to metformin are gastrointestinal symptoms, which are important to emphasize in patient consultation to ensure adherence to the treatment. The use of obesity drugs is limited by their high price and availability, but emerging evidence suggests their efficacy, especially glucagon-like peptide-1 (GLP-1) receptor agonists, in treating obesity in women with PCOS, compared with metformin (97). Future efforts should aim to assess the efficacy of combination therapies, for example metformin and GLP-1 receptor agonist agents, and to anticipate when these obesity drugs will become available in low-income countries and communities.

Reproductive outcomes

A recent meta-analysis concluded that letrozole improves live birth and clinical pregnancy rates and reduces time-to-pregnancy compared to clomiphene citrate and was it recommended as the first-line treatment for women with PCOS and infertility (70). As for metformin, a recent review suggests very modest improvement of ovulation and live birth with metformin over placebo. However, the benefit of combining metformin with clomiphene citrate was inconclusive (98). The data on the benefit of myoinositol for improving live birth rate or clinical pregnancy rate in subfertile women with PCOS undergoing in vitro fertilization are poor and therefore inadequate to form a recommendation. A recent Cochrane analysis was not able to draw a conclusion on inositol benefit due to insufficient data

(99). Future studies should focus on assessment of whether priming with metformin before ovulation induction with letrozole would have beneficial effects on live birth rates in PCOS. In cases where in vitro fertilization is needed, an antagonist protocol with GnRH trigger is preferred to reduce the risk for ovarian hyperstimulation syndrome.

Surgical interventions

Surgical interventions can sometimes relieve PCOS-related symptoms. Bariatric surgery is an effective treatment for obesity and PCOS symptoms after all other treatment options have failed and it should be offered to severely obese patients (100). The risks, however, include surgical and dietary complications and pregnancy should not be pursued during the 12 months following the surgery.

Laparoscopic ovarian drilling is a procedure in which ovarian tissue is destroyed with a laser beam or with a surgical needle using minimally invasive laparoscopic techniques, aiming to rebalance and improve ovarian function in PCOS. The procedure is not commonly used, but it has remained as an option in cases of clomiphene citrate-resistant ovaries and when letrozole is not an option due to off-label use. However, the recent Cochrane Review summarized that although reducing the number of multiple pregnancies and the risk for ovarian hyperstimulation syndrome, laparoscopic ovarian drilling may actually decrease the live birth rate in women with anovulatory PCOS and clomiphene citrate resistance compared with medical ovulation induction alone (101). One should also bear in mind that laparoscopic ovarian drilling also subjects women to the risks associated with surgery, such as complications from anesthesia, infection, and adhesions.

Cognitive behavioral therapy

Recent studies have also suggested that cognitive behavioral therapy (CBT) may be effective in treating women with PCOS (78). A recent randomized controlled trial reported 3-component treatment, including diet, exercise, and CBT, improved depression and self-esteem in obese women with PCOS (102).

Conclusions

Despite its prevalence in reproductive-aged women, the diagnosis and management of PCOS remains challenging. Some of these challenges are highlighted in Table 3. Clear diagnostic protocols should allow for more timely and accurate diagnosis, which will address the concerns of both clinicians and consumers resulting from diagnostic delay. The pathogenesis of PCOS is complex and multifactorial.

New insights into the pathophysiology of PCOS suggest that there may be antenatal drivers for development of PCOS, specifically, evidence of hyperandrogenism in mothers appears to influence development of PCOS features in offspring. Insulin resistance is a near-uniform finding in PCOS and is worsened by hyperandrogenism-related adiposity. The role for abnormal AMH in the pathophysiology is also emerging, but AMH is not yet a diagnostic tool for PCOS. Comorbidities in PCOS are well-described and it is important to evaluate and address these comorbidities early in the treatment course, including attention to mental health and quality-of-life measures. While metabolic abnormalities are well described, the role of PCOS in cardiovascular disease remains uncertain. Evidence-based treatment guidelines include recommendations for lifestyle intervention as primary management for metabolic disease, although

Table 3. Highlights of Controversial Areas in the Diagnosis and Treatment of PCOS

Controversy	Current recommendation
Use of AMH in diagnosis	While AMH is typically elevated in women with PCOS and reflects the increase in follicle pool, AMH is not currently recommended as a diagnostic criteria as there is overlap with normal reproductive measures and it does not sufficiently distinguish PCOS.
Diagnosis in adolescence	Adolescents must be at least 2 years post menarche to consider the diagnosis. Ultrasound is not recommended in this age group before 8 years post menarche due to overlap with normal physiologic findings. Consideration may be given to the label "at risk for PCOS" for those in transition where the diagnostic criteria are uncertain.
Diagnosis in perimenopause	Menstrual regularity improves with aging in PCOS; therefore, a retrospective diagnosis is necessary in this age group.
Use of metformin without evidence of diabetes	While there is little support as a single agent for use in ovulation induction, there is evidence of improved metabolic parameters with the use of metformin. There is modest impact to reduce weight and prevention of diabetes development noted in other populations and can be considered for these indications in PCOS.
Type of oral contraceptive	There is no evidence that one type of combined oral contraceptive is better than another for either improvement in menstrual cycles or for suppression of hyperandrogenism.
Use of combination therapy with metformin	There is evidence that adding metformin to combination oral contraceptives may improve response particularly in obese women with PCOS.

Abbreviations: AMH, anti-Müllerian hormone; PCOS, polycystic ovary syndrome.

specific benefit in reproduction is not yet defined in weight loss trials. Oral contraceptives remain a first-line therapy for management of hyperandrogenism and irregular cycles and the role for metformin, while limited, may still add benefit for metabolic dysfunction and weight management, including in adolescents. There remain a number of challenges in the management of PCOS. A high prevalence of obesity is a significant contributor to morbidity. Early attention to weight gain in childhood and adolescence in those at risk for PCOS may be an important measure of prevention, since early markers of PCOS are better defined.

Additional Information

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What Diet, Physical Activity and Behavioral Strategies Are Used by Women with Polycystic Ovary Syndrome and Where Are They Sourced From?

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Objectives: Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting 13% of reproductive-aged women. Lifestyle management is the first-line treatment for improving reproductive, metabolic and psychological complications in PCOS, however women experience challenges with implementing behavioral change. This indicates a clear need to better understand how women with PCOS engage with evidence-based dietary and physical activity (PA) interventions. The primary aim of this study was to identify the types and sources of dietary and PA interventions implemented by women with PCOS. A secondary aim was to understand how they use behavioral and cognitive self-management strategies to support behavioral change.

Methods: In this cross-sectional study an online questionnaire was disseminated via the PCOS Nutrition Centre (a consumer-based website) between May 2015-May 2016. Women ($n = 1167$) were aged

18–45 years, primarily born within the United States (70%) and self-reported a PCOS diagnosis.

Results: While only 33% and 16% of women reported following formal nutrition or PA guidelines (respectively), 57% had implemented a ‘special diet’ to help manage their PCOS. Many of these diets were not supported by evidence-based PCOS practice. Participants also displayed a low level of engagement with important self-management behaviors, including goal setting and positive self-talk. The internet was the primary source of nutrition (36%) and PA (32%) information, with few turning to health professionals including doctors (nutrition 16%; PA 13%) and dietitians (nutrition 4.8%; PA 2.4%).

Conclusions: These findings suggest that online information may promote inaccurate non-evidence-based lifestyle advice, and indicates a need to increase engagement with qualified health professionals. As current lifestyle advice for PCOS management utilized by health professionals are based on generic national guidelines, it is possible that this one-size-fits-all approach does not satisfy their desire for more personalized recommendations. It is also likely that health professionals will need to diversify their mode of communication through the delivery of online lifestyle education.

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concerned a squamous stratified epithelioma extending from a metaplastic fundal mucosa. It was combined with a large submucous myoma.
(c) The third was an adenocarcinoma combined with a submucous myoma which had undergone changes into a polymorphous spindle-cell sarcoma.

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AMENORRHEA ASSOCIATED WITH BILATERAL POLYCYSTIC OVARIES*

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ACCORDING to leading authoritative works on gynecology, the bilateral polycystic ovary is most commonly found in association with *uterine bleeding* (Fig. 1). This association has been recognized by the medical profession and is not infrequent in occurrence. Endometrial hyperplasia, multiple follicle cysts with granulosa cell lining, and a notable absence of corpora lutea in the ovary are the significant pathologic findings in such cases. The bleeding in these patients is readily explained by the fact that the increase in number of follicles lined by granulosa cells produces an excess of secretion of estrogenic hormone.

According to the same authoritative works, little or no mention is made of bilateral polycystic ovaries accompanied by *amenorrhea*, and inasmuch as we have encountered a series of cases exemplifying the latter conditions, we desire to present the results of our study of them.

Cyst formation in the follicular apparatus of the ovary is very common and is regarded to some extent as a physiologic process. When these structures are visible to the naked eye, they are regarded as cysts; when not, they are called follicles. When this process becomes excessive, persistent or progressive, the ovary becomes enlarged, tense, tender and painful, and produces what has been termed "cystic degen-

*Read at a meeting of the Central Association of Obstetricians and Gynecologists, November 1 to 3, 1934, New Orleans, La.

Assess the Effectiveness of Life Style Modification Regimen on Polycystic Ovary Syndrome among Adolescent Girls in Selected Colleges, Puducherry - Pilot study

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Abstract

Background: Polycystic ovary syndrome is a common endocrinopathy affecting women of reproductive age. Commonly manifested by polycystic ovary, menstrual irregularities and hyperandrogenism even though the presentation could be heterogeneous. Insulin resistance (IR) is considered to be accountable for the associated hormonal and metabolic derangements. Polycystic ovary syndrome has two phenotypes, overweight/obese and lean.

Objectives & Methodology: Quasi experimental one group pre and posttest timeseries research design was adopted to assess the effect of Life Style Modification Regimen on Polycystic Ovary Syndrome among 16 Adolescent Girls in selected Arts and Science Colleges, Puducherry. Baseline screening was done for 112 adolescent girls by census method using modified PCOS risk assessment questionnaire and identified adolescent girls with PCOS. Adolescent girls at moderate risk of PCOS with BMI 23 and above were included in the study. PCOS risk and Lifestyle habits were assessed before and after implementation of Lifestyle Modification Regimen, whereas clinical features of PCOS were assessed at baseline, at 2months (Posttest-1), 4 months (Posttest-2) and at 5 months (Posttest-3).

Results: Study results shows that significant difference between Pre and posttest PCOS risk (17.507) and lifestyle habits (Dietary habits: -3.873 and Physical activity: -2.236) at $p < 0.05$ level. Improvement found in the clinical features of PCOS including weight, BMI, menstrual cycle, Hirsutism and Acne at $p < 0.05$ level. Similar percentage (50%) of them had unfavorable and moderately favorable dietary habits during pretest, whereas in posttest 81.3% and 18.7% had moderately favorable and fa-

vorble dietary habits and highest percentage (62.5%) of them had Moderately favorable physical activity in pretest, whereas 75.8 and 24.2% had Moderately favorable and favorable physical activity respectively in posttest. Significant association found between the pretest level of PCOS risk and lifestyle habits of adolescent girls (dietary habits: 12.444 & Physical activity: 6.661) at $p < 0.05$ level and also observed association between the pretest level of PCOS risk and selected demographic variables such as age in years and monthly family income in Rs at $p < 0.05$ level.

Conclusion: Lifestyle Modification brings positive change in lifestyle habits, risk of PCOS and clinical features of PCOS among adolescent girls at risk of PCOS. Study concludes that Healthy lifestyle practices prevents the development of PCOS by risk reduction. Primordial prevention involving early identification of Risk of PCOS promotes reproductive health of the adolescent girls.

Key words

Adolescent Girls and Risk of PCOS, lifestyle habits, lifestyle modification regimen.

Imprint

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BACKGROUND

Health is a fuel that runs a human body with the regular activities and functions. In women's, reproductive health plays an important role of general health which needs universal concern. It is very important to care themselves during their reproductive age in order to prevent reproductive health related problems. Improper reproductive life pose risk to the life of a woman. Many times, woman has the risk of infertility, contraception, and other reproductive infections caused by sexual practices. Irregular menstrual periods among women cause such ovulatory dysfunctions and polycystic ovarian syndrome. Women with PCOS have no regular periods, and are not able to ovulate and get pregnant.⁽¹⁾

Polycystic ovary syndrome is a common endocrinopathy affecting women of reproductive age. Com-

monly manifested by polycystic ovary, menstrual irregularities and hyperandrogenism even though the presentation could be heterogeneous. Insulin resistance (IR) is considered to be accountable for the associated hormonal and metabolic derangements. Polycystic ovary syndrome has two phenotypes, overweight/obese and lean. The prevalence of lean PCOS is much less common comparatively overweight/obese PCOS.⁽²⁾

Poly Cystic Ovarian Syndrome (PCOS) is the common endocrine disorder globally increased the prevalence of overweight and obesity among women and young women. It is a heterogeneous disorder involved with multiple etiology that has been made it difficult to define the syndrome by diagnostic test. It is very important for women to take care of their health during their reproductive years because much reproductive health related problems can arise during this period. Any failure in living a healthy reproductive life could cause a risk to the life of women and adds to the maternal mortality rate. Women bear the risk of infertility and many other reproductive infections.⁽³⁾

NEED FOR THE STUDY

Polycystic ovary syndrome (PCOS) is a common endocrine disorder with a global prevalence of 5-10% and is an important cause of chronic anovulation in young women. PCOS is characterized by menstrual irregularity, signs of hyperandrogenism such as acne, excess body hairs, male-pattern baldness and infertility. In addition, PCOS is linked to many long-term health problems such as cardiovascular diseases and diabetes.⁽⁴⁾

Polycystic ovarian disease in teenager is characterized irregular or completely absent periods, heavier than normal menstrual bleeding, ovarian cysts, hirsutism and alopecia. Other symptoms range from acne, skin tags and brown skin patches to reduced sex drive, exhaustion or lack of mental alertness, depression anxiety, sleep apnea and thyroid problems. Teens with overweight are increasingly being linked with Polycystic Ovarian Disease.⁽⁵⁾ Women diagnosed with Polycystic ovary syndrome (PCOS) experienced poor quality of life, greater anxiety and depression than women without PCOS related to BMI status.⁽⁶⁾

A community based cross sectional study conducted on prevalence of PCOS among 778 young girls and adolescents aged between 15-24 years in Mumbai. Clinical, USG and biochemical investigations were completed by 600 adolescent girls. Results reveals that,

prevalence of PCOS was 22.5% by Rotterdam criteria and 10.7% by Androgen Excess Society criteria. Prevalence of PCOS among nonobese comprised of 71.8% diagnosed by Rotterdam criteria. Mild PCOS comprised of 52.6%.⁽⁷⁾

A cross sectional study was conducted to assess the dietary habits and life style among 384 pre-university college students, Raichur, India. Results reveals that 45.6 % were male and 54.4% were females. The mean age was 16.75 yrs. 184 (48%) students were predominantly vegetarians. 176 (45.8%) reported consumption of junk food more than once in a week and 338 (88%) reported to use fruits and vegetables occasionally in their diet. Only 147 (38.3%) students walked at least for 30 minutes and did exercise daily. The study concludes that prevalence of unhealthy dietary habits and life style are more also with obesity.⁽⁸⁾

Cross-sectional study was carried out among 420 girls residing in the social welfare hostels in urban area of Vizianagaram District, Andhra Pradesh, India. The result shows that 56.4 % girls were undernourished. 2.9% was found to be overweight and none of the girls was found to be obese. According to the new guidelines by the Government of India 56.4 % was found to be undernourished while 5.8 % was found to be Overweight.⁽⁹⁾

METHODOLOGY

Quasi experimental one group pre and posttest study was conducted to investigate the effect of Lifestyle modification Regimen on the risk of PCOS among Adolescent Girls in selected Arts and Science College, Puducherry.

Tool for data collection

Section -I: Modified PCOS risk assessment questionnaire consist of 09 items

Section -II: Demographic variable consist of 13 items

Section - III: Five-point rating scale on lifestyle habits consist of 30 items in two sections for dietary habits and physical activity

Section -IV: Tool to assess the clinical features of PCOS

Description of Intervention

Duration: Four months

1. Group Counseling Session

2. Aerobic exercise for weekly three days for 30 minutes

3. Structured dietary guidelines for PCOS

Ethical consideration

Formal permission taken from Institutional Review Board, Directorate of Technical & Higher Education and Principal of the College, Puducherry. Informed consent was taken after explaining the study purpose and assent and parent consent taken for the minors.

Data collection procedure

Data collection was carried out from four months in 2021. Baseline screening was done for 112 adolescent girls by census method using modified PCOS risk assessment questionnaire and identified adolescent girls with PCOS. Adolescent girls at moderate risk of PCOS with BMI 23 and above (16) were included in the study. SAQ used to collect data on demographic variable, PCOS risk and Lifestyle habits were assessed before and after implementation of Life Style Modification Regimen, whereas clinical features of PCOS were assessed at baseline, at 2months (Posttest-1), 4 months (Posttest-2) and at 5 months (Posttest-3).

RESULTS

Demographic characteristics shows that 62.5% of them were in 19 years, 62.5% belongs science background, 43.7% of them attained menarche at 14-15 years of age, similar percentage (87.5%) were non-vegetarian and Hindus, 31.3% had monthly family income of Rs.10,110 – 15,159, 81.2% of them were belongs to nuclear family, 56.3% from rural, similar percentage (37.5%) of the mother and father studied Higher secondary education, 31.3% and 6.3% had family history DM and PCOS respectively and 25.0% got previous information about PCOS. (Table no.1)

Table 1

Frequency and percentage distribution of Adolescent Girls according to socio demographic variables n = 16

Sl.No	Socio demographic variables	Frequency (f)	Percentage (%)
1.	Age in year		
	17	3	18.8
	18	3	18.8
	19	10	62.5
2.	Education		
	B.Sc	10	62.5
	B.Com	3	18.8
	BCA	3	18.8

3.	Age at Menarche in years		
	10-11	2	12.5
	12-13	6	37.5
	14-15	7	43.7
	> 15	1	6.3
4.	Dietary Pattern		
	Vegetarian	2	12.5
	Non-vegetarian	14	87.5
5.	Religion		
	Hindu	14	87.5
	Christian	2	12.5
6.	Monthly family Income in Rupees		
	≥ 40,430	1	6.3
	20,210 – 40,429	3	18.8
	15,160 – 20,209	3	18.8
	10,110 – 15,159	5	31.3
	6060 – 10,109	4	25.0
7.	Type of family		
	Joint	3	18.8
	Nuclear	13	81.2
8.	Place of residence		
	Urban	7	43.8
	Rural	9	56.3
9.	Father's Education		
	Secondary	3	18.8
	Higher secondary	6	37.5
	Diploma	5	31.3
	Undergraduate	2	12.5
10.	Mother's Education		
	Primary	2	12.5
	Secondary	4	25.0
	Higher secondary	6	37.5
	Undergraduate	4	25.0
11.	Family history of DM		
	Yes	5	31.3
	No	11	68.8
12.	Family history of PCOS		
	Yes	1	6.3
	No	15	93.7
13.	Previous source of information		
	Yes	4	25.0
	No	12	75.0

Similar percentage (50%) of them had unfavorable and moderately favorable and none had favorable dietary habits whereas, 81.3% had moderately favorable and 18.7% had favorable dietary habits in posttest. (Table no.2)

Table: 2

Distribution of Adolescent Girls according to Dietary Habits
n = 16

Dietary Habits	Pretest		Post test	
	f	%	f	%
Unfavorable	8	50.0	0	0
Moderately favorable	8	50.0	13	81.3
Favorable	0	0	3	18.7

Highest percentage (62.5%) of them had Moderately favorable and none had favorable physical activity whereas, 75.8% had moderately favorable and 24.2% had favorable physical activity in posttest. (Table no.3)

Table 3

Distribution of Adolescent Girls according to Habit of Physical activity
n = 16

Habit of Physical activity	Pretest		Posttest	
	f	%	f	%
Unfavorable	6	37.5	0	0
Moderately favorable	10	62.5	13	75.8
Favorable	0	0	3	24.2

Frequency of menstrual cycle shows that in pretest highest percentage (50.00%) had frequency of menstrual cycle 36-41 days whereas in Posttest 71.42% had their menstrual cycle at 21 – 35, Duration of menstrual blood flow depicts that during pretest similar percentage (35.72%) of them had duration of 3-5 days and < 3days, whereas in posttest highest percentage (71.42%) had duration of 3-5 days and Perceived blood loss shows that 64.28% of them perceived moderate blood loss in pretest, whereas in posttest 78.57% of them perceived moderate blood loss (Table no.4)

Significant difference in the Pre and posttest PCOS risk among adolescent girls and calculated t- value was 17.507 at p < 0.01 level. It concludes that there was positive improvement in PCOS risk after implementation of lifestyle modification regimen (Table no.5)

Significant difference in the Pre and posttest Lifestyle habits among adolescent girls and calculated t- value was -3.873 and -2.236 at p < 0.01 level respectively for dietary habits and physical activity. It concludes that there was positive improvement in lifestyle habits after implementation of lifestyle modification regimen. (Table no.6)

Significant difference in the Pre and posttest clinical features of the adolescent girls that during pretest mean weight score was 61.38 ± 4.90 whereas in posttest-3 the

Table 4

Percentage wise comparison of pre and Posttest menstrual pattern of Adolescent Girls
(N = 14)

Menstrual Pattern	Pretest		Posttest-3	
	f	%	F	%
Frequency				
< 21 Days	1	7.14	1	7.15
21-35 Days	5	35.72	10	71.42
36 – 41 Days	7	50.00	3	21.43
42 – 60 Days	1	7.14	-	-
Duration				
< 3 days	5	35.72	2	14.29
3 - 5 days	5	35.72	10	71.42
> 5days	4	28.56	2	14.29
Perceived blood loss				
Light	3	21.43	2	14.29
Moderate	9	64.28	11	78.57
Heavy	2	14.29	1	7.14

Table 5

Compare the effect of lifestyle modification regimen on PCOS risk
(n = 16)

Level of PCOS risk	MD	SD	t - value	P
Pretest and Posttest PCOS risk	3.563	0.814	17.507	.000

p < 0.01- significant

Table 6

compare the effect of lifestyle modification regimen on lifestyle habits
(n = 16)

Lifestyle habits	Mean	SD	t - value	p-value
Dietary habit	Pretest	.250	-3.873	.002
	Posttest	512		
Physical activity and Sleep	Pretest	.250	-2.236	.041
	Posttest	403		

p < 0.05 significant

mean weight score was 57.45 ± 4.190 and calculated t-value was 11.135 at p < 0.01 level, mean BMI score was 25.10 ± 1.805 during pretest, whereas in posttest-3 the mean BMI score was 23.48 ± 1.333 and calculated t-value was 10.767 at p < 0.01 level, pretest mean hirsutism score 10.91 ± 2.948 whereas in posttest-3 the mean hirsutism score was 9.09 ± 3.986 and calculated t-value was 4.303 at p < 0.05 level and pretest mean acne score 21.92 ± 5.760 whereas in posttest-3 the mean acne score was 11.33 ± 2.015 and calculated t-value was 8.474 at p < 0.01 level (Table no.7)

Table 7

Effect of lifestyle modification regimen on clinical features of PCOS

Clinical features of PCOS		Mean	SD	Mean Diff.	t-value	p-value
Weight (N = 16)	Pretest	61.38	4.9055	-	-	-
	Posttest-1	60.28	4.6780	1.10	8.375	.000
	Posttest-2	58.80	4.2531	2.58	9.045	.000
	Posttest-3	57.45	4.1901	3.93	11.135	.000
BMI (N = 16)	Pretest	25.10	1.8054	-	-	-
	Posttest-1	24.65	1.6729	0.45	8.332	.000
	Posttest-2	24.05	1.5060	1.05	9.206	.000
	Posttest-3	23.48	1.3336	1.62	10.767	.000
Hirsutism (N = 11)	Pretest	10.91	2.948	-	-	-
	Posttest-1	10.27	3.101	.636	2.609	.026
	Posttest-2	10.27	2.867	.636	3.130	.011
	Posttest-3	9.09	3.986	1.818	4.303	.002
Acne (N = 12)	Pretest	21.92	5.760	-	-	-
	Posttest-1	18.75	5.207	3.18	13.385	.000
	Posttest-2	14.67	3.284	7.25	7.864	.000
	Posttest-3	11.33	2.015	10.58	8.474	.000

p < 0.01 highly significant & p < 0.05 significant

Significant association found between the pretest level of PCOS risk and lifestyle habits of adolescent girls (dietary habits: 12.444 & Physical activity: 6.661) at p < 0.05 level (Table no.8) and also observed association between the pretest level of PCOS risk and selected demographic variables such as age in years and monthly family income in Rs at p < 0.05 level. (Table no.9).

Table 8

Association between the Pretest PCOS risk and lifestyle habits of adolescent girls
(N = 16)

Parameter	χ^2	p-value
Pretest PCOS risk and dietary habits	12.444a	.002
Pretest PCOS risk and Physical activity	6.661a	.036

p < 0.05 significant.

Table 9

Association between Pretest PCOS risk with selected Demographic variables of the adolescent girls
(N = 16)

S Sl.no	Demographic variable	Pretest PCOS risk	
		χ^2	p-value
1	Age in years	9.813a	.044
4	Diet	1.778a	.411
8	Monthly family income in Rs	18.560a	.017
9	Type of family	4.622a	.099
10	Residence	062a	.969
11	Family history of PCOS	2.216a	.330

p < 0.05 significant.

DISCUSSION

Study results suggests that significant reduction in posttest PCOS risk (17.507) and improvement in lifestyle habits (Dietary habits: -3.873 and Physical activity: -2.236) at p < 0.05 level, and also improvement found in the clinical features of PCOS including weight, BMI, menstrual cycle, Hirsutism and Acne at p < 0.05 level. Anju Krishnan Nair et.al⁽¹⁰⁾ also observed similar findings after implementation of lifestyle modification package among adolescent girls that 66.4% and 15.2% had weight loss and weight stabilization respectively. Lass et.al⁽¹¹⁾ also reported that weight loss after lifestyle intervention was significantly associated with positive change in the menstrual pattern.

Similar percentage (50%) of them had unfavorable and moderately favorable dietary habits during pretest, whereas in posttest 81.3% and 18.7% had moderately favorable and favorable dietary habits and highest percentage (62.5%) of them had Moderately favorable physical activity in pretest, whereas 75.8 and 24.2% had Moderately favorable and favorable physical activity respectively in posttest. Manijeh Alavi et.al⁽¹²⁾ also reported that 54.4% of the adolescent girls had moderate nutrition behavior and Binati Behera et.al⁽¹³⁾ reported that 52.3% and 46.4% of the adolescents and young adult students had slow and moderate physical activity respectively.

Significant association found between the pretest level of PCOS risk and lifestyle habits of adolescent girls (dietary habits: 12.444 & Physical activity: 6.661) at p < 0.05 level and also observed association between the pretest level of PCOS risk and selected demographic variables such as age in years and monthly family income in Rs at p < 0.05 level.

CONCLUSION

Lifestyle Modification brings positive change in lifestyle habits, risk of PCOS and clinical features of PCOS among adolescent girls at risk of PCOS. Study concludes that Healthy lifestyle practices prevents the development of PCOS by risk reduction. Primordial prevention involving early identification of Risk of PCOS promotes reproductive health of the adolescent girls.

Conflict of interest

nil

Source of funding

nil

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Assessment of Risk Factors of Polycystic Ovarian Syndrome Among Women: An Online Based Survey

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Abstract: Polycystic ovary disorder is a fluctuated and regularly intricate cluster of metabolic and endocrine anomalies. This study aims to assess the risk of PCOS among women aged 15-45 years. This is an online-based cross-sectional survey conducted among women of childbearing age in South India. The data was collected online by providing google links to fill out questionnaire forms by various social media platforms. The questionnaire consists of demographic details and assessment questions. Microsoft Excel was used to interpret data. Statistical analysis done by using chi-square test. A total of 466 women responded, among which the women of 15-25 years and 25-36 years, 32.46% have hirsutism, 22.7% have infertility and overweight problems, 24.7% have mood swings, 49.2% have sleep disturbances, 55.5% have tiredness, 41.9% people have good awareness regarding exercise and lifestyle modifications. This study reveals that there is no proper knowledge about PCOS in the population, especially among girls and women, therefore there is a need to educate the public regarding PCOS at a younger age for better health outcomes.

Keywords: PCOS, Overweight, Hirsutism, Anxiety, Lifestyle

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I. INTRODUCTION

Polycysticovarydisorderisafluctuatedandregularlyanintricateclusterofmetabolic and endocrine anomalies. The polycystic ovarian condition was first portrayed by Dr Irving Stein and Michael Leventhal in Chicago in 1935 alluding to a condition endured by women with feminine brokenness, weight, hirsutism and two-sided polycystic ovaries. At that point, it was known as a Stein-Leventhal disorder.¹ According to NIH measures and Rotterdam models, PCOS is characterized as a hormonal issue recognized by the presence of, in any event, one polycystic ovary joined by ovulatory brokenness and unnecessary emission of androgens.² It is the most widely recognized complex endocrine issue, which is regularly found in the regenerative time of women. The determinants of the polycystic ovarian disorder are connected to hereditary and natural variables. The early period of menarche Premature foetal advancement Family history of PCOS among first-degree relatives.³ The primary underlying defect in PCOS remains unknown, but critical features include insulin resistance, impaired gonadotropin and androgen excess. Anovulation is defined as menstrual cycles of more than 35 or <21 days while ovarian morphology is considered significant in the presence of follicles greater than equal to 12 with a diameter of 2-9mm or an ovarian volume of 10cm³.⁴ These diagnostic criteria cannot be applied to adolescents because changes that occur physiologically are associated with puberty overlap with pathological changes observed in PCOS.

1.1. Prevalence of PCOS

The polycystic ovarian syndrome is seen among 1 in 10 women of reproductive-aged women. Not only in women but it is also seen in the girls who enter the reproductive age nowadays. The prevalence of PCOS ranges from 2.2% to 26% in India among childbearing-aged women and affects 116 million women worldwide, according to WHO estimation.^{5,6} The yearly mean cost for the initial evaluation of PCOS was 2.1% of total costs, and further treatment was 31%. The factors like complications, expenses and the age in which it occurs make to study more about Polycystic ovarian syndrome. There are four sorts of PCOS: Insulin-safe PCOS, Inflammatory PCOS, Hidden-cause PCOS and Pill-incited PCOS.^{7,8} Infertility was one of the most originally characteristic symptoms of PCOS⁹. The evidence shows that PCOS is the most common cause of the ovulatory disorder and oligo anovulation is related to the increased risk of infertility.¹⁰ Obesity and insulin resistance were autonomously identified with an expanded danger of early termination and diminished pregnancy and live rates of birth.¹¹ Endometrial anomalies are additionally announced in PCOS ladies.¹² Gestational Diabetes Mellitus (GDM) is the most commonly described pregnancy complication in women with PCOS. In addition, women with PCOS have a high prevalence of classic risk factors for cardiovascular disease(CVD).¹⁴ Causes of PCOS include resistance to insulin, hormonal imbalance and genetics. The effects of yoga alone and its accessibility to individuals of all ages and fitness levels provide unique benefits and make it a powerful therapeutic option for women with PCOS. This study aims to assess the risk of PCOS among women aged 15-45 years. Need of the study is to find the risk of developing PCOS among women and associate the disorder's manifestation with lifestyle variations. It also aims to analyze the influence of lifestyle factors like

Diet, Physical Activity, Stress and Family History with PCOS manifestation.

2. MATERIALS AND METHODS

2.1. Study site

In and around South India

2.2. Selection of Study

Cross-sectional Study: As the study has to be conducted in a certain period, the cross-sectional study was used. In cross-sectional studies, data can be collected from as many participants only for a certain period.

2.3. Study criteria

The age group of women ranging from 15-45 years were included.

2.3.1. Inclusion criteria

The age group of women ranging from 15-45 years are included.

2.3.2. Exclusion criteria

Women of menopause were excluded. Other complications that mimic the conditions of PCOS were excluded. Women diagnosed with PCOS were excluded. Responses without appropriate information were excluded.

2.4. Study duration

The study was conducted for six months.

2.5. Ethical considerations

The study was conducted after getting ethical clearance from Institutional Review Board (RIPER/IRB/2021/035). As we conducted this study online, consent forms were obtained among the participants online. The confidentiality of the participants was maintained during and after the trial completion.

2.6. Sampling technique and Sample size

Non Probability sampling technique was used. The sample size was calculated using Epi-info software 7 with a confidence interval of 95%, a margin of error of 5% and design effect 1. The obtained sample size is 356.

2.7. Search strategy

Authors conducted a literature review in databases like Cochrane library, PubMed, and Google Scholar and collected suitable journals for the questionnaire preparation from September to November 2021. The search strategy is as follows, (PCOS OR Risk factors OR Cross-sectional studies OR Women's health OR Online study OR Questionnaire-based study OR polycystic ovarian syndrome). After conducting a literature review, a questionnaire was prepared for conducting the study. The prepared questionnaire was sent for face validation to the experienced professionals related to the healthcare sectors, the suggestions were

considered, and the final questionnaire was submitted to IRB. The IRB panellists approved the questionnaire for the study.

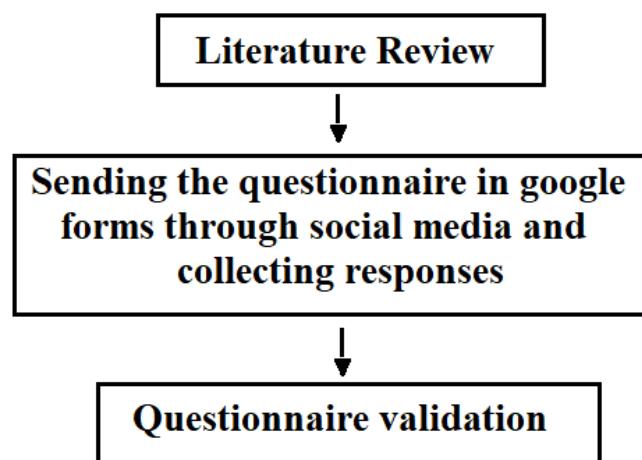
2.8. Study design and procedure

Authors planned to conduct a cross-sectional study in the female population of South India. The entire duration of the study is six months. The prepared questionnaire was presented in Google form and circulated among the female population through WhatsApp, Facebook, Telegram, and Gmail. Electronic consent was taken from participants before filling out the questionnaire, and responses were recorded. A total of 477 responses were collected, of which 466 were selected for final analysis because 11 did not meet the inclusion criteria.

2.9. Risk of bias

Out of 477 responses collected, we removed 11 study

2.11. Flow chart of data extraction



The data extraction process's outcome is 477 responses, of which only 466 were considered, as the remaining needed to meet the criteria.

3. RESULTS

A total of 477 responses were collected using an online questionnaire form. Eleven were excluded as they needed to meet the inclusion criteria. Therefore 466 were the final sample used for the analysis of the data.

Table 1: Weight of the study population (n=466)

Variable	15-25yrs	26-35yrs	36-45yrs	p-value
Weight				
30-50kgs	232(57.5%)	149(36.9%)	22(5.4%)	
51-70kgs	10(40%)	10(40%)	5(20%)	0.000
71-90kgs	7(18.42%)	28(73.68%)	3(7.89%)	

Study participants were categorized according to different age groups (15-25 years, 26-35years and 36- 45 years), and the weight was categorized, which is represented in the above (Table .01) and the obtained p-value was 0.000, which is statistically significant.

Table 2: Menarche started to age (n=466)

Variable	11-15yrs	16-20yrs	p-value
At what age did menarche has been started?			
15-25yrs	380(94.2%)	23(5.8%)	
26-35yrs	25(100%)	0(0)	0.39
36-45yrs	35(92.1%)	3(7.9%)	

Table2 menarche age of women who underwent the study was represented above (Table.02) according to the age groups (15-25 years, 26-35years and 36- 45 years) for the majority of the respondent's menarche started between the age of 11- 15 years

participants, as they did not meet our study criteria, so that we could get accurate results with the available data.

2.10. Statistical Analysis

Descriptive statistics were used for socio-demographic details; data was retrieved from google forms and interpreted in Microsoft excel. The chi-square test was used to determine the association between the categorical variables, i.e., the age of the participants and other variables like weight, age of menarche, and regularity history of PCOS correlated. The Correlation between the clinical features and physiological characteristics was determined by the Pearson correlation test using IBM SPSS statistics 26 version 26.0.0.0. We used the two-tailed Pearson correlation test to determine the Correlation between the clinical features and the psychological symptoms.

(92.2%, n=430) and remaining were in between the age of 16-20years (7.8%, n=26). Therefore, the obtained p-value was 0.39, which is not statistically insignificant.

Table 3: Regularity of menstrual cycle (n=466)

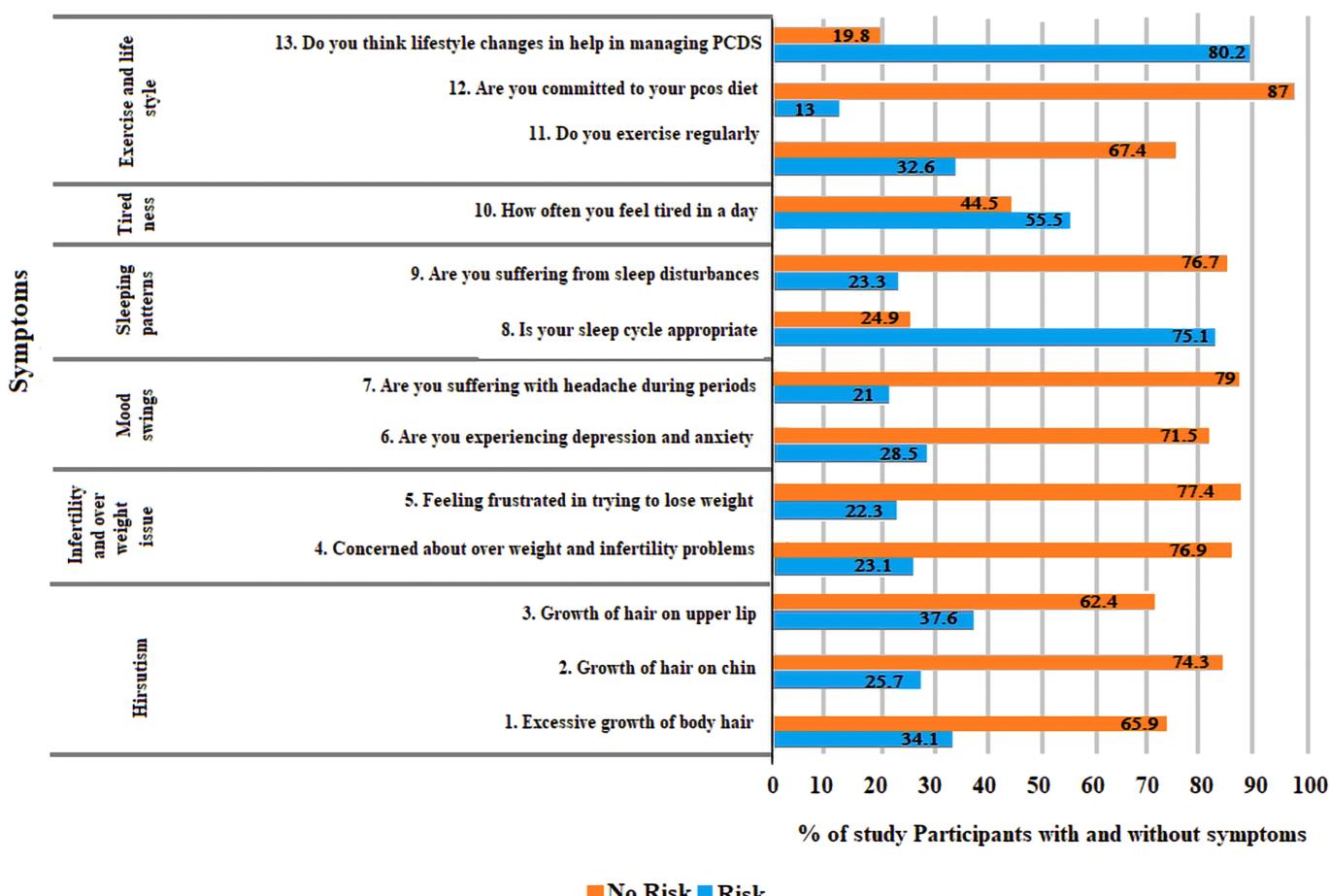
Variable	Yes	No	p-value
Is your menstrual cycle regular?			
15-25yrs	329(81.6%)	74(18.4%)	
26-35yrs	20(80%)	5(20%)	0.71 *
36-45yrs	29(76.3%)	9(2.34%)	

the regularity of the menstrual cycle of study participants. Was represented in the above (Table.03) which Majority of the respondents have a regular menstrual cycle (81.1%, n=378), while the remaining have irregular menstrual cycles (18.9%, n=88), and the obtained p-value was 0.71, which was not statistically significant

Table 4: History of PCOS (n=466)

Variable	Yes	No	Maybe	p-value
Is there a family history of PCOS?				
15-25yrs	21(5.21%)	338(83.8%)	44(10.9%)	
26-35yrs	1(4%)	19(76%)	5(20%)	0.23*
36-45yrs	3(7.89%)	27(71.05%)	8(21.05%)	

history of PCOS of study participants was represented in (Table 4). The majority responded that there is no family history of PCOS (82.4%, n=384). Some responded that there might be a history of PCOS (12.2%, n=57), and the remaining respondents had a history of PCOS (5.36%, n=25), and the obtained p-value was 0.23, which was statistically insignificant.

**Fig 1: Risk Assessment of PCOS based on symptoms**

In the current study, the symptoms related to PCOS are mostly concentrated, which are represented in the above graphical presentation (Figure.01), which include hirsutism: excessive growth of body hair (34.1%), growth of hair on the chin (25.7%), growth of hair on the upper lip (37.6%). Infertility and overweight issues: concerned about being

overweight and infertility (23.1%), feeling frustrated in trying to lose weight (22.3%). Mood swings: Are you experiencing depression and anxiety (28.5%), are you suffering from headaches during periods (21%). Sleeping patterns is your sleep cycle appropriate (75.1%), sleep disturbances (23.3%). Tiredness: How often you feel tired in a day (55.5%).

4. DISCUSSION

The current study on polycystic ovarian syndrome was conducted in and around the Anantapuramu region, Andhra Pradesh, in an online population-based survey. The sample size was 477, out of which 11 were deleted due to inappropriate data. The sample size was calculated using Epiinfo software with a confidence interval of 95%. In the current study, we assessed PCOS risk by using the associated symptoms⁽¹³⁾. Irregularity of the menstrual cycle was observed as a major problem in the age group of 26-35 years (20%) which is majorly associated with the symptoms of PCOS. Among the three age groups, 15-25 years of the respondent population had severe and moderate problems

with the growth of hair on the body (35.66%) and on the upper lip (39.44%), the respondent population of 26-35 years had severe and moderate problems associated with the hair on the chin (32%). Respondents among 26-35 years were majorly concerned with infertility (28%) and being overweight (24%). Depression and anxiety were observed prominently in the 26-35 age group (32%), and headaches during periods were seen mostly in the age group of 15-25 years (21.5%). Sleep cycle was inappropriate in the age group of 26-35 years (28%), and sleep disturbances were seen mostly in the age group of 26-35 years (24%)⁶. Population among 15-25 years exhibited tiredness most of the day (55.6%), and performing exercises were not included in their daily routine (68.4%)^{5, 10}.

Table 5: Pearson Correlation

		Depression and anxiety	Headache during periods	Tiredness	Appropriate sleep cycle	Sleep disturbances
Regularity of menstrual cycle	Pearson correlation	-.193**	.020	-.111*	.229**	-.161**
	Sig. (2-tailed)	.000	.663	.017	.000	.000
Excessive growth of body hair	Pearson correlation	.259**	.041	.140**	-.101*	.145**
	Sig. (2-tailed)	.000	.376	.002	.029	.002
Growth of visible hair on the chin	Pearson correlation	.132**	.081	.161**	-.083	.1428**
	Sig. (2-tailed)	.004	.081	.000	.074	.006
Growth of visible hair on the upper lip	Pearson correlation	.185**	.028	.191**	-.082	.144**
	Sig. (2-tailed)	.000	.547	.000	.076	.002
Infertility concerns	Pearson correlation	.301**	.072	.131**	-.091	.196**
	Sig. (2-tailed)	.000	.120	.005	.050	.000
Overweight	Pearson correlation	.293**	.166**	.054	-.149**	.263**
	Sig. (2-tailed)	.000	.000	.245	.001	.000

** Correlation is significant at the 0.01 level (2-tailed).

*Correlation is significant at the 0.05 level (2-tailed).

Symptoms associated with PCOS and psychological disturbances are correlated as in (Table 05). which is mentioned above.

PCOS is the major cause of psychological morbidity and has a negative impact on women's HRQOL¹⁷. The different aspects of the QOL in PCOSQ were evaluated, including physical, psychological and social. Therefore, the major factors, which cause a reduction in quality of life in PCOS, were found to be different in a variety of respondents. The physical aspect of quality of life predicted by obesity and hirsutism²⁰. In adolescents, excessive body weight is widely reported as an important concern in PCOS women. Obesity is the primary source of poor HRQOL¹⁷ and contributes to negative psychological symptoms in women with PCOS. Changes in body weight and physical beauty, as well as an imbalance of hormones, could reduce QOL.⁹ Anxiety symptoms are very common in the general female and occur at an early age,²⁴, along with other mood disorders such as depression. HRQOL¹⁷ surveys suggest that women with PCOS may be at higher risk of anxiety symptoms related to the clinical signs of hyperandrogenism, weight gain, and health problems, including infertility.^{19,21} Coexisting GAD in depressed patients, may worsen the outcome by increasing the risk of suicide, worsening overall symptoms, increasing the number of unexplained clinical symptoms, and high functional disability.⁵ Untreated GAD is also associated with increased rates of co-

morbidity and high utilization of medical health care²². Studies concerned about the risk of PCOS among women in particular age groups were very less; most of the studies were regarding the co-morbidities associated with the syndrome and the interventions to prevent PCOS.² Hirsutism¹⁵, irregular menstrual cycle and infertility problems¹⁸, and Obesity¹⁹ are different aspects of PCOS which showed a negative impact on HRQOL that would not easily be detected by employing only a self-administered questionnaire by using PCOSQ, and it was demonstrated that clinical symptoms of PCOS especially excess body weight and hirsutism, could compromising the women QOL. Zahra BehboodiMoghadam, BitaFereidooni, and Ali Montazeri performed a study on PCOS titled polycystic ovary syndrome and its impact on Iranian women's quality of life: a population-based survey, the findings of the study indicated that hirsutism followed of infertility and menstrual irregularity had a greater impact on the quality of life of menstruating women. The difference between their study and our current study is that they recruited the sample population with PCOS and focused on the impact of the quality of life of women.¹⁴ Some published articles show that women with PCOS may have a greater prevalence of anxiety

symptoms compared with normal women.²³ It is suggested that childbearing-aged women with PCOS should undergo regular screening tests for anxiety and mood disorders using screening tools and for appropriate diagnostic evaluation and appropriate therapy. Most of the studies were regarding the co-morbidities associated with the syndrome and interventions to prevent PCOS, but our study was concerned about the risk of PCOS among women at particular age¹⁴

5. STRENGTHS AND LIMITATIONS

The online-based survey is more convenient and gets better responses, is significantly less cost and can be accessed from any device like a computer, laptop or mobile. As the study is an online based survey, illiterates were not able to participate in the study. Furthermore, the sampling technique used is a snowball technique; therefore, the sample recruitment may be biased, as there are no Ultra sonographic (USG) and blood tests concerned with PCOS the risk assessment is not profound.

6. CONCLUSION

The study results showed that females between 15-25 years and 26-35 years are at higher risk of developing PCOS. The study revealed that there is no proper knowledge about PCOS in the population, which is the need of the hour;

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therefore, there is a need to educate the public regarding PCOS at an age for better health outcomes. Most importantly, adolescent girls and women of childbearing age should be aware of PCOS. How to identify the root cause, how to understand the symptoms, the treatment that should be followed, the lifestyle that should be made, and physical activity should be made aware by conducting campaigns about PCOS in schools, colleges and hospitals. As 1 in 5 women is suffering from PCOS nowadays, the government should actively take the initiative to increase awareness about PCOS.

7. ACKNOWLEDGEMENT

We thank every participant for actively participating in the study.

8. AUTHORS CONTRIBUTION STATEMENT

Dr SMG. Ishrar conceptualized and designed the study. Next, Goruntla Narayana reviewed the data. R.Swetha, C.Priya, AsmaAneesa.K.S discussed the introduction, methodology, and result and prepared the original draft. All the authors reviewed and approved the final version.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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Awareness of Lifestyle Modifications in the Management of Polycystic Ovarian Syndrome: A Hospital-Based Descriptive Cross-Sectional Study

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Abstract

Objective: Polycystic ovarian syndrome (PCOS) is a prevalent endocrinological disorder in reproductive-age women. Due to varied presentations, it's often difficult to diagnose and manage women with PCOS. Management usually focuses on treating the symptoms and preventing long-term sequelae of the disease. This study was planned to assess the knowledge among reproductive-age women (15-44 years) regarding the risk factors, symptoms, complications, and management of PCOS.

Material and methods: This is a hospital-based descriptive cross-sectional study. A pre-validated well-structured questionnaire which included basic demographic data, menstrual history, knowledge about PCOS symptoms, risk factors, complications, prevention, and treatment, was administered. Completed questionnaires were analyzed to calculate the knowledge score of the participants and its association with their education level and occupation was seen.

Results: A total of 350 women participated but only 334 completed questionnaires were included for final evaluation. The mean age of the study population was 28.70 ± 6.29 years. Around 9.3% of the participants were already diagnosed with PCOS. Most of the women (43.4%) had heard about PCOS. The source of information was doctors (26.6%), the internet (6.28%), teachers (5.6%), and friends (4.7%). Obesity (33.5%), unhealthy dietary habits (35%), and genetic predisposition (40.7%) were thought as risk factors for PCOS. Most of the participants were aware that subfertility (40.1%), abortions (34.4%), diabetes (28.7%), hypertension (31.7%), cardiovascular disease (33.5%), endometrial carcinoma (35.9%), and psychological disturbances (37.1%) are among the known PCOS related complications. Eating a healthy diet (37.1%) and weight reduction (41%) can help in the management of PCOS. Around 60.5% of women showed poor knowledge, 14.7% fair knowledge, and 24.9% good knowledge regarding PCOS. Education level and occupation status were found to be significantly related to the knowledge score ($P < 0.001$).

Conclusion: PCOS is a prevalent condition with varied presentations which significantly affects one's quality of life. Since there is no definitive treatment for PCOS the management generally aims at managing symptoms and reducing the risk of long-term complications. To reduce the burden of PCOS-related long-term complications behavioral changes in terms of regular exercise and healthy dietary habits need to be incorporated from childhood.

Categories: Obstetrics/Gynecology, Preventive Medicine, Public Health

Keywords: polycystic ovary syndrome, adolescent pcos, knowledge attitude, lifestyle behaviour, pcos and metabolic syndrome

Introduction

Polycystic ovarian syndrome (PCOS) has emerged as a new epidemic in the last few decades. The prevalence of PCOS varies between 6% and 25% globally [1-6]. Due to the complex presentation of the disease diagnosis is difficult and is often delayed [7-9]. Women with PCOS may present with menstrual irregularities, subfertility, obesity, and dermatological manifestations like hirsutism and acne. The long-term sequelae of the disorder include metabolic disorders, impaired glucose tolerance, diabetes, hypertension, and cardiovascular disorders. Due to chronic anovulation and the unopposed effect of estrogen on the uterus, these women are at higher risk of developing endometrial cancer later in life. Adolescent women with PCOS may suffer from various psychological issues like depression, anxiety, sleep disturbances, and body image disorders which significantly affect their quality of life. The exact etiology of the disorder is not known however oxidative stress, genetic predisposition, and certain gene polymorphisms are thought to be the culprit for PCOS [10-14]. Various environmental factors, sedentary lifestyles, and unhealthy eating habits are also seen to be related. Rotterdam criteria, National Institute of Health (NIH), and androgen excess-PCOS Society criteria are used to diagnose the disorder. The management is usually targeted to treat the symptoms and prevent long-term sequelae. Lifestyle modifications in terms of adopting an active lifestyle, healthy and balanced diet, avoiding junk and unhealthy eating habits, weight reduction in those who are overweight and stress management have been seen to be effective. Even in those who need pharmacotherapy coupling drug

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therapy with lifestyle modification has shown better results [15,16].

This study was planned to assess the level of knowledge among the reproductive age woman about PCOS, risk factors and complications, and the source of information about the disease so that strategies can be planned to disseminate awareness regarding PCOS at the community level.

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Materials And Methods

A hospital-based descriptive cross-sectional study was done in reproductive-age women attending the outpatient department of Gynaecology at a tertiary care hospital. After obtaining ethical clearance from the ethical committee of the institute, a pre-validated well-structured questionnaire containing 40 items was administered by the interviewers after explaining the purpose of the study and obtaining informed consent. All the women between the age group of 15-50 years who attended the Gynecology OPD of the hospital and were able to understand either Hindi or English language were invited to fill out the questionnaire. For those who could not read or write but consented to participate in the study, the questionnaire was read out to them by the investigator and answers were marked as per the response by the participants. A total of 350 women participated. Out of all around 16 forms were incomplete so were not included in the final analysis. Demographic data (Item no. 1-7), information related to the menstrual history (Item no. 8-11), presence of any symptom of PCOS (Item no. 9-18), information regarding knowledge about PCOS, source of information, its symptoms and complications related to it (Item no. 19-30), regarding their knowledge about the prevention and treatment of the PCOS related symptoms and complication (Item no. 31-36) were collected. Information was also collected about the healthy lifestyle activities being practiced by the study cohort (Item no. 37-40).

Statistical analysis

In the present study, descriptive and inferential statistical analysis has been carried out. Results on continuous measurements are presented as mean \pm SD (Min-Max). Results on categorical measurements are presented as numbers (%). Significance is assessed at a 5% level of significance. The one-way analysis of variance (ANOVA) is employed to determine whether there are any statistically significant differences between the means of three or more independent (unrelated) groups. The significance of the parameters on the categorical scale between two or more groups has been calculated using Chi-square/Fisher Exact test. The non-parametric setting was used for qualitative data analysis. For very small cell samples Fisher Exact test is used. P-value: $0.05 < P < 0.10$ was taken as suggestive significant, P-value: $0.01 < P < 0.05$ as moderately significant, and P-value: $P < 0.01$ as strongly significant. Statistical software namely Statistical Product and Service Solutions (SPSS) (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY), and R environment ver. 3.2.2 were used for the analysis of the data, and Microsoft Word and Excel have been used to generate graphs, tables, etc.

Results

The demographic data of the study participants are depicted in Table 1. The mean age of the study population was 28.70 ± 6.29 years. Most of the women in the study group were between 21 and 30 years (61.4%). The majority of the study participants had normal BMI (49.4%). Only 13.5% were underweight (<18.5), and around 28.7% were overweight (25.0-29.9). Around 8.4% of participants were obese (>30). Most of the women in the study group were graduates (42.8%). Most of them were housewives (49.4%) and more than half of the study participants were married (61.7%).

Variable	N=334	% age	Mean ± SD
Age (in years)			
15-20	09	2.7%	
21-30	205	61.4%	28.70±6.29
31-40	102	30.5%	
41-50	18	5.4%	
BMI			
<18.5	45	13.5%	
18.5-24.9	165	49.4%	23.61±4.54
25.0-29.9	96	28.7%	
>30.0	28	8.4%	
Education			
Illiterate	62	18.6%	
Primary	27	8.1%	
High School	74	22.2%	
Graduate	143	42.8%	
Postgraduate	28	8.4%	
Occupation			
Housewives	165	49.4%	
Working (private/Government/Self)	79	23.6%	
Students	90	26.9%	
Marital Status			
Married	206	61.7%	
Unmarried	128	38.3%	
Age at Menarche			
<13 years	24	7.2%	
13-15 years	271	81.1%	13.48±1.00
ears	31	9.3%	
>18 years	none	none	
Cycle Length			
<21 days	30	8.9%	
21-35 days	215	64.4%	21.56±3.28SD
35-60 days	78	23.4%	
>60 days	05	1.5%	
Totally invariable	06	1.8%	

TABLE 1: Demographic Profile of Study Population

The mean age of menarche in the study cohort was found to be 13.48 ± 1 years. The mean cycle length was 21.56 ± 3.28 days with cycle lengths of 21-35 days in 64.37%, <21 days in 8.9%, 35-60 days in 23.35%, and >60

days in 1.49%.

Table 2 shows the distribution of symptoms related to PCOS among the study participants. Among all 35.6% of the participants experienced a change in the cycle length in the past six months. Around 9.0% said they were having frequent cycles (<21 days), 24.8% reported delayed cycles (>35 days), 1.5% reported scanty flow, and 0.3% were having heavy flow during the cycle. Out of all 9.8% of the participants had taken medication for the regularization of their menstrual cycles. Among the study participants, 6.3% experienced weight gain, and 1.2% weight loss in the past six months. However, the majority experienced no change in their weight in the previous six months. Around 2.4% of women experienced excessive hair growth on the body, 9.0% said they were having excessive hair fall, and 8.7% reported acne and needed treatment. Around 8.1% of the women were desirous of pregnancy out of which 6.6% were having some difficulty in spontaneous conception and 4.4% were already on treatment for subfertility. In the present study, 9.3% of the participant were already diagnosed to have PCOS.

S.No.	Symptoms Present	N=334	% age
1.	Change in cycle length in previous 6 months		
	Yes	119	35.6%
	No	215	64.4%
2.	What change		
	Frequent Cycle	30	9.0%
	Delayed Cycles	83	24.8%
	Heavy Cycles	1	0.3%
	Scanty Cycles	5	1.5%
3.	Treatment taken to correct menstrual irregularity in past 6 months		
	Yes	33	9.8%
	No	301	90.1%
4.	Change in weight in previous 6 months		
	Yes	25	7.5%
	No	307	91.9%
5.	What Change		
	Weight Gain	21	6.3%
	Weight Loss	4	1.2%
	No Change	307	91.9%
6.	Excessive hair growth on body in past 6 months		
	Yes	8	2.4%
	No	326	97.6%
7.	Excessive hair fall		
	Yes	30	9.0%
	No	304	91.0%
8.	Acne		
	Yes	29	8.7%
	No	305	91.3%
9.	Are you trying to conceive		
	Yes	27	8.1%
	No	307	91.9%
10.	Any problems in conception		
	Yes	22	6.6%
	No	312	93.4%
11.	Taking any fertility treatment	15	4.4%

TABLE 2: Presence of Symptoms Related to PCOS

PCOS: polycystic ovarian syndrome

Table 3 depicts the knowledge of study participants regarding PCOS. It was seen that only 43.4% of the women had heard about PCOS and the most common source of their information was doctors (26.6%) followed by the internet (6.28%), teachers (5.6%), and friends (4.7%). Assessment of knowledge for risk factors showed that out of those who had heard of PCOS, a significant proportion of women were aware of the association of obesity (33.5%), unhealthy dietary habits (35%), and genetic predisposition (40.7%) with PCOS. When asked about complications and long-term sequelae of PCOS 40.1% of women said that patients with PCOS can have problems in conception, 34.4% said it PCOS women are at higher risk of pregnancy loss, 28.7% said women with PCOS are prone to develop diabetes, 31.7% said they can have hypertension, 33.5% said it can raise the chances of cardiovascular disease, 35.9% said there could be an association with endometrial carcinoma and 37.1% said it could be related to psychological problems, sleep disturbances, body image disorder, and anxiety in women. Around 37.1% were aware that eating a healthy and balanced diet can be one of the management methods, 41% believed weight reduction could help, and 35.6% said trying ways to reduce stress could be one of the methods to manage the stress and mood-related symptoms in PCOS women. However, 34.1% said only medications can treat the condition and 2.7% believed only surgery can treat PCOS.

Question	N=334	% age
Heard about PCOS		
Yes	145	43.4%
No	189	56.6%
Have you been diagnosed as PCOS		
Yes	31	9.3%
No	303	90.7%
Source of Information	N=145	
Teacher	19	5.6%
Doctor	89	26.6%
Friend	16	4.7%
Television	0	0%
Newspaper	0	0%
Internet	21	6.3%
Symptoms: PCOS can manifest as	N=145	
Menstrual Irregularity	142	42.5%
Hirsutism	90	26.9%
Acne	70	20.9%
Weight gain	119	35.6%
Difficulty in conception	117	35.02%
Abortions	115	34.4%
Hair fall	82	24.8%
Risk Factor	N=145	
Obesity	112	33.5%
Unhealthy eating habits	117	35%
Sedentary lifestyle	121	36.2%
Genetic	136	40.7%
Complications	N=145	
Infertility	134	40.1%
Abortions	115	34.4%

Diabetes	96	28.7%
Hypertension	106	31.7%
Cardiovascular Disorders	112	33.5%
Endometrial Carcinoma	120	35.9%
Psychological problem, anxiety, sleep disturbances	124	37.1%
Management	N=145	
Avoiding junk food and healthy eating habits	124	37.1%
Exercise and weight loss	137	41%
Stress management	119	35.6%
Medications	114	34.1%
Surgery	96	2.7%

TABLE 3: Awareness Regarding Symptoms, Risk Factors, Complications, and Management of PCOS

PCOS: polycystic ovarian syndrome

A total of 14 items were used to assess the knowledge regarding risk factors, symptoms, long-term complications, prevention, and treatment of PCOS. For every correct answer participants were given one mark each. The total score was 14 and those who scored <5 were categorized as having poor knowledge, between 6 and 10 as fair knowledge, and >10 as good knowledge. On analyzing the data, it was seen that out of those who had heard of PCOS around 60.5% showed poor knowledge. However, 14.7% had fair knowledge, and 24.9% had good knowledge regarding PCOS. When we analyzed the score categories with the education level and occupation status of the women it was seen that those who are graduates and postgraduates scored better and the results were statistically significant ($P \leq 0.001$). Those who were working had better knowledge than the rest of the participants ($P \leq 0.001$) (Tables 4-5). Lastly, we inquired about the healthy lifestyle practices followed by the study group in their day-to-day life and it was found that around 23.9% of women were doing some kind of exercise.

Total Score	Education					Total
	ILLITERATE	PRIMARY	HIGH SCHOOL/PUC	GRADUATE	POSTGRADUATE	
0	59 (95.2%)	27 (100%)	52 (70.3%)	44 (30.8%)	8 (28.6%)	190 (56.9%)
1-5	0 (0%)	0 (0%)	4 (5.4%)	8 (5.6%)	0 (0%)	12 (3.6%)
6-10	0 (0%)	0 (0%)	7 (9.5%)	32 (22.4%)	10 (35.7%)	49 (14.7%)
11-15	3 (4.8%)	0 (0%)	11 (14.9%)	59 (41.3%)	10 (35.7%)	83 (24.9%)
Total	62 (100%)	27 (100%)	74 (100%)	143 (100%)	28 (100%)	334 (100%)
Mean ± SD	0.68±3.03	0±0	2.99±4.83	7.41±5.67	7.89±5.71	4.62±5.71

TABLE 4: Correlation between Education Level and Knowledge Score

Total Score	OCCUPATION			Total
	HOUSEWIFE	STUDENTS	WORKING WOMEN	
0	151 (91.5%)	16 (20.3%)	23 (25.6%)	190 (56.9%)
1-5	0 (0%)	4 (5.1%)	8 (8.9%)	12 (3.6%)
6-10	1 (0.6%)	26 (32.9%)	22 (24.4%)	49 (14.7%)
11-15	13 (7.9%)	33 (41.8%)	37 (41.1%)	83 (24.9%)
Total	165 (100%)	79 (100%)	90 (100%)	334 (100%)

TABLE 5: Correlation of Knowledge Score and Occupation Status of the Women

Out of all 9.8% go for walk daily, 1.76% were practicing weight training, 2.69% were doing aerobic exercises, 23% were doing yoga, and 2.64% were doing swimming. Around 11.7% of the study population was practicing meditation as stress-relieving management. Around 54.6% of the women were taking healthy food items most of the time in their diet and take junk food only occasionally, however, the rest were taking junk food quite often (45.40%).

Discussion

PCOS is a complex endocrine disorder affecting women across all stages of their life. Adolescent girls often present with menstrual irregularities, acne, hirsutism, and obesity which can further lead to body image disorders, low self-esteem, anxiety, and depression in them. Women with PCOS may have difficulty in spontaneous conception and often need fertility treatment. These women can also experience repeated pregnancy losses. Later in life, they are at increased risk of diabetes, hypertension, and cardiovascular disorders. Due to the unopposed estrogen, they are at risk of developing endometrial hyperplasia and endometrial cancer [17]. Management often includes measures targeted to reduce the symptoms or to prevent the complications associated with the disorder. There is no permanent cure but the lifestyle modifications in PCOS women like weight reduction, exercise, meditation, and a healthy diet is seen to help them to fight their symptoms. Hence it is very important to spread knowledge and awareness in the community regarding the risk factors, symptoms, complications when to seek help, and whom to seek help from. In today's world where a sedentary lifestyle, preserved food, pollution, and stressful day-to-day life have become a new norm, the importance of adopting a healthy lifestyle should be stressed upon. Several studies done previously by researchers have shown a lack of knowledge regarding the signs and symptoms of PCOS among the general population [18,19].

In the present study, researchers found that around 43.4% had heard about the term PCOS. The above findings are similar to the findings published by Alessa et al. in their study where researchers found that 56.7% of the women had heard about PCOS [20]. A significant percentage of women had heard about the disorder but still, awareness is not 100%, and a lot of efforts are required to disseminate this knowledge in the community. The most common source of information in our study was health care provider/doctor (26.6%) followed by the internet (6.28%), teacher (5.6%), and friends (4.7%), and the results are similar to studies were done by Abu-Taha M et al. and Alshdaifat E et al. [21,22]. However, the most common source of information in the study conducted by Alessa et al. was the internet (21.3%) followed by PCOS patients (10.4%), doctors (10.8%), and books (3%). Government websites and PCOS support groups were the other mentioned sources in the study. The difference could be because in our study the study participants were those attending the Gynaecological OPD for various reasons however the study done by Alessa et al. included college students. Around 9.3% of the study population was already diagnosed to have PCOS in contrast to 15.3% of the women in the study by Alessa et al. and 28.5% in a study by Rao et al. [23]. The difference can be explained by the regional variation in the distribution and variation in the sample size of the studies. In the present study, researchers found that the women who were not diagnosed with PCOS also had certain symptoms which need further evaluation. Around 35.6% reported a change in their cycle length, 9.0% had excessive hair fall, 8.7% had acne, 6.6% had a problem with conception, 6.3% reported weight gain, and 2.4% had excessive hair growth. Rao et al. in their study also found that around 40.5% of women not formally diagnosed with PCOS had PCOS-like symptoms. While assessing knowledge regarding risk factors associated with PCOS it was found that around 35% knew unhealthy eating habits can be related to PCOS while 33.3% were aware that excess weight is associated with PCOS. Around 32% said it is familial. When asked about complications related to PCOS it is seen that similar to the study by Alessa et al. in the present study participants are aware of its association with subfertility (40% vs 39%), psychological disturbances (37.1% vs 34.1%), endometrial cancer (35.9% vs 30.2%) and diabetes (28.7% vs 14.5%). Both studies found that the participants were aware that exercise and losing weight can help reduce the symptoms and related complications (37.1% vs 39.9%). Around 41% of the women were aware that eating a healthy and balanced diet is helpful and the findings are similar to the finding in the study by Alessa et al. where 34.2% were aware

of the benefits of eating healthy food. In the present study around 34% of women said that medications and surgery are the other options to manage PCOS while in a study by Alessa et al. around 29.4% of women were aware of the medical management. In the study done by Alessa et al., the author has not mentioned the awareness of surgical procedures for PCOS. The present study shows education level and working status of the women were significantly associated with high knowledge scores among the study participants and the results are similar to the studies done by Alessa et al. and Alshdaifat E at el.

With increasing education levels the percentage of women who know about the risk factors, symptoms, complications, and management is also rising across the globe but is this knowledge getting translated into actual practice? To assess that we asked the study participants what health lifestyle practices they are following. In this study, only 23.95% of the study participants were exercising daily, and only 11.7% were practicing meditation. However, a significant proportion of women were taking a healthy diet and avoiding junk food (54.60%). These findings suggest that only disseminated knowledge and awareness are not enough it requires a tremendous effort to bring about behavioral changes at the community level. To bring about these behavioral changes authors suggest that knowledge and awareness about a healthy lifestyle need to be incorporated right from childhood so that they become an integral part of our lives. Behavioral modification can start from home where the parents need to be educated, schools where teachers need to be educated to disseminate the knowledge, and then social media, the internet, government websites, and television advertisements can play an important role. At community levels, teams of volunteers can arrange nuked Natak and stage shows. Hospitals and support groups should provide educational material and can arrange talks in the outpatient area of the hospital or in the community regarding PCOS awareness and the benefits of lifestyle modifications for PCOS women.

Limitations of the study

This study is done in the hospital setting so the study population is not the true representative of the general population. The knowledge regarding PCOS is assessed only in female participants and male partners are not included. The sample size is also small so the findings cannot be generalized to the whole population.

Conclusions

PCOS is an endocrine disorder affecting women at every stage of their life. The presentation of the disorder is varied and if not diagnosed earlier can lead to dreadful long-term sequelae. No definitive management is available. The management is targeted to treat the immediate symptoms and reduce the risk of long-term sequelae. Lifestyle modifications in terms of an active lifestyle and healthy dietary habits are the first line of management and can significantly reduce the symptoms and morbidity related to the disorder. Since habits are difficult to change, hence incorporating these healthy habits early in life is vital. Despite the increasing prevalence of PCOS globally the knowledge and awareness related to the disease remain poor among the general population and calls for measures to increase community-level educational programs. Spreading awareness regarding PCOS, its risk factors, symptoms, and complications, and adherence to a healthy lifestyle is essential to reduce the burden of disease and related complications. Education level and working status are seen to be directly associated with better knowledge.

Appendices

Annexure I: Questionnaire

Name (Optional):

1. Age:

2. Weight:

3. Height: BMI:

4. Age of menarche:

5. Educational Qualification:

6. Occupation:

7. Marital Status:

Question 8. What is your cycle length:

1. <21 days

2. 21-35 days

3. 35-60 days

4. >60 days

5. Invariable

Question 9. Any change in cycle recently?

1. Yes

2. No

Question 10. If Yes? what changes?

1. Frequent cycles

2. Delayed cycles

3. Scanty periods

4. Heavy flow

5. Others (Specify)

Question 11. Have you taken any treatment for menstrual irregularity in the past 6 months?

1. Yes

2. No

Question 12. Have you experienced any weight changes recently?

1. Yes

2. No

Question 13. If Yes, what changes?

1. Weight gain

2. Weight loss

3. No Change

Question 14. Have you ever taken any treatment for excessive hair growth in the body in the past 5 years?

1. Yes

2. No

Question 15. Did you need to visit a dermatologist for excessive hair loss in the past 6 months?

1. Yes

2. No

Question 16. Did you need to visit a dermatologist for any excessive acne not responding to home remedies?

1. Yes

2. No

Question 17. Are you trying for pregnancy?

1. Yes

2. No

Question 18. If yes is there any problem in conception for which you are seeking or planning to seek treatment?

1. Yes

2. No

Question 19. Have you heard about PCOS?

1. Yes

2. No

Question 20. Have you been diagnosed with PCOS?

1. Yes

2. No

Question 21. From where did you hear about PCOS?

1. Teacher

2. Doctor

3. Friend

4. TV

5. Newspaper

6. Others

Question 22. Who do you think is more prone to PCOS?

1. Overweight

2. Underweight

3. Normal weight

4. Any weight

Question 23. Do you think eating unhealthy and junk food is associated with PCOS?

1. Yes

2. No

Question 24. Do you think PCOS has any problem in future childbearing?

1. Yes

2. No

Question 25. Do you think PCOS can lead to pregnancy loss?

1. Yes

2. No

Question 26. Do you have PCOS and can have any risk of deranged sugars or diabetes in the future?

1. Yes

2. No

Question 27. Do you think PCOS can have the risk of hypertension in the future?

1. Yes

2. No

Question 28. Do you think PCOS can be associated risk Cardiovascular Disorder?

1. Yes

2. No

Question 29. Do you think PCOS can be associated risk of cancer?

1. Yes

2. No

Question 30. Do you think PCOS can lead to psychological problems like depression, anxiety, and sleep disturbances?

1. Yes

2. No

Question 31. Do you think weight-changing management can help women with PCOS?

1. Yes

2. No

Question 32. Do you think exercise can help in PCOS?

1. Yes

2. No

Question 33. Do you think eating healthy and avoiding junk food can help women with PCOS?

1. Yes

2. No

Question 34. Do you think stress-relieving activities can help women with PCOS?

1. Yes

2. No

Question 35. Do you think medication is the only cure for PCOS?

1. Yes

2. No

Question 36. Do you think Surgery is the only cure?

1. Yes

2. No

Question 37. Do you exercise regularly?

1. Yes

2. No

Question 38. What kind of exercise do you do?

1. Regular walk

2. Swimming

3. Aerobic

4. Weight Training

5. Yoga

7. Other

6. None

Question 39. Do you practice any kind of meditation?

1. Yes

2. No

Question 40. How often do you eat junk food?

1. Very Often

2. Sometimes

3. Rarely

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Dr. Baba Saheb Ambedkar Medical College and Hospital issued approval IEC-11/2022. This study was approved by the Institutional Ethics Committee. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Behavioural Hypochondriacs and Life Style Management in PCOS: A Review

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Abstract:- Polycystic ovary syndrome (PCOS) is habitually linked with psychological and physiological anguish. Etiology of PCOS still remains unclear. It is mainly associated with obesity. Women with PCOS endure from pregnancy complications during their reproductive age. Several reviews and studies suggest that women suffering from PCOS can develop mental distress like depression, anxiety, body dissatisfaction, Food and eating habits and Disaffection about their sexual life. These all factors are key factors for behavioral hypochondriacs as it increases stress, anxiety and depression in women with PCOS. There are several evidences that appropriate weight management strategies and modification in lifestyle is helpful for the women with PCOS for to improve the hormonal imbalance, infertility and obesity. It is also helpful to reduce symptoms for PCOS. This literature review is about effect of PCOS on behavioral hypochondriacs and how a little modification in life style management will positively affect the women with PCOS.

Keywords:- PCOS, Depression, Hirsutism, Life Style Management, Pregnancy, Infertility, Hypochondriacs.

I. INTRODUCTION

Polycystic ovary syndrome is an endocrine disorder which mainly affects the women with reproductive age. First case for PCOS was observed in 1976. PCOS affects the 5-10% of all women. Irregular menstrual cycle, biochemical hyper androgenism and presence of polycystic ovaries on ultrasound are clinical and diagnostic feature of PCOS. This also have reproductive and metabolic (insulin resistance) malfunction. 50% are the women with obesity. As the amount of adipose tissue increases it results in various abnormalities of sex steroid metabolism as increase in amount of androgen and repression of globulin which bind to sex hormones. It can also give rise to severe infertility and an-ovulation. Furthermore it also causes breast cancer, cardiovascular disease, endometrial cancer, type 2 diabetes etc. They are more vulnerable to coronary artery disease and hypertension. So these were the physical consequences which are observed in women with PCOS but in spite of these some behavioral hypochondriacs which includes anxiety, depressed mood, body shaming, sleep disturbance, low appetite, negative thoughts, less self confidence etc. Depression among women with PCOS very high which varies between 28% to 64%. Sometimes it leads to suicide case also. Hirsutism and skin acne problem is also a major

factor for depression in women with PCOS. As above mentioned 50% of girls are obese in PCOS that's why various study has undertaken that how life style management and weight management will help in PCOS. Objective of this literature review is to understand that how PCOS affects behaviour of a patient and how lifestyle management will help to reduce symptoms of PCOS.

II. MATERIALS AND METHOD

Literature review was conducted by reviewing different research articles and review articles. The papers were collected from various online sources like GOOGLE SCHOLAR, SCIENCE DIRECT, PUBMED, WILEY, SPRINGER, ELISVERE. Keywords used to search this research and review article were PCOS, infertility, depression, life style management etc. Papers that show relation of PCOS with behavioral change and life style management were also taken.

III. RESULTS AND DISCUSSION

- **Behavioural Hypochondriacs:-**

Hypochondriac are a condition in which patients lives in a fear of having some serious illness, and is also known as illness anxiety disorder. This kind of condition is often seen in patients with PCOS. It is commonly due to having insecurity of infertility, hirsutism, body dissatisfaction, difficulty in pregnancy, obesity, eating disorder, bipolar disorder etc. Women.

Infertility is common cause in women with PCOS due to anovulation which is a cause of hypochondriacs, but it is curable. Hormonal imbalance and high amount of estrogens leads to poor growth and release of egg from ovules and results in deficient ovulation. When ovulation does not occur, it increase amount of testosterone and as a result it affects the egg quality and lead to insulin resistance. There are some other factors which can also negatively affect the fertility. Despite of this Women with PCOS suffer with body shaming which causes depression, frustration and difficulty in self acceptance. A persuasion of own self acceptance leads to unsatisfaction with sex life especially in women with obesity and hirsutism. Another reason for infertility is “infertility stress” which includes lose of interest in daily activities, difficulty in maintaining interpersonal relationship, depression and high level of anxiety. Moreover infertility stress leads to sleep disorder, a feeling of helpless,

guilt and lose of concentration and attention. Women with PCOS can also get pregnant with appropriate treatment. First step to get rid of infertility is modification in life style management and daily exercise. Another step is to provide some fertility medications which are estrogens receptor modulators. Sometimes fertility injections (Follistim®, Gonal-F®, Bravelle®, and Menopur®) are also required to release eggs.

Hirsutism is another cause of behavioral hypochondriacs. It is a condition in which PCOS patients slowly results in excess hair growth. 70-80% of women with PCOS shows symptoms of hirsutism. It is because of excess level of androgen. It is related with appearance like "male pattern" appearance like acne, excess hair at chest, abdomen, face, arms, increase in body weight, loss of menstruation cycle, baldness etc. Moreover this can cause psychotic symptoms which includes high level of anxiety and tension. They are more susceptible to social phobia and insecure about their body appearance. They often have feeling of shame, loneliness Hyperandrogenism. Various short term treatments can be used for hirsutism like use of chemical depilatories or bleaching cream, plucking of hair. For long term treatment electrolysis and laser can be used. Eflornithine cream can be used for slow down the topical hair growth.

Body image distress is most commonly seen in women with PCOS. It is mainly because of the obesity. To maintain a ideal body weight is another reason for anxiety and depression on women with PCOS. Obesity give rise to decreased self confidence and negative thoughts and often looks for strict dieting which can put additional stress on person. Eventually this can cause eating disorder in women. This all parameters can lead to hypochondriacs.

➤ Life style management

Obesity is a major challenge for clinicians in women with PCOS. Health risk of obesity cannot be ignored that why it is important to maintain healthy weight which needs a slight change in daily lifestyle. It includes an extra 2000-3000 steps per day, regular 30 mins physical activity, replacement of artificial sweetened drinks and sugars with health options, having cereals for breakfast. Overall reduction of calories is more important in weight loss. It needs a long term practice otherwise after short time of physical activity one may starts to gain weight again. Diet with high fibre content and low carbohydrate is recommended. Food with low glycemic index like cereals, soy, lentils can be included in diet. This can be accomplished by daily exercise or physical activity. Exercise in combination with diet will reduce muscle mass and, exercise with muscle strengthning will improve insulin activity.

IV. CONCLUSION

Preceding literature review on various parameters for behavioral hypochondriacs indicates that a little support from society and changed perspective to consequences of PCOS can improve the psychotic symptoms of stress, anxiety and depression. According to a cross sectional survey lifestyle management awareness is well recognized by women but awareness about psychological distress is not recognized well. In rural areas, awareness about PCOS is not well acknowledged. Hirsutism, obesity, infertility is not accepted by the community which is the main reason for depression and excess level of anxiety. PCOS is not a severe condition but it can be controlled by various awareness programmes for PCOS, nutrition and exercise counselling, prescribed medication for hormonal imbalance etc.

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Clinical and Biochemical Features of Polycystic Ovarian Disease

JOSEPH W. GOLDZIEHER, M.D., and LEONARD R. AXELROD, Ph.D.

THE EXISTENCE of bilateral polycystic ovarian disease and its occasional improvement following cuneiform ovarian resection was known before the turn of the century.¹⁻⁴ Additional clinical and surgical observations were reported sporadically in the ensuing years,⁵⁻⁸ but a broad interest in this disorder did not develop until 1935 when an associated syndrome consisting of "menstrual irregularity featuring amenorrhea, a history of sterility, masculine type hirsutism, and less consistently retarded breast development and obesity" was described.⁹ Excellent therapeutic results following wedge resection were reported by these authors over a span of many years; their results, however, have never been duplicated in any other substantial series of cases. In the eyes of many investigators, the clinical features of this syndrome were neither definitive nor satisfactory, and additional criteria such as a normal urinary 17-ketosteroid excretion¹⁰ were employed in an effort to improve diagnostic accuracy and the consistency of surgical results. With time, increasing numbers of patients with polycystic ovarian disease and atypical clinical findings were observed,¹¹ and in a significant number of even these cases, a normalization of function followed wedge resection. Netter *et al.*¹² in typical Gallic style, remarked that: "the syndrome of Stein is a fugitive syndrome, with limits less well defined than those of the Sahara or the Sudan." In England, Roberts and Haines¹³ studied 14 cases and entitled their report, "Is there a Stein-Leventhal syndrome?" It is noteworthy that these questions were raised from a clinical point of view and not because of the superficial resemblance of polycystic ovaries to the ovarian

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sclerosis and other pathology which is known to accompany androgenic^{14, 15} or Cushingoid¹⁶ adrenocortical hyperfunction.

Since there appeared to be growing doubt as to the existence of a clinical syndrome associated with sclerocystic ovaries, we undertook a survey of the world literature in a search for the incidence of certain signs and symptoms in patients who were found at operation to have polycystic ovarian disease. A total of 187 pertinent references yielded acceptable information from 1097 cases, as shown in Table 1. Amenorrhea was observed in only half of the patients, and the per cent of frequency with which this symptom occurred in different series varied tremendously—from 15 to 77%. On the other hand, cyclic menses were noted in a significant number of patients (12%), and functional bleeding was exceedingly common (65%) in some series. The incidence of infertility also varied widely, ranging from 35 to 94% with an over-all average of 74%. However, since infertility is one of the major reasons why patients consult a physician in the first place, the figures probably have a positive bias. By contrast, there appeared to be unequivocal evidence of ovulation in patients with polycystic ovaries as shown by reports of primary dysmenorrhea, by biphasic basal temperature curves in 12–40% of subjects, and finally by the finding of corpora lutea in an average of 22% of the cases where the presence or absence of this feature was specifically mentioned. Hirsutism was observed in an average of 69% of the subjects, but again the incidence varied widely. Virilization appeared with some frequency. Taken together, these statistics make it most difficult to accept as a distinct entity a group of symptoms of which only two nonspecific ones (hirsutism, infertility) are present much more than half the time, where cyclic menses or functional uterine bleeding occur nearly as often as the supposedly important amenorrhea, and where positive evidence contradicts

TABLE 1. Signs and Symptoms Associated with Polycystic Ovarian Disease

<i>Symptom</i>	<i>Usable No. cases</i>	<i>Incidence (%)</i>	
		<i>Mean</i>	<i>Range</i>
Obesity	600	41	16–49
Hirsutism	819	69	17–83
Virilization	431	21	0–28
Cyclic menses	395	12	7–28
Functional bleeding	547	29	6–65
Amenorrhea	640	51	15–77
Dysmenorrhea	75	23	—
Biphasic basal temperature	238	15	12–40
Corpus luteum at operation	391	22	0–71
Infertility	596	74	35–94

Data tabulated from 187 references with a total of 1079 cases.

the postulated anovulation which is thought to cause the infertility. As a matter of fact, in a study of the gross appearance of the ovary in a series of 12,160 gynecological laparotomies, 170 instances (1.4%) of polycystic ovaries were observed.¹⁷ It is difficult to avoid the conclusion that Stein and Leventhal's symptomatology calls attention to a small and perhaps not especially unique fraction of polycystic ovarian disease. It has been claimed in rebuttal that these clinical variations are simply different stages of an evolving disease process. We have indicated elsewhere¹⁵ that this explanation is unsupported by positive findings, and that there is no detectable association between the duration of the disease and the "completeness" of the alleged syndrome.

The success of wedge resection in correcting the infertility and menstrual disorders associated with polycystic ovaries has been in large measure responsible for the wide and continued interest in this disease. Examination of the literature, however, indicates that success is by no means uniform. Where published data are adequate for evaluation, as seen in Table 2, regular cycles are re-established in an average of 80% of operated patients, but in some hands, the rate of success is as low as 6%; results in terms of pregnancies are also most unpredictable, ranging from 13 to 89%. It is quite evident that the clinical material which forms the basis of these studies is inhomogeneous, and that criteria for the selection of candidates for wedge resection are neither uniform nor adequate. In our experience, there has been no difference in the results of wedge resection whether the urinary 17-ketosteroids were normal or elevated; as a matter of fact, the elevated steroid excretion was unaltered by surgery in two-thirds of the patients. The corticosteroid suppression test (see below) has not been helpful, nor has ovarian size, since normal-sized ovaries have responded at about the same rate as enlarged ovaries. One correlation, apparently valid but extremely difficult to evaluate quantitatively, was suggested to us by Southam:¹⁸ the more estrogenic activity and the less androgenic activity there is, the better the results of wedge resection are likely to be.

Efforts to find additional clinical signs and symptoms which would im-

TABLE 2. Results of Wedge Resection in Patients with Polycystic Ovarian Disease

<i>Result</i>	<i>Usable No. cases</i>	<i>Frequency (%)</i>	
		<i>Mean</i>	<i>Range</i>
Regular cycle	447	80	6-95
Pregnancy	640	63	13-89
Decreased hirsutism	205	16	0-18

Data tabulated from 187 references with a total of 1079 cases.

prove the diagnostic and therapeutic "score" have not met with much success, and investigators have turned to cytological and biochemical studies for help. There have been a number of recent reports¹⁹⁻²¹ of chromosomal anomalies associated with polycystic ovarian disease. This unexpected finding awaits confirmation and correlation. The occurrence of polycystic ovaries in sisters^{15, 22, 23} may be mere coincidence or another intimation of genetic involvement.

Criteria of classic morphology have not provided much assistance, and indeed there is controversy at the present time whether any of the histological changes observed in polycystic ovaries are at all specific^{15, 24} or whether they can be observed with frequency in other clinically unrelated conditions. From the practical point of view, Plate²⁵ has shown that the presence or absence of hyperthecosis was not significantly correlated with the results of wedge resection.

Biochemical studies until very recently were confined to analysis of urinary steroid metabolites. The extensive literature dealing with this aspect of the problem has been reviewed elsewhere.²⁶ For the enormous amount of effort expended in this direction, the results have been disappointingly meager. Our improved understanding of ovarian and adrenal steroidogenesis goes a long way to explain some of these difficulties. Elevated excretion of urinary 17-ketosteroids has been observed by many investigators, while others rule out the diagnosis of "Stein-Leventhal syndrome" in the face of elevated excretion. Figure 1 shows the ranges of values of total urinary 17-ketosteroids and 17-hydroxycorticoids observed by us in a series of patients with polycystic ovaries. It is evident that there is a diffuse spread of values which does not permit the categorization of these patients into distinct sub-

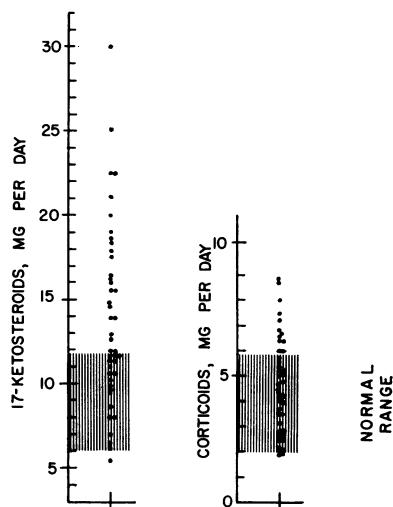


Fig. 1. Urinary excretion of total 17-ketosteroids and 17-hydroxycorticoids in patients with polycystic ovarian disease.

groups. Some of the 17-hydroxycorticoid values significantly exceed our normal range and suggest that certain patients may have had adrenocortical hyperfunction. It should be noted that these elevated values were not associated with extreme obesity, which would tend to increase the level of urinary excretion.²⁷

Important methodological difficulties²⁸ stand in the way of correct interpretation of "total 17-ketosteroid" excretion. Chromatographic separation and measurement of the individual 17-ketosteroids has not been particularly helpful, since both ovarian and adrenal ketosteroids are metabolized to the same excretory products (androsterone and etiocholanolone), and since dehydroepiandrosterone, the major "adrenal" ketosteroid, is now known to be produced by the ovary as well.²⁹⁻³¹ As a consequence, dynamic tests of steroid metabolism have been developed in an attempt to distinguish the ovarian contribution from that of the adrenal. In an early study, we examined the effects of adrenal suppression by a small dose of prednisolone (2.5 mg., t.i.d.) given over a period of 10 days. There appeared to be a significant difference in the response of normal women vs. women with hirsutism but without menstrual disorders (Fig. 2). The higher the initial

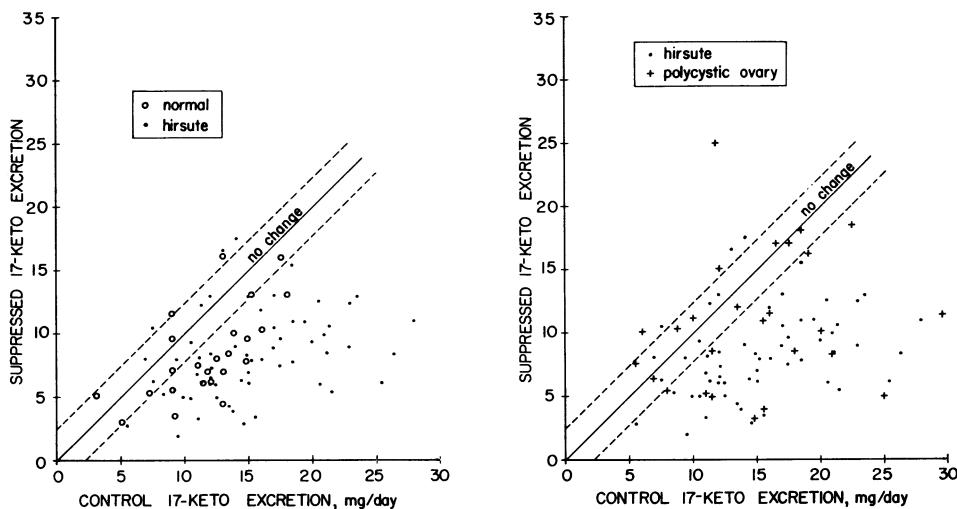


Fig. 2 (left). Urinary 17-ketosteroid excretion before and after minimal adrenal suppression. No change in excretion would yield points lying along diagonal line \pm the error of measurement. Values below diagonal line indicate degree of suppression. Results were obtained in normal vs. cyclic, but hirsute, women. **Fig. 3 (right).** Urinary 17-ketosteroid excretion before and after minimal adrenal suppression. No change in excretion would yield points lying along diagonal line \pm the error of measurement. Values below diagonal line indicate degree of suppression. Results are from hirsute cyclic women vs. patients with polycystic ovaries.

17-ketosteroid excretion in the hirsutism cases, the greater was the decrease following adrenal suppression. We interpreted these findings as indicating a hyperresponsiveness of the pituitary-adrenal axis in certain cases of hirsutism.³² When the situation was examined in women with polycystic ovaries, Fig. 3, some were found to show the minimal response seen in normals or certain hypertrichotic women, while others showed the pattern which we interpreted as pituitary-adrenal hyperresponsiveness. This might possibly be an indication of a role of the adrenal cortex in certain cases, but the evidence was equivocal and at any rate offered no clearcut, useful diagnostic index. Netter and others³³⁻³⁵ have developed dynamic tests involving the use of dexamethasone for adrenal suppression and an estimation of urinary steroid changes following the superimposed administration of large doses of chorionic gonadotropin. Some interesting differences in the excretion of neutral and phenolic steroids have been noted, but the acid test of broad clinical application, especially in diagnostically difficult situations, remains to be carried out.

On the basis of so much work and so little yield in the attempt to distinguish ovarian from adrenal factors, one might well begin to wonder if there is not indeed an adrenocortical component in some cases of polycystic ovarian disease. Sherman³⁶ has found increased excretion of 11-ketopregnanetriol, undoubtedly an adrenal metabolite, in 16 cases. Wedge resection of the ovaries has frequently failed to alter an elevated excretion of urinary 17-ketosteroids,^{26, 37, 38} which could be decreased promptly upon adrenal suppression with corticosteroids. Moreover, in some therapeutic failures of wedge resection, satisfactory results have been achieved subsequently with corticosteroid treatment. On the other hand, there is no reason to believe that adrenal hyperfunction is inevitably associated with polycystic ovarian disease, hence the finding of histologically normal adrenal tissue in a few instances³⁹ comes as no surprise. It is known, furthermore, that histologic normalcy is no indication of normal function: the adrenals may appear quite unremarkable in full-blown cases of Cushing's syndrome.

There are many indications that the pituitary-adrenal and pituitary-ovarian circuits are not completely isolated from each other, but that there is a good deal of functional "crosstalk" which can be demonstrated in a variety of ways. Some years ago Sohval and Soffer⁴⁰ demonstrated that the administration of corticosteroids or ACTH can cause an increase in urinary gonadotropin excretion. In chickens, even ovulation can be triggered by this procedure.⁴¹ Clinically, the occasional appearance of uterine bleeding after administration of ACTH is well known. Looking at the other side of the relationship, it has been shown that estrogenic compounds which are potent gonadotropin inhibitors significantly alter cortisol and aldosterone

secretion rates.⁴² Gemzell *et al.*⁴³ noted in one unusual patient with hirsutism and elevated 17-ketosteroids that the administration of gonadotropin not only increased urinary estrogens but also tripled the 17-ketosteroids and corticoids, suggesting an action of pituitary gonadotropin on the adrenal. Finally, in rats the production of persistent estrus and polycystic ovaries by hypothalamic injury is associated with adrenal hypertrophy,⁴⁴ an observation we feel to be of considerable theoretical importance.

The co-existence of adrenal and ovarian disturbances is therefore not entirely unexpected. This complicates the question of the pathogenesis of polycystic ovarian disease, and it becomes necessary to delve more deeply into ovarian endocrine function in an effort to understand the physiologic problems involved.

OVARIAN STEROIDOGENESIS

While the main elements of steroid biosynthesis in adrenal tissue were fairly well clarified 10 years ago, it has been only recently that an equivalent understanding of ovarian steroidogenesis has been achieved. The cyclic nature of ovarian function clearly makes the problem more difficult than with the adrenal. The ovary stores very little steroid material, thus increasing the problems of detecting steroids in its tissue. Even the secreted quantities of ovarian estrogens and androgens are so small that actual isolation (to say nothing of definitive identification) of the compounds strains the reliability of the best methods available. New technics involving the determination of secretion rates by isotope dilution are beginning to yield more precise and meaningful information.

In view of these difficulties, the majority of efforts to establish the steroid biosynthetic pathways have relied on the incubation of precursor substances with ovarian tissue and the isolation and identification of the resulting products. Many of these investigations yielded only tentative identification of the metabolites and were therefore of limited value, but definitive identification of all the steroid intermediates between cholesterol and the estrogens has finally been achieved.²⁹ In 1962 definitive identification of the complete series of steps from pregnenolone to estrogen in single samples of ovarian tissue was accomplished.²⁹

A diagrammatic outline of the ovarian biosynthetic mechanism is shown in Fig. 4. Using readily available cholesterol, the ovarian enzymes first cleave the side chain, yielding Δ^5 -pregnenolone. This compound then undergoes hydroxylation to 17-hydroxypregnenolone. Another side-chain-cleaving enzyme system removes the rest of the side chain, leaving the 17-ketosteroid dehydroepiandrosterone. During all this time, an enzyme system

called 3β -ol dehydrogenase has been actively switching the position of a certain double bond (Fig. 5), converting pregnenolone to progesterone, dehydroepiandrosterone to androstenedione, and probably acting at all the intermediate stages as well. Progesterone itself also undergoes the same trans-

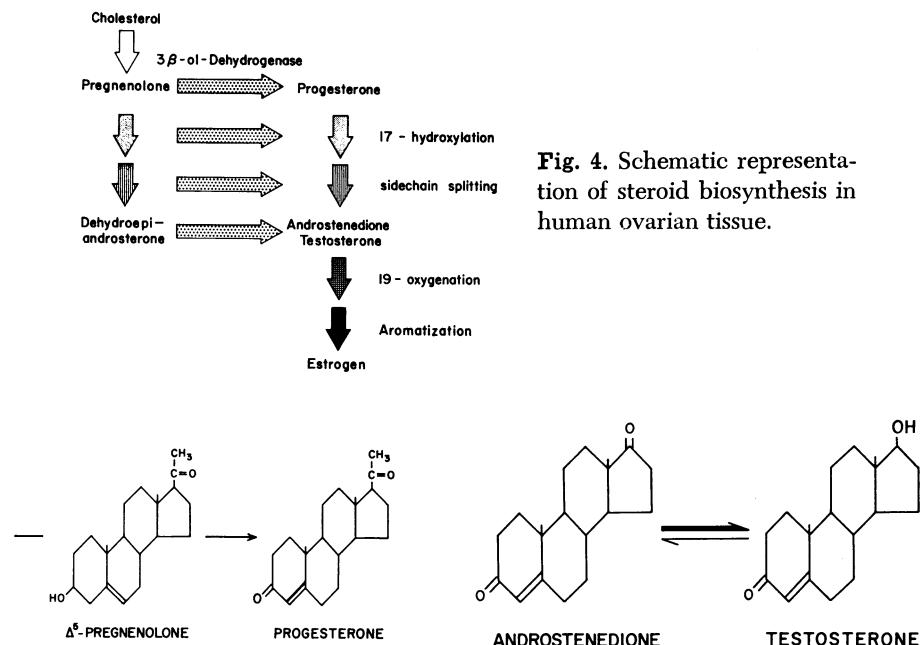


Fig. 4. Schematic representation of steroid biosynthesis in human ovarian tissue.

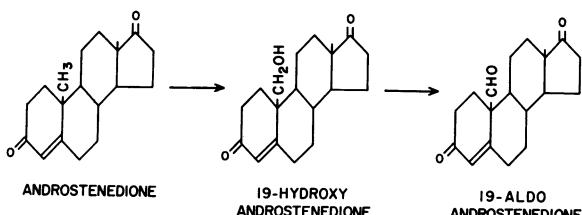
Fig. 5 (left). Conversion of Δ^5 -pregnenolone to progesterone by 3β -ol dehydrogenase system. **Fig. 6 (right).** Conversion of androstenedione to testosterone by 17-reductase enzyme system.

formations of 17-hydroxylation and side-chain cleavage to form androstenedione. Thus parallel biosynthetic pathways, with interactions at each stage, are formed. It is important to recognize at this point what the ovarian biosynthetic mechanism has accomplished: *pregnenolone and progesterone formed from still earlier precursors, have been transformed into 17-ketosteroids (dehydroepiandrosterone and androstenedione)*. Both are relatively weak androgens, but androstenedione is readily convertible to testosterone (Fig. 6) by a reductase which is present in ovarian tissue and blood and in peripheral tissues as well. Thus, the formation of testosterone by the ovary, long suspected on the basis of circumstantial evidence,* was finally proved in definitive fashion.⁴⁶ Biosynthesis of these 17-ketosteroids has been amply confirmed in both normal and polycystic ovaries.^{31, 47-51}

*See Parkes⁴⁵ for a masterful review.

Studies of ovarian venous blood^{52, 53} have demonstrated the presence of 17-ketosteroids, and elevated levels of blood testosterone have been observed in virilized patients with polycystic ovaries.^{54, 55} Thus, there is no longer any doubt as to the existence and identity of the ovarian androgens. These

Fig. 7. Progressive oxidation of 19-methyl group of andro-
stenedione.



findings explain the different levels of urinary 17-ketosteroid excretion associated with adrenal vs. ovarian virilization. Since the major adrenal steroid is dehydroepiandrosterone (apparently little or no testosterone is produced by the adrenal), it requires large quantities of this weak androgen to bring about pronounced clinical manifestations, and this elevated output is reflected in a high level of urinary 17-ketosteroids. The ovary, on the other hand, produces testosterone, a much more potent androgen, and consequently extreme degrees of virilization (as with arrhenoblastomas) may be the result of quantitatively much smaller production of steroid, causing little or no elevation of urinary 17-ketosteroids.

Before turning to a consideration of abnormalities of ovarian androgen production, it is necessary to complete the discussion of ovarian steroidogenesis by examining the mechanism which transforms these various androgens into the natural estrogens. This transformation takes place in two major stages. The first stage consists of an oxidative attack on the C-19 methyl group, which sticks out at right angles from the front face of the steroid molecule. This methyl group is first oxidized to an alcohol (forming 19-hydroxyandrostenedione or testosterone), then to an aldehyde (19-aldo-androstenedione or testosterone), Fig. 7. These intermediates have been identified in biosynthetic experiments with normal and polycystic ovarian tissue.²⁹ The second stage which involves aromatization of ring A begins by an enzymatic removal of the oxidized methyl group together with a nearby hydrogen atom. This results in an unstable intermediate which spontaneously rearranges to form the phenolic ring-A characteristic of the natural estrogens (Fig. 8). Evidence in support of this mechanism has been presented elsewhere.⁵⁶ By this route, therefore, androstenedione is converted to estrone, testosterone into estradiol. It is interesting to note that in our biosynthetic studies with normal or polycystic ovarian tissue, estradiol has always been the predominant estrogen formed.

Biosynthetic experiments in vitro reveal the potentialities of tissue under the given conditions, and presumably this reflects the activity of the organ in vivo; however, the relationship between in vitro and in vivo conditions is in need of further study. This question involves some surprising complications. Falck⁵⁷ in a technical *tour de force* transplanted vaginal epithelium and small nests of ovarian cells side by side in the anterior chamber of the eye of experimental animals, and showed that no single cell type produced cornification of the adjacent vaginal epithelium. When two types of ovarian cells in various combinations (theca interna or interstitial cells combined with granulosa or corpus luteum cells) were transplanted, however, cornification (i.e., estrogen production) occurred. In rabbits, it has been found that the interstitial tissue can produce as much progestagen as control ovaries with intact follicles,⁵⁸ and in humans, the medullary portion of polycystic ovaries is as active as the cortical zone in steroidogenesis.⁵⁹ Some workers have chosen to examine the steroid content of ovarian tissue in an effort to find correlations with the functional state of the ovary. Some of the data on tissue steroid concentration are summarized in Table 3.^{30, 60-65} It is

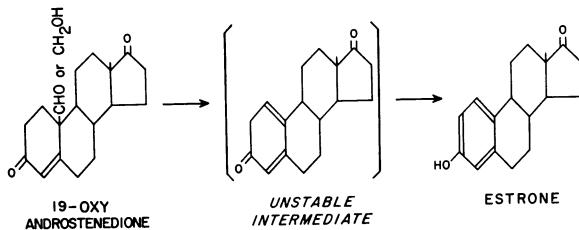


Fig. 8. Conversion of 19-oxygenated 17-ketosteroid into estrogen ("aromatization").

TABLE 3. Concentration of Steroids in Ovarian Tissue

<i>Steroid</i>	<i>Concentration (μg./gm.)</i>	
	<i>Normal</i>	<i>Poly cystic</i>
Progesterone	0-90	
17-hydroxypregnenolone	0	0-4.5
17-hydroxyprogesterone	0-1.7	3-6
"20-hydroxyprogesterone"	0-19	
Δ ⁴ -androstenedione	0.6	0-15
Testosterone	<0.3	
Dehydroepiandrosterone	0-1	0-7
Estrone	0.07-2	0.3-1.5
Estradiol	0.01-0.9	1.1-2.5
Estriol	0-0.6	0-0.9

Summary of results by various authors. Since different technics were used, the results are not necessarily comparable.

evident that ovarian tissue does not store appreciable quantities of steroids; indeed, the levels are so low in most instances as to be at the limit of detectability (to say nothing of reliability) of current technics. This approach to the problem therefore presents formidable difficulties. Moreover, since little is known of the relationship of tissue storage to the level of hormonal activity of the organ, the results are difficult to relate to ovarian function.

The escape of some of the intermediate steroid compounds from the ovarian biosynthetic "factory" into the peripheral circulation and hence into the urine might theoretically prove of value as an index of ovarian activity. Indeed, urinary excretion of Δ^5 -pregnenetriol,^{66, 67} pregnanetriol,⁶⁸ and other metabolites has been examined with this aspect in mind, but as with the urinary 17-ketosteroids, the contribution from the adrenal confuses the findings.

The technic of determining steroid secretory rates by isotope dilution has been widely employed in studies of adrenal function where determinations of cortisol or aldosterone secretory rates are fairly routine research procedures. It is only recently, however, that this methodology has been applied to the androgens,⁶⁹ estrogens,⁷⁰ and progesterone. Dominguez *et al.*⁷¹ have found a progesterone secretory rate of 2.5–5.4 mg./day in the preovulatory phase, rising to 22–43 mg./day during the postovulatory phase. At the ovulatory peak, estradiol secretory rates of 0.2–0.5 mg./day have been observed.⁷⁰ Important studies in normal and hirsute patients have been carried out by MacDonald *et al.*³¹ using dual-label technics to overcome the difficulty presented by the fact that both dehydroepiandrosterone and testosterone (or androstenedione) are metabolized to the same urinary excretory products. Normal ovaries were estimated to produce 1–2 mg. dehydroepiandrosterone and up to 1.6 mg. testosterone+androstenedione per day. By comparison, the adult testis produces 4–5 mg. dehydroepiandrosterone and 2.8–4.5 mg. testosterone+androstenedione per day. In hirsute women with normal 17-ketosteroid excretion and in some instances with polycystic ovaries, secretory rates were determined with the adrenals suppressed by dexamethasone. Under these conditions, increased secretion of dehydroepiandrosterone and/or testosterone+androstenedione was demonstrated. In one instance the ovaries produced 16 mg. dehydroepiandrosterone (but no testosterone+androstenedione) per day, while in another instance 4.5 mg. dehydroepiandrosterone and 5.6 mg. testosterone+androstenedione were produced—a rate comparable to that of the normal testis. Suppression of the pituitary gonadotropic stimulus with norethindrone acetate invariably resulted in a prompt drop of ketosteroid secretion, thus further confirming their ovarian origin. Studies such as these are time-consuming and require highly sophisticated technics, and when complications such as the secretion

of conjugated dehydroepiandrosterone by the adrenal are taken into consideration the mathematics become quite complex. There is also the important possibility that the state of the pituitary-ovarian axis may be altered by the dexamethasone used for adrenal suppression during these studies. Nevertheless, it will require methods such as these to provide fundamental information about the *in vivo* activity of the ovaries.

To explore these and other areas of endocrine abnormality in polycystic ovaries, many investigators, including ourselves, have concentrated on the information to be gained by examining the *in vitro* biosynthetic potential of polycystic ovarian tissue. Table 4 shows a comparison of the definitively identified metabolites from incubations of normal and polycystic ovarian tissue with progesterone and pregnenolone. The normal ovarian tissue is seen to metabolize all but 10.7% of the starting material at the end of 2 hr., the majority of the metabolites being in the form of 17- and/or 20-hydroxyprogesterones. Formation of androstenedione and testosterone is found; there is of course no dehydroepiandrosterone since the precursor was progesterone. There are considerable quantities of 19-oxygenated steroids and 4.8% conversion of the starting material to estradiol. No estrone or estriol was detected. The polycystic ovaries A and B also incubated with radioprogesterone were, if anything, even more active than the normal ovary, since they metabolized 99 and 100% of the starting material, and since much less 17- and/or 20-hydroxylated progesterone was left. However, a

TABLE 4. Steroids Produced by the Incubation of Normal and Polycystic Ovarian Tissue with Various Precursors

Steroid	Normal ovary with progesterone	% conversion		
		Polycystic ovary		
		With progesterone		With pregnenolone
		A	B	
Unconverted substrate	10.7	0.9	0.0	63.9
17- and/or 20-hydroxylated metabolites	78.2	43.1	46.8	6.1
Androstenedione	1.1	22.6	25.1	1.9
Testosterone	0.4	2.2	3.4	9.1
Dehydroepiandrosterone				15.1
19-oxygenated androstenedione or testosterone	3.9	31.3	24.4	3.5
Estrone	0.0	0.0	0.0	0.0
Estradiol	4.8	0.0	0.0	0.0

tremendous quantity of androstenedione (22.6 and 25.1%) and testosterone (2.2 and 3.4%) accumulated. Equally impressive is the conversion to 19-oxygenated steroids, being 6 to 10 times as great as that seen in the normal. However, no detectable estrogen was formed by these particular ovaries, immediately suggesting that the aromatizing mechanism which converts 19-oxygenated compounds to estrogens was defective and that the accumulation of androgens and 19-oxy compounds represents a "backing up" of steroid material behind the roadblock.

In the polycystic ovary incubated with pregnenolone, there is a very poor conversion of the starting material and also an accumulation of dehydroepiandrosterone, in addition to the abnormalities already seen in polycystic ovaries A and B. This would suggest an inadequacy of the 3β -ol dehydrogenase system in this particular ovary, as well as the aromatizing defect, which is clearly present in view of the 3.5% conversion to 19-oxygenated steroids with no detectable conversion to estrogen. These findings are entirely consistent with secretion rate studies of MacDonald *et al.*³¹ described above.

Such observations do not imply the uniform existence of invariable, all-or-none enzyme defects in polycystic ovarian tissue. The very fact that measurable urinary estrogen excretion along with more or less cornification of the vaginal epithelium does occur proves that in certain cases and at certain times biosynthesis can go on to aromatization. (In one polycystic ovary incubated with radiotestosterone, we have observed 10.1% conversion to estradiol and 3.2% conversion to estrone.) It appears, however, that there is still some obstruction to aromatization in these cases, as shown by the disproportionately large ratio of androstenedione and testosterone to estrogen formed. To put it another way, in the process of producing a particular amount of estrogen, the ovary is forced to synthesize and therefore secrete excessive amounts of androgen. Short and London⁷² have examined cyst fluid from human ovaries, and in "Stein-Leventhal" instances found an increased content of androstenedione and an absence of estrogens. On this basis, they also concluded that there was a defect in estrogen synthesis of polycystic ovaries. Confirmatory results by means of tissue incubation have been reported although unfortunately the necessary technical details were lacking.⁵³

It would appear incontrovertible then, that the androgenic manifestations associated with polycystic ovaries are in part due to an overproduction of ovarian androgens as a consequence of variable enzymatic defects in the aromatizing mechanism, the 3β -ol dehydrogenase system, and possibly other enzyme functions as well. That these defects do *not* define a clinical entity is shown by consideration of the cases which provided incubations A and

B in Table 4. The biosynthetic pattern of these two tissues is virtually identical. Clinically, however, "polycystic ovary A" presented a typical picture of androgenic adrenal hyperfunction (adrenogenital syndrome) without obesity or amenorrhea. Virilization and infertility were present; the 17-ketosteroid excretion ranged from 19 to 23 mg/day and was readily suppressed by minimal corticosteroid therapy, and a corpus luteum was found at wedge resection of the slightly enlarged, polycystic ovaries. "Polycystic ovary B" had all the symptoms associated with the "Stein-Leventhal syndrome." The urinary 17-ketosteroids ranged from 18 to 27 mg. per day and were not diminished by the standard corticosteroid suppression test. No corpus luteum was found on wedging the polycystic ovaries. It is paradoxical that the patient with the adrenal disorder became pregnant after wedging, whereas the "Stein-Leventhal" did not. Findings such as these, together with the established fact that surgical damage of the ovaries normalizes their function in a significant per cent of cases, indicate that the enzymatic defects found in polycystic ovaries are not irreversible, and that they may be the consequence of still more recondite influences which initiated the ovarian pathology. A search for these factors leads to the hypothalamic-pituitary mechanism which largely governs ovarian activity.

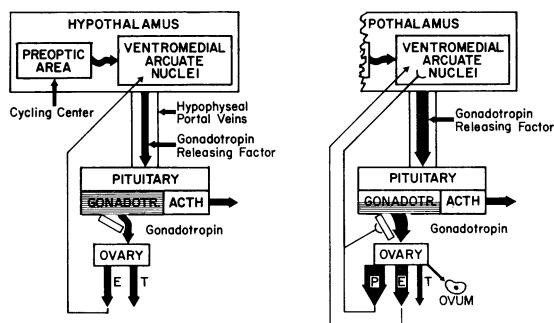
HYPOTHALAMIC-PITUITARY-OVARIAN RELATIONSHIPS

Our knowledge of hypothalamic regulation of the menstrual cycle in primates and especially in humans is far less advanced than one might suppose. Most of the information available has been derived from studies of rodents, particularly those having an estrus cycle.⁷³ It is usually assumed that the basic features of the estrus cycle are comparable to those of the primate menstrual cycle, but there is reason to believe that future research will show important fallacies in this assumption. Nevertheless, one must deal with the information at hand, recognizing its tentative and very possibly species-specific character.

Our current concept of the neural-pituitary-ovarian circuit is diagrammed in Fig. 9. A region in the preoptic area of the hypothalamus, possibly the suprachiasmatic nucleus, appears to act as a biological "clock," imparting a cyclic character to the rest of the mechanism and thus accounting for the estrus cycle and the menstrual rhythm. These neural impulses are registered in the region of the median eminence of the hypothalamus, probably the ventromedial and arcuate nuclei.⁷⁴ These centers produce a neurohormone⁷⁵ which has been called the gonadotropin-releasing factor (GRF). GRF is transported by means of the hypophyseal portal veins (note the similarity to the role of corticotrophin-releasing polypeptide in the pituitary-adrenal axis)

to the adenohypophysis, where it causes a synthesis and release of pituitary gonadotropin. Thus, the median eminence area of the hypothalamus exerts a tonic stimulation on the pituitary, and the preoptic area superimposes a cyclic variation on this mechanism. The released gonadotropin (whatever its

Fig. 9. Hypothalamic-pituitary-ovarian mechanism. At left, preovulatory relationships; At right, post-ovulatory relationships. E = estrogens; T = testosterone (androgens); P = progesterone.



true qualitative character may be) stimulates the ovary to secrete androgens and estrogens approximately in the ratio of 7:1. The estrogens released into the circulation have a stimulatory effect on the nuclei near the median eminence (a "positive feedback" effect), causing increased secretion of GRF, which in turn increases gonadotropin secretion, and so on. At a certain point, the rising estrogen output triggers ovulation.⁷⁶ With the occurrence of ovulation and the production of an egg, dramatic changes in the ovarian steroid output occur. In addition to estrogen, there is now a tremendous output of progesterone (milligrams of progesterone as compared to micrograms of estrogens). Progesterone inhibits the release (but not the formation) of pituitary gonadotropins^{77, 78} (Fig. 9), and also has an inhibitory effect on the hypothalamic centers. This "negative feedback" mechanism serves to diminish the gonadotropic stimulus of the ovary, and together with the waning phase of the preoptic "cycling" center brings about the termination of the cycle.

The mechanism permits an interpretation of some remarkable experiments based on the rediscovery of certain simple methods for producing persistent estrus in rats.⁷⁹ Electrolytic lesions or single massive injections of steroids in the first few days of life apparently damage the cycling center of the rat hypothalamus; the results are shown in Fig. 10. There is now a *tonic* discharge of GRF from the ventromedial and arcuate nuclei, causing a continuous release of pituitary gonadotropin. The resulting tonic secretion of estrogen and positive feedback turn this into a situation where the pituitary never gets a chance to pause and store up gonadotropin for the large burst needed in the process of ovulation. Thus an anovulatory mechanism is set up, with a continuous low-level stimulation of the ovary. As these

rats grow to maturity, the ovaries become enlarged and polycystic, and there also occurs a hypertrophy of the adrenals.

Under these conditions of continuous, noncyclic ovarian stimulation it is conceivable that changes in the ovarian steroid biosynthetic mechanism might occur. For this reason, we incubated a number of such enlarged, polycystic rat ovaries in the same manner as used for the studies on human ovaries. The results of one such experiment are shown in Table 5. Keeping in mind the possibility of species-specific differences in ovarian steroidogenesis,^{80, 81} one fact emerges with great clarity: *although there is ample conversion of the pregnenolone to androgens, no aromatization to estrogens is detectable*. The similarity to one of the enzymatic abnormalities observed in human polycystic ovaries is apparent. It is possible that experimental modifications which take into account the fact that rat tissue metabolizes much faster than human tissue (a cycle is complete in 4 days vs. 28 days for man) might have demonstrated the presence of other intermediates such as 19-oxygenated compounds. It is also evident from the fact that these animals are in persistent estrus that *some* estrogen is being formed (although other steroids are known to be able to produce vaginal cornification),⁸²⁻⁸⁴ but the important fact, as seen with human tissue also, is that the ratio of androgen to estrogen formed must be extremely high. This overproduction of androgen, now observed in both rat and man, might have some bearing on the formation of capsular fibrosis in human polycystic ovarian disease, since the

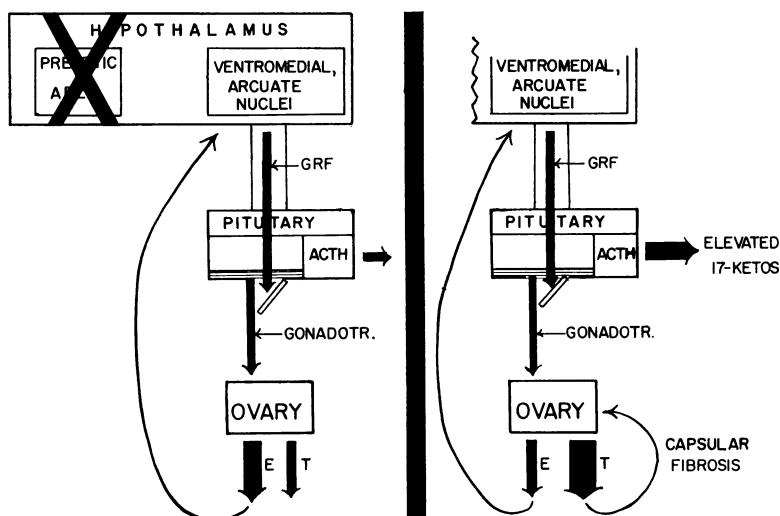


Fig. 10. Genesis of polycystic ovaries. Disruption of hypothalamic-pituitary-ovarian mechanism in persistent-estrus rat. At left, early stage; At right, breakdown of enzyme systems and possible cause of ovarian fibrosis seen in human disease.

TABLE 5. Steroidogenesis in Ovarian Tissue of Persistent-Estrus Rats

<i>Metabolite</i>	<i>Substrate: pregnenolone-4-C-14</i>	<i>Total DPM</i>
Unconverted pregnenolone		391,540
Δ^5 -pregnen-3 β , 20 β -diol		10,870
17 α -hydroxyprogesterone		6,890
Dehydroepiandrosterone		8,620
Δ^4 -androstenedione		20,100
Testosterone		12,470
Estrogens		None

administration of androgens to primates for prolonged periods of time has been shown to cause such a lesion.⁸⁵ This is shown diagrammatically in Fig. 10.

There are other important experiments which have been performed with these persistent-estrus rats. If the estrogenic "positive feedback" mechanism is interrupted by removing one ovary and resecting most of the second (or inactivating its hormones by transplanting it to the portal circulation), the character of pituitary function changes and luteinization of the remaining ovary occurs.^{86, 87} Still another experiment affirms this line of thought: Electrical stimulation of the hypothalamus of persistent-estrus rats fails to produce ovulation unless the animals are pretreated with large doses of progesterone (causing a storage of pituitary gonadotropin).⁷⁴

These experiments may well suggest an answer to the perpetual question, why wedge resection restores cyclic function in some women with polycystic ovaries. By analogy with these rodent experiments, consider the endocrine situation which may develop in certain instances of human polycystic ovarian disease. Characteristically, menarche occurs at about the normal age and there is some menstrual function for a time. The histories often suggest that this phase of early ovarian function is anovulatory. If, for some reason, the human hypothalamic "cycling center" does not straighten matters out, the ovary remains exposed to a more or less tonic gonadotropic stimulus, without the beneficial gonadotropin-accumulating influence of progesterone. Thus the vicious circle of noncyclic GRF secretion, noncyclic and possibly qualitatively abnormal gonadotropin secretion, and finally uninterrupted estrogenic positive-feedback develops. Ultimately certain ovarian steroid-biosynthetic enzymes become exhausted. (In this connection it is worth noting that the testis, under its *noncyclic* gonadotropic control biosynthesizes androgens physiologically. When the ovary is exposed to noncyclic gonadotropic influences, its production of female hormones breaks down and it

reverts to a testicular pattern of steroidogenesis.) Chronic exposure of the ovary to these gonadotropic stimuli produces cystic changes, and the constant presence of high local concentrations of androgens may account for the ovarian fibrosis. Now, the surgeon inflicts a major trauma on the ovary, especially if he follows the customary recommendations to resect a *generous* portion of tissue and to extend his incision *well down into the hilus*, where the major blood supply is found. This procedure so affects the ovary that its steroid production is greatly reduced or perhaps even interrupted for a time. Positive feedback and the vicious circle are broken; secretion of gonadotropin is slowed or halted and accumulation can occur; the exhausted ovarian steroidogenic enzymes may be able to recover. If the cycling center is intact, it may be able to take over and initiate a rhythm which the rested pituitary and ovary may be able to follow. The fact that infertility is corrected less often than the menstrual rhythm may be due to mechanical problems, irreversible pathology of the ovary, or to as yet unknown factors. Leclercq⁸⁸ examined a successfully resected polycystic ovary some years later and described its appearance as "entirely normal." Others, including ourselves, have observed recurrence of the symptoms and again a typical gross pathology at the time of the second wedging. Whether these changes persisted or recurred is impossible to say.

There are, of course, many additional and perhaps very important factors which this tentative working hypothesis has not included. Puzzling instances of unilateral polycystic disease have been reported.⁸⁹⁻⁹¹ There is the question of the intrinsic responsiveness of the ovarian tissue to gonadotropin. Many animal experiments have shown that the administration of gonadotropin will produce a type of polycystic ovary in the hypothyroid animal, whereas that same treatment will be ineffective in euthyroid controls.^{92, 93} The excessive enlargement of human polycystic ovaries in response to gonadotropin^{94, 95} or clomiphene is an observation which requires further clarification. Taymor and Barnard⁹⁶ have recently supported the observations of Ingersoll and McArthur⁹⁷ of an intermittent elevation of urinary LH in some patients with polycystic ovaries and found these changes in patients with both normal-sized and enlarged ovaries. Many technical difficulties as well as troublesome day-to-day variation in gonadotropin output beset these investigations; improved methods and additional studies may explain the "normal" results and hopefully provide correlations with the neurohypophyseal studies in rodents.

At all events, these advances in ovarian biochemistry and neurohypophyseal relationships have suggested new approaches for research on the polycystic ovary problem and a working diagram which can be tested and will no doubt be modified, perhaps greatly, by future observations. The clinical

implications of the findings we have summarized are equally important. A more flexible attitude and a critical re-examination of our diagnostic criteria is evidently needed. Which cases of "secondary amenorrhea" or "functional uterine bleeding" might be associated with polycystic ovaries? What functional or in vitro studies will improve our ability to select those cases most likely to benefit from wedge resection, and what factors are present in those cases where surgery fails? Would the action of progesterone in the persistent-estrus rat be duplicated in the human—i.e., would there be a beneficial result from giving large doses of progesterone postoperatively to promote storage of gonadotropin in the pituitary? These and many other vital questions await further research in polycystic ovarian disease.

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Abstract

Polycystic ovary syndrome predisposes alterations which contribute to the reduction of quality of life. This randomized controlled clinical trial study was to evaluate the effect of two protocols of aerobic exercise on quality of life in women with polycystic ovary syndrome. Women were allocated to three groups: continuous aerobic training ($n=28$), intermittent aerobic training ($n=29$), and control group (no training; $n=30$). Testosterone levels, body composition indices, and quality of life were assessed at baseline and after 16 weeks of intervention. Both protocols were effective to improve testosterone levels, anthropometric indices, and quality of life in polycystic ovary syndrome women. Thus, these protocols should be included in the clinical environment to improve clinical parameters psychological, biological and social health to this population.

Keywords

aerobic exercise, anthropometric indices, polycystic ovary syndrome, quality of life, testosterone

Introduction

Polycystic ovary syndrome (PCOS) affects 5%–16% of women of reproductive age (Ding et al., 2017) and is characterized by the presence of at least two of the following factors: clinical and biochemical hyperandrogenism, polycystic ovaries, and oligomenorrhea or anovulation (Consensus Amsterdam, 2012; Consensus Rotterdam, 2004). PCOS is marked by hormonal and anthropometric changes, as well as by metabolic disorders, which increase

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the risk of cardiovascular disease (Alves et al., 2017; Anagnostis et al., 2018; Consensus Rotterdam, 2004; Ribeiro et al., 2016). Furthermore, all of these changes and disorders associated with PCOS culminate in an increased risk of sexual dysfunction, reduced quality of life (QoL), and altered emotional state for those affected by this syndrome (Borghi et al., 2018; Elsenbruch et al., 2003; Lopes et al., 2018; Shafti and Shahbazi, 2016; Stapinska-Syniee et al. 2018).

Previous evaluations of QoL through the use of the 36-Item Short-Form Health Survey (SF-36) in women with PCOS have shown differences in the domains of social functioning, vitality, emotional functioning, and sexual dysfunction (Aliasghari et al., 2017; Elsenbruch et al., 2003; Panico et al., 2017). Possibly, an increase in body mass index (BMI) and hirsutism are factors that interfere with these QoL scores (Aliasghari et al., 2017; Jones et al., 2011; Shishehgar et al., 2016), since these characteristics may cause self-image distortion, leading to a negative self-assessment with implications on the psychological condition of women with and without PCOS (Becker et al., 2017; Campbell and Hausenblas, 2009; Hahn et al., 2005; Kowalczyk et al., 2012). Furthermore, it has been shown that many of the characteristics associated with PCOS contribute to lower self-esteem with negative impact on QoL (Benetti-Pinto et al., 2015; Hahn et al., 2005; Panico et al., 2017; Shishehgar et al., 2016).

Isolated pharmacological treatment has been found to be ineffective in controlling the clinical condition of PCOS, and complementary measures such as lifestyle changes and exercise are recommended (Costa et al., 2018; Kogure et al., 2016; Lara et al., 2015; Lopes et al., 2018; Ribeiro et al., 2016; Thomson et al., 2010). Previous studies conducted by our research group have demonstrated the positive effects of physical strength training on QoL (Ramos et al., 2016), while in another study, the benefits of aerobic exercise in PCOS were demonstrated (Costa et al., 2018). Relatedly, the positive effects of exercise on QoL have been demonstrated in different clinical conditions and different populations (Brown et al.,

2018; Hayashino et al., 2018; Vasiliadis and Bélanger, 2018). However, there is a lack of research comparing different protocols of exercise to discriminate which is more effective in improving the QoL of women with specific clinical conditions such as PCOS. This information is relevant as there are indications that intermittent aerobic exercise is associated with greater satisfaction for those performing the exercise, which favors adherence to the exercise program (Thum et al., 2017). Thus, identifying the best exercise protocol is essential for the development of care programs for women with PCOS. Therefore, this study aimed to verify and compare the effects of continuous aerobic exercise and intermittent aerobic exercise protocols on the QoL of women with PCOS.

Methods

Study design and participants

This study was registered in ISRCTN10416750 and approved by the Institutional Review Board of the University Hospital, Ribeirão Preto Medical School, University of São Paulo (protocol no. 9640/2014).

This study was designed as a randomized controlled clinical trial in which women with a diagnosis of PCOS, based on the Rotterdam criteria (Consensus Rotterdam, 2004), were recruited as participants. Advertisements in the city newspaper and on the university website were used to recruit participants for the study.

The women selected as participants were invited to follow up at the Gynecological Endocrinology Outpatient Clinic of the Human Reproduction Sector of the Department of Gynecology and Obstetrics of the Ribeirão Preto Medical School, University of São Paulo, the setting for this study. All participants signed an informed consent form prior to being allowed to participate in the study.

Exclusion criteria were age less than 18 years and greater than 39 years, BMI less than 18 and greater than 39.9 kg/m^2 , women using drugs that interfered with the hypothalamic-pituitary hormone function (i.e. hormonal contraceptives,

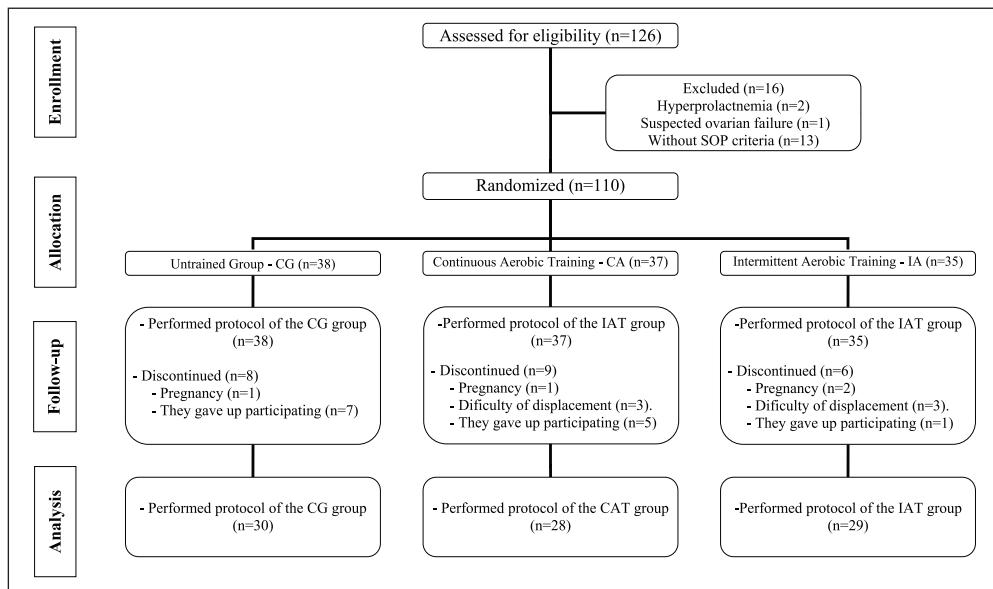


Figure 1. Selection of participants.

estrogen and progestin drugs, hormone therapy, gonadotropin-releasing hormone (GnRH) analogues and antagonists), pregnant women, smokers, and women with diabetes, congenital adrenal hyperplasia, thyroid diseases, hyperprolactinemia, Cushing's syndrome, or musculoskeletal disorders.

In this study, 126 volunteers were recruited. Of these, 16 were excluded during the initial evaluations. Thus, the remaining 110 started the physical training protocols. Of these, 23 were lost in the course of the study and 87 completed the study which were divided into continuous aerobic training (CAT; $n=28$), intermittent aerobic training (IAT; $n=29$), and control group without training (CG; $n=30$). The reasons for exclusions and withdrawals are described in Figure 1.

Randomization

The sample was randomly allocated by placing written assignments in sequentially numbered, sealed, opaque envelopes that were grouped in blocks of 15 participants, with five blocks for each group. The envelopes were consecutively

and separately collected, depending on each participant's BMI at the time of inclusion. A list of random numbers was generated by a computer and, after the participant consented to participate, the envelope was opened, and the participant was allocated into one of the three groups, according to the contents of the envelope. The generation of the random sequence was performed by a researcher and the sealing of the envelopes was performed by an assistant, neither of whom participated in the recruitment nor the allocation of the participants. Another researcher recruited and allocated participants to the groups.

Intervention and evaluation

Before and after the intervention, measurements were conducted, with all post-exercise intervention assessments occurring 72 hours after the last exercise training session. The first part of the evaluation included anthropometric measurements. Waist circumference (WC) was measured with the participant in the standing position, with arms at the side of the body, feet together, and with a relaxed abdomen. For WC, a horizontal measurement was obtained on the

Table I. Protocols of CA and IA physical training.

Week	Duration	CA training	IA training			
			Intensity (% HR maximum)	Series	Recovery intensity (% HR maximum) (3 minutes)	Upper intensity (% HR maximum) (2 minutes)
1	30	65	6	60	70	
2	30	65–70	6	60	75	
3	30	70	6	60	80	
4	35	70	7	60	80	
5	35	70–75	7	65	85	
6	35	70–75	7	65	85	
7	40	70–75	8	65	85	
8	40	70–75	8	65	85	
9	40	75	8	65–70	85	
10	40	75	8	65–70	85	
11	45	75	9	65–70	85	
12	45	75	9	65–70	85	
13	45	75–80	9	65–70	85–90	
14	50	75–80	10	65–70	85–90	
15	50	75–80	10	65–70	85–90	
16	50	75–80	10	65–70	85–90	

CA: continuous aerobic; IA: intermittent aerobic; HR: heart rate.

Added 5 minutes of heating and 5 minutes of cool down.

narrower part of the dorsum (above the navel and below the xiphoid process; Ciconelli et al., 1997). Hip circumference (HC) was measured using the same positioning, as the region with the largest circumference of the buttocks (American College of Sports Medicine (ACSM), 2014). Waist-to-hip ratio (WHR) was measured by dividing the WC value by the HC value (ACSM, 2014).

Testosterone was measured before and after the intervention, through the use of the chemiluminescence method (Immulite 1000, Siemens). Prolactin, thyroid stimulating hormone (TSH), and 17-hydroxyprogesterone (17-OHP) were measured before the intervention using the chemiluminescence method (Immulite 2000, Siemens XPI). For these measurements, 20 mL of whole blood was collected until the eighth day of the menstrual cycle (early follicular phase), or any day if the patient was in amenorrhea. Ovary morphology was assessed by ultrasound, using the Voluson E8 Expert (GE

HealthCare, Zipf, Austria) equipped with a 5–9 MHz vaginal probe (RIC5-9D).

QoL was assessed by the validated Portuguese version of the self-reported MOS SF-36, which consists of eight subscales: (1) Physical Role Function, (2) Physical Functioning, (3) Bodily Pain, (4) General Health Perception, (5) Vitality, (6) Social Role Functioning, (7) Emotional Role Functioning, and (8) Mental Health. Subscale scores range from 0 to 100, with a lower score indicating lower QoL for that subscale (Ciconelli et al., 1997; Martinez et al., 2004).

Participants were instructed to maintain the same daily diet for the duration of the study. Using Embreex 570-L and Embreex 570-Pro treadmills, the two protocols of aerobic training were performed: Continuous and intermittent aerobic exercise. The duration of the exercise intervention was 16 weeks, with three sessions per week (Table 1). The intensity of the training was monitored by a heart rate monitor (Polar RS810). To ensure equivalent training volume

for both protocols, heart rate percentage was multiplied by the session duration (in minutes; ACSM, 2014). To calculate intensity, a formula of [maximum heart rate (HR_{max}) \times % intensity] was used (ACSM, 2014). The training protocol included a 5-minute warm up and a 5-minute cool down between 50% and 60% of the maximum heart rate. The target intensity areas of training followed the recommendations of ACSM (2014). The IAT and CAT protocols were performed in the Cardiovascular Physiology and Physiotherapy Laboratory. Participants' adherence to the training intensity was monitored by a team of personal trainers and physiotherapists.

Sample size

The sample size was calculated using the GPower program, version 3.1.92 (see <https://pt.freedownloadmanager.org/Windows-PC/GPower-GRATUITO.html>). The sample size was obtained considering a Cohen's d effect size of 0.6, a significance level of 5%, and a test power of 80%. According to Cohen's agreement, 24 patients are necessary to achieve a moderate difference between groups (CAT, IAT, and CG). The final sample was increased by to cover the losses (Figure 1; Miot, 2011).

Statistical analyses

Means and standard deviations were calculated for all variables and included a 95% confidence interval (CI), where appropriate. Anthropometric and laboratory measurements, as well as scores on the SF-36 were compared using a planned orthogonal contrast in the mixed effects linear regression model. Repeated measures from the same participant were considered as random effects (i.e. more than one measurement for the same participant). Age, group, time, BMI, WHR, testosterone, and interaction between group and time were examined as covariates for all analyses to evaluate the training effects both within and between groups. All statistical analyses were performed using SAS® Software Version 9.4 (SAS Institute Inc., University of

North Carolina, Chapel Hill), with $p < 0.05$ considered to be statistically significant.

Results

Anthropometric and laboratory data

Upon examination of the baseline measurements, no significant differences were found between the three groups with regard to age, height, and levels of prolactin, 17-OHP, and TSH. The groups were also homogeneous with regard to the BMI, WC, and WHR variables. However, the CAT showed significantly higher values of testosterone in relation to the CG ($p = 0.014$) in the baseline measurement (Table 2).

Following the intervention, a significant reduction in WC was found in the CAT ($p = 0.045$) and IAT ($p = 0.049$) groups. Conversely, a significant increase in WC was found in the CG group ($p = 0.014$). HC was significantly reduced in the CAT group ($p = 0.032$). Furthermore, there was a significant reduction of WHR in the IAT group ($p = 0.012$). Finally, testosterone levels in the CAT ($p < 0.001$) and IAT ($p = 0.019$) groups were significantly lowered (Table 2).

QOL—SF-36 scores

At baseline, there was no significant difference between the three groups regarding SF-36 scores. Following the 16-week intervention period, there were no significant differences found in the CG when compared with baseline scores. However, with regard to the CAT group, there was a significant increase in Physical Functioning ($p = 0.022$), Physical Role Functioning ($p < 0.001$), General Health Perception ($p < 0.001$), Vitality ($p < 0.001$), Social Role Functioning ($p < 0.001$), Emotional Role Functioning ($p < 0.001$), and Mental Health ($p = 0.001$). For the IAT group, significant increases were found in Physical Functioning ($p < 0.001$), Physical Role Functioning ($p = 0.027$), General Health Perception ($p < 0.001$), Vitality ($p < 0.001$), Social Role Functioning ($p < 0.001$), Emotional Role Functioning ($p = 0.011$), and Mental Health ($p < 0.001$) (Table 3).

Table 2. Anthropometric and laboratory data of women with PCOS before and after without training (CG) or 16-week physical training.

	CG (N=30)			CAT (N=28)			IAT (N=29)		
	Before	After	Estimation of difference (CI 95%)	Before	After	Estimation of difference (CI 95%)	Before	After	Estimation of difference (CI 95%)
Age (year)	28.5 (5.8)	—	—	29.1 (5.3)	—	—	29.0 (4.3)	—	—
BMI (kg/m ²)	29.1 (5.2)	29.3 (5.4)	-0.24 (-0.56 to 0.08)	28.4 (5.6)	28.2 (5.7)	0.25 (-0.07 to 0.58)	28.7 (4.8)	28.5 (4.8)	0.13 (-0.19 to 0.45)
WC (cm)	89.5 (13)	91.0 (13)*	-1.46 (-2.91 to -0.01)	88.1 (14)	86.6 (13.1)*	1.54 (0.04 to 3.05)	90.5 (11.3)	88.7 (12.4)*	1.87 (0.39 to 3.35)
HC (cm)	106.3 (10)	107.2 (9.7)	-0.88 (-2.05 to 0.28)	106 (9.58)	104.5 (10.3)*	1.33 (0.12 to 2.54)	107.3 (9.5)	104.2 (11.0)	0.14 (-1.04 to 1.33)
WHR	0.84 (0.08)	0.85 (0.07)	-0.01 (-0.02 to 0.01)	0.83 (0.08)	0.82 (0.07)	0.01 (-0.01 to 0.02)	0.84 (0.06)	0.83 (0.07)*	0.02 (0.01 to 0.03)
Testosterone (mg/dL)	86 (37)	100 (46)	-13.4 (-29.7 to 2.86)	117 (50)	93 (38)*	24.0 (7.2 to 40.8)	108 (52)	88 (54)*	19.9 (3.30 to 36.4)

PCOS: Polycystic ovary syndrome; CG: control group; CAT: continuous aerobic training; IAT: intermittent aerobic training; CI: confidence interval; BMI: body mass index; WC: waist circumference;

HC: hip circumference; WHR: waist-to-hip ratio.

Data are presented as mean and standard deviation and CI.

* $p < 0.05$; ** $p < 0.001$.

Discussion

This study aimed to evaluate the effects of continuous and intermittent aerobic exercise protocols on QoL in women with PCOS. Both protocols were found to be effective in improving physical, emotional, and social functioning as well as vitality, mental health, and the perception of general health, as indicated by increased scores on the SF-36, a measure of QoL. In addition, there was a reduction of WC, HC, and testosterone in the CAT group and WC, WHR, and testosterone in the IAT group. Furthermore, there was an increase in WC in the CG group.

Based on a review of related research, it appears that this is the first study to compare the effects of two aerobic exercise protocols on QoL in women with PCOS, making this study particularly relevant to improving care for this population. Although there was no improvement in BMI as previously demonstrated (Frène et al., 2015; Stener-Victorin et al., 2013), this study provided evidence of various benefits from physical exercise. Consistent with the results of this study, a recent study evidenced the effectiveness of a lifestyle and physical exercise program in promoting QoL in women with PCOS, even without improvement in BMI (Frène et al., 2015). Similarly, another study provided evidence of improved depression and QoL in women who were identified as overweight or obese (Thomson et al., 2010).

Different protocols have been used to prove the beneficial effects of exercise on QoL in other populations such as older persons and individuals with cancer and type II diabetes (Brown et al., 2018; Hayashino et al., 2018; Vasiliadis and Bélanger, 2018). In studying women with PCOS, the most recent protocols have involved physical strength training and aerobic exercise (Costa et al., 2018; Ramos et al., 2016). A study by Ramos et al. (2016) included a protocol of progressive intensity with a frequency of three times per week, over a 16-week period. The results of the study showed improvement in the Physical Role Functioning score of the SF-36 and a reduction

Table 3. Comparison of the SF-36 questionnaire scores of women with PCOS before and after the period without training (CG) or 16-week physical training.

	CG (N=30)			CAT (N=28)			IAT (N=29)		
	Before	After	Estimation of difference (CI 95%)	Before	After	Estimation of difference (CI 95%)	Before	After	Estimation of difference (CI 95%)
Physical role functioning	73.8 (21.5)	77.8 (2.1)	-4.63 (-11.60 to 2.32)	81.6 (15.3)	91.3 (13.0)*	-8.53 (-15.85 to -1.26)	76.0 (21.1)	93.5 (7.1)**	-17.04 (-24.21 to -9.87)
Physical functioning	69.2 (38.1)	59.2 (38.0)	10.10 (-3.37 to 23.57)	67.0 (34.7)	90.2 (19.7)**	-23.37 (-37.48 to -9.26)	78.4 (33.2)	93.1 (17.5)*	-15.66 (-29.53 to -1.79)
Bodily pain	53.5 (21.4)	54.6 (23.2)	-0.54 (-8.60 to 7.53)	64.4 (21.2)	68.4 (21.8)	-5.35 (-13.82 to 3.12)	66.9 (21.4)	71.0 (22.8)	-4.92 (-13.26 to 3.41)
General health perception	54.8 (16.3)	54.0 (17.2)	0.28 (-5.17 to 5.74)	53.9 (16.3)	62.5 (17.3)**	-7.97 (-13.7 to -2.23)	53.5 (22.3)	67.3 (6.3)**	-13.26 (-18.91 to -7.62)
Vitality	46.0 (22.1)	51.5 (22.2)	-5.38 (-12.32 to 1.55)	51.4 (17.9)	65.2 (16.7)**	-13.24 (-20.54 to -5.95)	47.8 (21.3)	66.4 (17.4)**	-18.12 (-25.30 to -10.94)
Social role functioning	63.8 (28.3)	70.1 (27.8)	-6.89 (-15.43 to 1.64)	65.7 (25.8)	82.3 (18.1)**	-15.73 (-24.71 to -6.75)	68.9 (24.5)	82.0 (19.9)**	-11.97 (-20.81 to -3.13)
Emotional role functioning	62.2 (42.6)	58.9 (44.4)	1.23 (-14.03 to 16.49)	54.8 (41.8)	82.2 (28.0)**	-23.89 (-39.90 to -7.88)	55.2 (36.0)	79.4 (32.6)*	-20.54 (-36.28 to -4.79)
Mental health	54.3 (21.9)	57.2 (23.1)	-3.54 (-10.17 to 3.08)	55.1 (15.6)	70.1 (16.7)**	-13.96 (-20.93 to -6.98)	60.4 (18.2)	73.0 (15.4)**	-11.68 (-18.54 to -4.81)

PCOS: Polycystic ovary syndrome; CG: control group; CAT: continuous aerobic training; IAT: intermittent aerobic training; CI: confidence interval; IA: intermittent aerobic (physical training group); SF-36: 36-item Short-Form Health Survey.

Data are presented as mean and standard deviation and CI.

* $p < 0.05$; ** $p < 0.001$.

of WC in this population (Ramos et al., 2016). Similarly, Costa et al. (2018) used a three times per week, 16-week, open-field aerobic exercise protocol which evidenced the improvement of the Physical Role Functioning, General Health Perception, and Mental Health domains of the SF-36 questionnaire. In this study, which included a larger sample size, all of the SF-36 questionnaire scores were increased, with the exception of the Bodily Pain subscale, both in the intermittent and continuous training protocols, thus demonstrating improvement across a broader span of variables related to QoL.

Women with PCOS are frequently dissatisfied with their body image (Micskei et al., 2014). This study found a significant reduction in the anthropometric indices following the exercise protocols, which may have contributed to the improved perception of body image as evidenced by an improvement in QoL scores, mainly with regard to physical and emotional perceptions (Micskei et al., 2014). In addition, there was a significant reduction in the serum concentration of testosterone following both protocols, which may have also contributed to the improvement of QoL scores. Therefore, it is possible that the reduction of testosterone, as observed in this study, may be a predictive factor of improvement in QoL, mainly with regard to emotional functioning and overall general health status. Furthermore, aerobic physical exercise has been found to promote an adjustment in cortisol levels and increase levels of anandamide and serotonin which, together, promote the improvement of mood (Heijnen et al., 2015; Park et al., 2017). Similarly, treadmill exercise has been shown to improve serotonergic function by reducing depressive symptoms (Shin et al., 2017). Previous research has shown that improvements in mood and depressive symptoms may lead to an improved QoL (Böttcher et al., 2018; Wright et al., 2013).

Care was taken in the design of the protocols used in this study to avoid injuries by standardizing the same training volume and duration of the sessions, both for the CAT and IAT interventions. Previous studies have demonstrated that intermittent aerobic exercise allows individuals to perform the same volume as continuous exercise training but with a shorter duration, which

seems to favor greater adherence to the exercise program (Thum et al., 2017). In this study, the same training volume intensity and duration of sessions were maintained in order to compare the efficacy of the continuous and intermittent protocols. Furthermore, the intensity of the training was diluted throughout the sessions to avoid injuries, which allowed the training of individuals with a large variation in BMI (18–39.9 kg/m²), without any cases of orthopedic injury. Although there were cases of participant withdrawal throughout the study for various reasons, there was considerable permanence in the groups trained in both protocols (Figure 1). It is possible that the inclusion of group exercises favored the creation of bonds between the participants, which may have been a stimulus for adherence to the program, as previously demonstrated (Thum et al., 2017).

Strengths and limitations

The main strengths of this study are that this was a randomized clinical trial, and the structure of the two different training protocols was well defined. However, one limitation was the lack of menstrual cycle control and hirsutism observed in some participants after training, which may have directly interfered with the QoL results. In addition, the sample of participants in the training groups did not reach the desired quantitative goal of 30 per group.

Future research

For future research, an objective evaluation of hirsutism through the use of the Ferriman–Gallwey Scale (Ferriman and Gallwey, 1961) after the end of the exercise and control period is suggested in order to control for this variable, which is known to interfere with self-image (Morotti et al., 2013) and may influence the evaluation of QoL of women with PCOS.

Conclusion

Continuous and intermittent aerobic exercise protocols were found to be equally effective in reducing anthropometric indices and hyperandrogenism,

and in the improvement of QoL in women with PCOS. Thus, these protocols should be included in the clinical environment to improve clinical parameters psychological, biological and social health to this population.

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Availability of data and materials

Data sets generated during and/or analyzed during this study are available to the corresponding author upon reasonable request, subject to the privacy of the participants.

Declaration of conflicting interests

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DEVELOPMENT OF KAP TOOL AND ITS APPLICATION IN ASSESSMENT OF YOUNG FEMALES WITH PCOS.

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ABSTRACT **BACKGROUND:** Polycystic ovary syndrome (PCOS) is the most common endocrine disorder amongst women of reproductive age associated with various clinical and psychological manifestations. Promoting awareness and lifestyle modifications is essential to empower the female PCOS population to take health care decisions for the treatment and management. **OBJECTIVE:** Assessment of knowledge, attitude and practice(KAP) among PCOS population is significant in behavioral and lifestyle modification. Thus, the present study was undertaken to develop a KAP tool. **METHODS:**An observational, non-controlled study was conducted using random sampling in the age range of 15-25 years. A total of 600 subjects were screened with the help of a standardized screening questionnaire and the presence of PCOS was confirmed using the Rotterdam criteria (2003).A KAP tool validated by an expert panel was given to the subjects confirmed for PCOS to assess knowledge, attitude and practices. The validity was assessed using exploratory factor analysis. The Spearman-Brown correlation coefficients helped to assess reliability for knowledge, attitude and practice domains, which were found to be 0.83, 0.63 and 0.47 respectively. **RESULTS:** Significant knowledge was found among confirmed PCOS subjects, but had low attitudes and their practices did not commensurate with their knowledge about PCOS and Nutrition. **CONCLUSION:** The present research contributes to the understanding of a growing PCOS epidemic in urban India and document the need to screen knowledge, attitude and practice, to develop supportive interventions addressing quality of life issues to reduce the distress among women with PCOS.

KEYWORDS : PCOS; Rotterdam Criteria; glucose tolerance; insulin resistance; KAP; lifestyle modification; development; validation; reliability

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the commonest endocrine disorders seen in young women characterized by three classic symptoms: Irregular menstrual periods ,excessive hair growth and or Polycystic ovaries.[1]

In a survey, it was found to be 9.13% prevalent among south Indian adolescent girls.[2] World Health Organization (WHO) indicated that PCOS affected 116 million (3.4%) of women worldwide.[3]

Women with PCOS are also at an increased risk of psychological implications. Lifestyle management is currently advised as the first line management strategy for PCOS. Therefore, assessment of knowledge, attitude and practice is significant in behavioral and lifestyle modification.

OBJECTIVES

The study aimed at assessing the knowledge, attitude and practices among subjects confirmed for PCOS.

2. MATERIAL AND METHODS

Sample size and Selection of subjects:

Random sampling technique was used to select subjects .Screening questionnaire was distributed to 600 subjects. Responses were received from 521 subjects. Based on the inclusion criteria, 56 subjects were considered for the study. Average age of the selected subjects was 21.5 years.

INCLUSION CRITERIA:

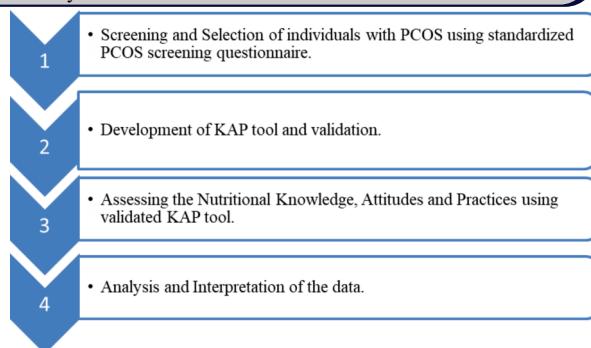
Females aged between 15-25 years of age.

- Confirmed cases of PCOS based on Rotterdam Criteria which requires the presence of any two of the following:
- Oligo/anovulation
- Clinical or biochemical signs of hyperandrogenism
- Polycystic Ovaries on Ultrasound
- Subjects willing to be a part of the study.

EXCLUSION CRITERIA:

- Subjects beyond the required age group.
- Individuals with congenital adrenal hyperplasia, androgen secreting tumors, Cushing syndrome, thyroid dysfunction and hyperprolactinemia as mentioned in the Rotterdam criteria of PCOS diagnosis.

Research Design



EVALUATION TOOLS

a) SCREENING QUESTIONNAIRE

A pre-developed screening questionnaire was used to screen and identify women with PCOS. The questions were based on Awareness, Diagnosis, symptoms of PCOS and presence of any psychological conditions such as stress, depression, body image issues etc.

b) KAP questionnaire- KAP questionnaire was constructed and validated with the aim of assessing knowledge, attitudes and practice of the subjects.

Knowledge, attitude and practice play main roles in the Knowledge-Attitude-Practice (KAP) model, which proposes that accumulated knowledge in a health aspect initiates changes in attitude, and results in gradual behavior change.[4]

Development - The aim was to develop and examine the validity and reliability of the KAP questionnaire towards the syndrome among PCOS women aged 15-25 years. Various literatures were reviewed using journal databases, existing reports, books, opinion from the experts and inputs from the diagnosed PCOS cases. The retrieved information was included in knowledge, attitude and practice domains.

Validation-Validity has been described as the agreement between a test score or measure and the quality it is believed to measure. [5]

Face validity- The retrieved information was included in knowledge, attitude and practice domains. Following this, a guided self-administered questionnaire was developed which comprised 25

knowledge items, 19 attitude items and 27 practice items. Items were generated with emphasis on features of PCOS.

Content validity- Content validity refers to the extent to which the items on a measure assess the same content .[6] Content Validity is based on the extent to which a measurement reflects the specific intended domain of content.[7]It refers to the conceptualization of the statements for developing the scale for the study. The developed KAP questionnaire was reviewed by a panel of 12 experts including registered dietician, academicians, gynecologist, psychologist and confirmed PCOS cases. The experts reviewed each item of the questionnaire based on content relevance, clarity, simplicity and ambiguity and rated each question on the following scale of 5[8]

- Not necessary
- Less than average
- Average
- Significant
- Most significant

The comments from content and face validation were considered and items were either edited, removed or remain unchanged with the help of factor analysis.

Factor analysis - It assesses the degree to which the individual items on a scale truly cluster around one or more concepts. Items designed to measure the same concept should load on the same factor. .

Reliability- reliability is the extent to which the instrument yields the same results on repeated measures. It is concerned with consistency, accuracy, precision, stability and homogeneity.

Assessment of knowledge, attitude and practice

In diagnosed and confirmed cases knowledge, attitudes and practices were assessed based on their awareness about the disease, symptoms, consequences, personal experience and concern towards the disease and their adopted lifestyle modifications.

This was followed by Statistical interpretation of the data.

Ethical considerations

The protocol was approved by the institutional human ethical committee-Nutri-Explore ethics committee (NEEC BU 012).An approved consent was also obtained from the study participants.

RESULTS

Screening questionnaire

General information of the subjects

It was observed that the 67% of the subjects were in the age group of 15 – 18 years, 30% and 3% of the subjects were between 19 – 22 and 27-30 years of age respectively.

99% of the subjects were single whereas 1% of the population was married.

Table 1. Menstruation related symptoms

Average age of menarche in the study population was found to be 12.7 years.

	Number	Percentage
Occurrence of regular menstruation		
Yes	384	74
No	56	11
Sometimes	81	15
Total	521	100
Frequency of occurrence of menstrual cycle	Number	Percentage
Less than 25 days	58	11
Every 25 th day	200	38
More than 30 days	110	21
Variable days	153	30
Total	521	100
Time of noticing irregular menstrual cycle	Number	Percentage
No irregularity	189	36
A year after attaining puberty	178	34
Two years later	40	8
After more than two years	114	22
Total	521	100
Observation during menstruation	Number	Percentage

Heavy bleeding	82	16
Moderate bleeding	373	72
Spotting	11	2
Blood clots	55	10
Total	521	100

It can be observed from the above table that 26% of these subjects showed irregularity in the menstruation. For 11% of the subjects, the duration of menstrual cycle was found to be less than 25 days, 34% of the subjects noticed irregularity in menstruation a year after attaining puberty and 16% of the subjects had heavy bleeding during menstruation.

Table 2 Diagnosis and Clinical signs of PCOS among the subjects.

Subjects diagnosed with PCOS	Number	Percentage
	Yes	11
	No	89
Specific test done by the subjects for the diagnosis of PCOS	Total	100
	Yes	12
	No	88
Excess of hair growth on face	Total	100
	Yes	11
	No	89
Presence of coarse hair growth at 3 or more sites	Total	100
	Yes	17
	No	83
	Total	100

The above table shows that among the study population 11% of the subjects were diagnosed with PCOS. Though from the same study it was found 26% of the study population was at risk of PCOS.

It was also observed that 12% of the subjects got specific test done for the diagnosis of PCOS and 11% of the subjects were found to have excess hair growth on the face whereas 17% of the subjects had coarse hair growth at 3 or more site.

Table 3. Correlation between PCOS and menstruation Irregularity

Undergone tests to confirm PCOS	Notice of irregular Menstrual cycle				Significance of Chi square test
	No irregularity	A year after attaining puberty	Two years later	After more than two years	
Yes(56)	1	24	10	21	18.2345**
No(465)	188	154	30	93	

** Significant at 1% level

The above table suggests that confirmation of PCOS had significantly higher association with irregularity of menstrual cycle with the chi square value being 18.2345.

Table 4 Correlation between PCOS and clinical sign

Undergone tests to confirm PCOS	Excess growth of hair on face		Significance of Chi square test
	Yes	No	
Yes	21	35	21.1607**
No	37	428	
** Significant at 1% level			
Undergone tests to confirm PCOS	Coarse hair growth at 3 or more sites		Significance of Chi square test
	Yes	No	
Yes	20	36	16.3090**
No	67	398	
** Significant at 1% level			

It can be concluded from table 4 that there was a significant association seen between confirmation of PCOS and coarse hair growth at 3 or more sites and the chi square value was found to be 16.3090.

KAP Questionnaire

Content validity

For the content validation, the KAP questionnaire was given to the

expert panel. Several suggestions and feedbacks were received related to the framing of questions and every item in the questionnaire was rated as adequately relevant, clear, simple and non- ambiguous. With this, the tool was made adequate for the present study.

Construct validity

Based on the comments provided by the expert panel, factor analysis was done to assess construct validity which helped to check the importance of each questions. It was found that knowledge section of the instrument had 25 questions initially. Among 25 questions, factor analysis showed 7 components with cumulative percentage variance of 94% which were later plotted on scree plot to derive eigen values. These component matrix were then rotated with the Varimax with Kaiser Normalization method in which question no. 9 and 24 were discarded and rest 23 were selected for the further study.

Attitude section had 19 questions initially among which factor analysis showed 6 components with cumulative percentage variance of 89% which were later plotted on scree plot to derive eigen values. These component matrix were then rotated with the Varimax with Kaiser Normalization method in which question no. 12, 14, 15 and 17 were discarded and rest 15 were selected.

Practice section had 25 questions initially among which factor analysis showed 7 components with cumulative percentage variance of 94.6% which were later plotted on scree plot to derive eigen values. These component matrix were then rotated with the Varimax with Kaiser Normalization method in which question no. 11, 21 and 24 were discarded and rest 23 were selected for the further study.

Reliability

Reliability analysis was done to assess the reliability of the instrument. For this, split of reliability was worked out to find the correlation

Table 5. Reliability analysis

	Reliability	Cronbach's Alpha I	Cronbach's Alpha II
Knowledge	0.83 (83%)	.712	.301
Attitude	0.63 (63%)	.481	.272
Practice	0.48 (48%)	.630	.810

The Knowledge tool had an association (Correlation) of 83%. Higher the value of reliability coefficient, higher will be the correlation i.e. the instrument was found to be more reliable for further use.

The Cronbach's Alpha for part I and part II gives the strength when the items are divided in two parts. (Split half) The significance of reliability coefficient is not tested.

Assessment of knowledge, attitudes and practices

The analysis of validated KAP questionnaire showed that knowledge scores among the subjects (n=40) was found to be 80.5 ± 15.02 , attitude scores was 43.95 ± 6.61 and practice score was found to be 60.10 ± 6.86

Table 6. Correlation between Knowledge, Attitude and Practice among subjects

	Knowledge	Attitude	Practice
Knowledge	1.0000		
Attitude	0.7356**	1.0000	
Practice	0.5249**	0.5693**	1.0000

** Significant at 1% level

The above table shows that there was a significant correlation between Knowledge and Attitude (0.7356). A significant correlation also exists between Knowledge and Practice (0.5249) and Attitude and Practice (0.5693) among the subjects.

DISCUSSION

The conducted study showed that PCOS has a great association with menstrual irregularity and facial hair growth.

In one of the study conducted it was observed that the prevalence of Polycystic Ovaries increased significantly with the irregularity of the menstrual cycle pattern. [9]

Similar findings were reported where it was observed that the excess amount of androgens production in PCOS women prevents ovulation, may cause infertility, acne and abnormal hair growth, such as excess facial hair or male pattern baldness.[10]

In another study conducted in New Delhi to study the clinical manifestations in PCOS women it was found that the prevalence of menstrual irregularities, clinical hyperandrogenism, endometrial hyperplasia (EH), and type 2 diabetes mellitus was significantly higher in the PCOS women.[11]

There is an escalation in the prevalence of PCOS due to the nutritional transitions of developing countries towards obesogenic lifestyle. The rising incidence coupled with the etiological complexity of PCOS calls for the effective management of this condition to improve the quality of life.

The Developed KAP Questionnaire helped in acquiring the information regarding Knowledge, Attitude and Practices of the selected subjects pertaining to Nutrition and PCOS .It was clearly evident that the subjects had low attitude and their practices were not commensurate with the knowledge they had about PCOS and Nutrition. Contrasting results were observed in one of the study conducted by Patel et al ,2018 in young central Indian Population, where among 400 participants, only 41% of the women were aware of the term PCOS and very few young women understood the earliest symptoms that should alarm them to consult a physician.

Another study observed that most of the subjects in the study had poor knowledge regarding polycystic ovarian syndrome. After the educational sessions there was enhancement of knowledge score on polycystic ovarian syndrome. [12]

Similar findings were obtained in one more study where nutrition education improved KAP scores significantly and Ninety-seven per cent of the participants rated the overall intervention and its delivery as 'very good to excellent', reporting that they would recommend this educational intervention to colleagues.[13]

CONCLUSION

The study is helpful in addressing the gaps in knowledge, attitudes and practices and encourage females to consult health professionals for effective management of PCOS .The study also paves the way for the development of nutrition education material and initiation of awareness generation programs for PCOS.

Many studies have shown that Educational program conducted regarding PCOS, Diet and Lifestyle intervention have improved the knowledge, attitudes and practices among women with PCOS. The developed questionnaire can be used to identify the gaps among the target population and would further help in designing the various awareness and educational programs for PCOS population.

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'The author(s) declare that they have no competing interests'

Conflict of interest-NIL

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BMJ Open Diagnosis and management of polycystic ovary syndrome in the UK (2004–2014): a retrospective cohort study

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ABSTRACT

Objective: To estimate the incidence and prevalence of polycystic ovary syndrome (PCOS) in UK primary care and investigate prescribing patterns before and after a PCOS diagnosis.

Design: Retrospective cohort study.

Setting: UK primary care (2004–2014).

Participants: Women aged 15–45 years.

Primary and secondary outcome measures: The incidence and prevalence of diagnosed PCOS and probable PCOS (ie, those without a confirmed diagnosis but with at least 2 PCOS features recorded within 3 years). Among women with diagnosed or probable PCOS, the prevalence of prescribing of drugs typically used to treat PCOS was calculated prior to and in the 24 months after the diagnosis of PCOS.

Results: We identified 7233 women with PCOS diagnoses and 7057 women with records suggestive of probable PCOS, corresponding to incidence rates of 0.93 and 0.91 per 1000 person-years at risk (PYAR) and an overall rate of 1.84 per 1000 PYAR. Women aged 20–24 years and women living in deprived areas had the highest incidence of PCOS. The prevalence of PCOS in 2014 was ~2%. The proportion of women with a prescription in the 24 months after their PCOS index date varied by drug type: 10.2% metformin, 15.2% combined oral contraceptives, 18.8% acne-related treatments, 1.93% clomiphene, 1.0% spironolactone, 0.28% cyproterone and 3.11% eflornithine. Acne-related treatments were more commonly used to treat probable (28.3%) than diagnosed (12.3%) cases, while metformin was prescribed much more commonly in diagnosed cases.

Conclusions: In conclusion, compared to rates estimated in community samples, the incidence and prevalence of women presenting in primary care with PCOS diagnoses and features are low, indicating that PCOS is an under-recognised condition. Although considerable variation is observed in treatments prescribed to women with PCOS, the treatments initiated following a confirmed diagnosis generally reflect the long-term prognostic concerns raised in PCOS consensuses.

BACKGROUND

Polycystic ovary syndrome (PCOS) is associated with a wide range of reproductive,

Strengths and limitations of this study

- The current study is the first to investigate the incidence and prevalence of polycystic ovary syndrome (PCOS) in the primary care setting in the UK and the longitudinal nature of the database allowed us to examine trends over a long time period, which has not been captured by previous epidemiological studies.
- Underdiagnosis was the main concern for the current study as only data considered relevant at the time of a consultation are recorded by clinicians although we attempted to include women with two or more features of PCOS as potential cases.
- Our study investigated the prescribing patterns of PCOS in the UK primary care, which has not been well explored in previous studies. These findings reflected the current management of PCOS in the clinical practices and provide important indications for general practitioners.

cardiometabolic and dermatological abnormalities. One of the most prominent symptoms in patients with PCOS is oligomenorrhea. Consequently, women with PCOS are highly likely to be infertile and potentially develop endometrial hyperplasia due to continuing secretion of oestrogen without ovulation.^{1 2} Furthermore, emerging evidence has suggested that ~50–70% of patients with PCOS have insulin resistance regardless of their body weight or body mass index.³ Consequently, women with PCOS are at an elevated risk of developing various common metabolic disorders compared with the general population.⁴ In addition, many patients with PCOS are observed to have an elevated androgen level, which leads to hirsutism, alopecia and acne.¹

While the epidemiology of PCOS in the community has been well studied,^{5–8} the proportion of women who present in routine clinical practice with PCOS features and the extent to which these women are subsequently diagnosed are less clear. Similarly,



while a range of treatments have been suggested for the management of PCOS,⁹ there is very little information regarding which of these drugs are actually prescribed in routine clinical practice. Such 'real-world evidence' can help identify priority areas for research, training and health promotion efforts. The current study sought to provide such evidence by investigating the recording of PCOS features and diagnoses in UK general practice between 2004 and 2014 and the subsequent prescribing of pharmacological treatments.

METHODS

Data source

The Health Improvement Network (THIN) is one of the largest primary care data sources in the UK, including data from over 500 general practices, covering ~6.2% of the total population in the UK. Available data include patient demographics, medical history, test results, drug prescriptions and social deprivation as measured by quintiles of the Townsend score.¹⁰ Symptoms and diagnoses are recorded using a hierarchical clinical coding system (Read codes),¹¹ with additional information recorded as unstructured text. The information stored as unstructured text was not available in this study. Notably, as the data are collected in routine clinical practice, only information deemed clinically relevant is entered in a patient's record.

In our study, data were included from each practice that met minimum quality criteria, for example, acceptable computer usage (a time point when a practice is considered to use their computer system adequately, ie, at least one medical record, one additional health data record such as body mass index, laboratory test results and two therapy records are computerised annually for a practice) and acceptable mortality reporting (a time point which the observed death rates for a practice reach the standard predicted numbers of deaths derived from National statistics given the practice's demographics).^{12–14}

Study population

Women aged 15–45 years, who were permanently registered for at least 1 year, were included in the study population. Women with conditions that can cause similar symptoms to PCOS were identified and excluded. These conditions include prolactinoma, Cushing's syndrome, Nelson's syndrome, adrenal-related disorders (ie, adrenal tumours, adrenal hyperplasia) and pituitary disorders.

Case definition

PCOS cases were identified using two methods. First, Read codes for 'polycystic ovary syndrome' (C165.00), 'Stein-Leventhal syndrome' (C164.12) and 'endoscopic drilling of ovary' (7E25300) were used to identify those women who had been clinically diagnosed as PCOS cases (diagnosed cases). Women with two or more Read

codes indicative of PCOS features (menstrual/ovarian dysfunction, clinical and biochemical hyperandrogenism, polycystic ovaries) recorded in a 3-year period were then selected and we considered these as probable cases. These women were considered as those who were likely to meet at least one of the three major definitions of PCOS^{15–18} but who may not have been clinically diagnosed as having the condition. The index date for probable cases was considered to be the date the second PCOS feature was recorded. A full list of the codes used to define cases is provided in online supplementary table SI.

Covariates and prescription indicators

We extracted data on each woman's year of birth, ethnicity and deprivation level of the area in which the woman lived;¹⁰ data on prescriptions of interest (ie, combined oral contraceptives (COCs), progestin oral contraceptives (POCs), intrauterine devices, clomiphene, metformin, spironolactone, gonadotrophins, cyproterone, flutamide, eflofene, weight control/loss drugs, lipid regulators and acne-related drugs) were also included and information on prescribing of these drugs before and in the 24 months after each PCOS case index data was extracted.

Statistical analysis

For incidence estimation, the rate was computed as the total number of new PCOS cases recorded between 2004 and 2014 divided by the total number of person-years of follow-up. Person-time for the denominator was estimated by summing each woman's follow-up from the latest among (1) their 15th birthday, (2) 1 year after registration, (3) the date at which their practice met minimum quality criteria and (4) the 1 January 2004, to the earliest of the date among (1) their first incident diagnosis, (2) their date of death, (3) the date they left the practice, (4) the date data were last collected from their practice and (5) the 31 December 2014. All incidence rates were reported per 1000 person-years at risk (PYAR).

Hierarchical (patients were considered to be nested in each practice) multivariate Poisson regression models were used to estimate incidence rate ratios and 95% CIs comparing the incidence of first PCOS diagnoses across 5-year age bands, Townsend score quintiles and calendar period (ie, 2004–2007, 2008–2011 and 2012–2014).

The period prevalence of the diagnosis of PCOS was evaluated for the calendar year 2014. The denominator for the prevalence calculation consisted of any women with at least 1 year of postregistration follow-up, of which at least 6 months must have occurred in 2014. The prevalence of PCOS was also estimated within 5-year age bands. Secondary analysis was carried out to assess the sensitivity of the prevalence estimate to the length of the postregistration period (ie, 1 year, 2 years) and the minimum period registered within 2014 (ie, 3, 6 and 9 months).

Among the women with a diagnosis of PCOS, we calculated the number and proportion with a prescription for one of the drugs of interest at any point prior to their PCOS index date. Among the women without prescription for each drug of interest prior to the index date, we then calculated the proportion of women with a prescription for that drug within 2 years after the PCOS index date. We used cumulative incidence plots to describe how the proportion initiating different drugs increased over the 2 years following the PCOS index date for the time period 2004–2012.

All analyses were performed using STATA V.13.0 and were carried out for all PCOS cases and stratified by case definition (diagnosed PCOS vs probable PCOS).

RESULTS

In total, 7233 diagnosed and 7057 probable PCOS cases were identified among 2 087 107 female individuals aged 15–45 years old between 2004 and 2014. Table 1 describes the number of PCOS features identified in each group. The incidence rate of diagnosed PCOS cases was 0.93 per 1000 PYAR (95% CI 0.91 to 0.96), whereas the rate for probable cases was 0.91 per 1000 PYAR (95% CI 0.89 to 0.93). This equated to an overall combined incidence rate of 1.84 PYAR (95% CI 1.81 to 1.87).

The overall incidence of PCOS increased from 1.67 (95% CI 1.58 to 1.77) per 1000 PYAR in 2004 to 2.00 (95% CI 1.89 to 2.10) per 1000 PYAR in 2010, after which the rate remained relatively constant at ~2 per 1000 PYAR (figure 1). The incidence was the highest for those in the 20–24 year age group (3.59 per 1000 PYAR, 95% CI 3.47 to 3.70), whereas the 40–44 year age group had the lowest incidence (0.62 per 1000 PYAR, 95% CI 0.58 to 0.66). The age-specific trend of PCOS diagnoses was similar for diagnosed and probable cases. After adjusting for the effects of year and social deprivation, significant differences still remained in the incidence of PCOS (table 2). In terms of social deprivation, the incidence of PCOS for individuals who were least deprived was 1.59 (95% CI 1.53 to 1.65) per 1000 PYAR, whereas among the most deprived, a rate of 2.23 (95% CI 2.15 to 2.32) per 1000 PYAR was estimated. This difference in

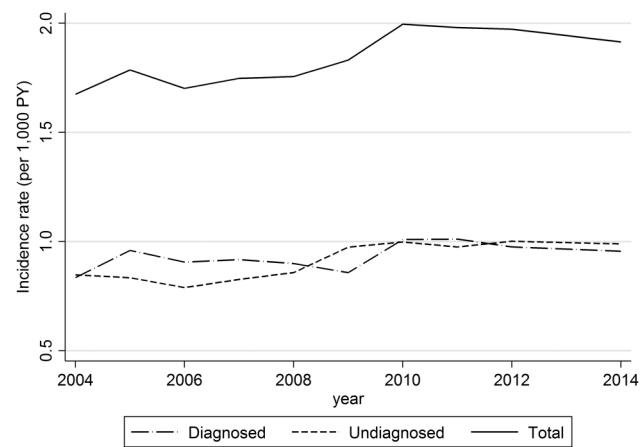


Figure 1 Time trends in PCOS diagnosis recorded (for diagnosed, probable and total cases). PCOS, polycystic ovary syndrome.

rates remained statistically significant after adjusting for effects of other covariates (ie, age and year) and after stratifying by case definition (table 2).

The overall prevalence of PCOS in 2014 was ~2.27% (95% CI 2.23% to 2.31%), with a prevalence of 1.34% and 0.93% in diagnosed and probable cases, respectively. The age-specific prevalence peaked in the 30–34 year age group, and decreased for older age groups. Prevalence estimates were not sensitive to varying the postregistration period and the time period registered within 2014, remaining consistently ~2%.

The proportion of women using one of the PCOS-related drugs before or after their index date varied widely across drugs groups (see table 3). At the time of their PCOS index date, over 40% of women had previously been prescribed COC, ~30% had been prescribed acne-related drugs before diagnosis, >18% had been prescribed POCs and ~18% had previously been prescribed at least one of the other drugs (table 3). Acne-related drugs, COC and metformin were the most commonly used drugs in the 24 months after a PCOS record (table 3). Plots describing the cumulative incidence of women with a prescription for each drug type over the 24 months following their index date are provided in online supplementary figure SI. The plots show that while all drugs show an initial surge in prescribing on or just after the PCOS index date, this is greater for some drugs (eg, metformin, acne-related drugs) than for others (COCs and POCs).

Prescription results stratified according to whether PCOS cases were diagnosed or probable are provided in online supplementary table SII. These results indicate that acne-related treatments and POCs were more commonly used to treat probable than diagnosed cases, while COCs, metformin, clomiphene, cyproterone, eflornithine and weight loss drugs were prescribed more commonly in diagnosed than probable cases. Cumulative incidence plots stratified according to whether a case was diagnosed or probable illustrate the

Table 1 Number and proportion of diagnosed and probable cases with major PCOS features

Features	Diagnosed cases (n=7233)	Probable cases (n=7057)
Menstrual dysfunction	2055 (28.4)	6265 (88.8)
Hyperandrogenism	2836 (39.2)	6221 (88.2)
PCO	199 (2.8)	1636 (23.2)
Two or more features	597 (8.3)	7057 (100)

Values are represented as n (%).

PCOS, polycystic ovary syndrome.

Table 2 Recorded rate of PCOS diagnoses by social and demographical characteristics

	Diagnosed PCOS			Probable PCOS			Overall		
	Rate per 1000 PYAR (95% CI)	Adjusted* IRR (95% CI)	p Value	Rate per 1000 PYAR (95% CI)	Adjusted* IRR (95% CI)	p Value	Rate per 1000 PYAR (95% CI)	Adjusted* IRR (95% CI)	p Value
Townsend quintile			<0.001			<0.001			<0.001
1	0.80 (0.76 to 0.84)	1		0.80 (0.76 to 0.84)	1		1.59 (1.53 to 1.65)	1	
2	0.90 (0.85 to 0.95)	1.14 (1.06 to 1.23)		0.79 (0.75 to 0.84)	0.99 (0.92 to 1.07)		1.69 (1.62 to 1.75)	1.08 (1.02 to 1.14)	
3	0.94 (0.90 to 0.99)	1.12 (1.04 to 1.21)		0.91 (0.86 to 0.96)	1.07 (0.99 to 1.15)		1.85 (1.78 to 1.92)	1.10 (1.05 to 1.16)	
4	1.02 (0.97 to 1.07)	1.15 (1.06 to 1.24)		0.97 (0.92 to 1.02)	1.06 (0.98 to 1.15)		1.98 (1.91 to 2.05)	1.11 (1.05 to 1.17)	
5	1.07 (1.01 to 1.13)	1.15 (1.05 to 1.25)		1.17 (1.11 to 1.23)	1.21 (1.11 to 1.32)		2.23 (2.15 to 2.32)	1.19 (1.11 to 1.26)	
Age (years)			<0.001			<0.001			<0.001
15–19	1.20 (1.14 to 1.27)	0.69 (0.64 to 0.74)		0.54 (0.50 to 0.59)	0.29 (0.27 to 0.32)		1.75 (1.67 to 1.83)	0.49 (0.46 to 0.51)	
20–24	1.72 (1.64 to 1.80)	1		1.87 (1.79 to 1.96)	1		3.59 (3.47 to 3.70)	1	
25–29	1.51 (1.44 to 1.58)	0.86 (0.80 to 0.91)		1.49 (1.42 to 1.56)	0.78 (0.73 to 0.83)		2.98 (2.88 to 3.08)	0.81 (0.78 to 0.85)	
30–34	1.03 (0.98 to 1.09)	0.58 (0.54 to 0.62)		0.86 (0.81 to 0.91)	0.46 (0.42 to 0.49)		1.88 (1.81 to 1.96)	0.51 (0.49 to 0.54)	
35–39	0.45 (0.42 to 0.49)	0.26 (0.24 to 0.28)		0.55 (0.51 to 0.59)	0.30 (0.27 to 0.32)		0.99 (0.94 to 1.05)	0.27 (0.26 to 0.29)	
40–44	0.17 (0.15 to 0.19)	0.10 (0.08 to 0.11)		0.45 (0.42 to 0.48)	0.24 (0.22 to 0.26)		0.62 (0.58 to 0.66)	0.17 (0.16 to 0.18)	
Year			<0.001			<0.001			<0.001
2004–2007	0.91 (0.87 to 0.94)	1		0.82 (0.79 to 0.86)	1		1.73 (1.68 to 1.78)	1	
2008–2011	0.94 (0.91 to 0.98)	1.00 (0.95 to 1.06)		0.95 (0.92 to 0.99)	1.13 (1.07 to 1.19)		1.89 (1.84 to 1.94)	1.06 (1.02 to 1.10)	
2012–2014	0.96 (0.92 to 1.01)	0.98 (0.92 to 1.04)		0.98 (0.93 to 1.02)	1.13 (1.07 to 1.20)		1.92 (1.86 to 1.98)	1.04 (1.00 to 1.09)	

*IRR from multilevel Poisson distribution accounted for practice-level variability and adjusted for other variables considered.

IRR, incidence rate ratio; PCOS, polycystic ovary syndrome; PYAR, person-years at risk.

Table 3 Number and percentage of PCOS women prescribed relevant drugs for PCOS prior to and following the diagnosis of PCOS

Types of drugs	Before diagnosis of PCOS, number (%)	After diagnosis of PCOS, number (%)		
		2004–2007	2008–2011	2012–2014
Combined oral contraceptives	12 349 (40.22)	901 (17.01)	912 (18.87)	459 (17.88)
POC	5806 (18.91)	474 (6.45)	691 (10.22)	272 (7.80)
IUDs	728 (2.37)	43 (0.50)	64 (0.75)	25 (0.52)
Clomiphene	518 (1.69)	210 (2.46)	165 (1.92)	70 (1.43)
Metformin	1278 (4.16)	1212 (14.77)	1102 (13.25)	495 (10.52)
Gonadotrophins	435 (1.42)	29 (0.34)	13 (0.15)	13 (0.26)
Spironolactone	235 (0.77)	109 (1.26)	111 (1.28)	43 (0.87)
Cyproterone	91 (0.30)	28 (0.32)	19 (0.22)	3 (0.06)
Flutamide	6 (0.02)	4 (0.05)	1 (0.01)	0
Eflornithine	550 (1.79)	354 (4.10)	407 (4.81)	172 (3.58)
Weight control/loss drugs	1330 (4.33)	403 (4.84)	364 (4.43)	91 (1.95)
Lipid regulators	194 (0.63)	69 (0.79)	46 (0.53)	8 (0.16)
Acne-related drugs	9000 (29.31)	1182 (19.52)	1234 (20.78)	582 (18.32)

Values are represented as n (%).

COC, combined oral contraceptive; IUD, intrauterine device; PCOS, polycystic ovary syndrome; POC, progestin oral contraceptive.

differences listed in online supplementary table SII and further to this show that these differences are typically established on or immediately after the index date (figure 2).

DISCUSSION

Summary

We present data on >14 000 potential PCOS cases among women aged 15–45 years in primary care across the UK between 2004 and 2014. 51.2% of these women had a PCOS diagnosis recorded, while 49.9% did not, corresponding to incidence rates of 0.93 per 1000 PYAR (95% CI 0.91 to 0.96) and 0.91 per 1000 PYAR (95% CI 0.89 to 0.93), respectively. The prevalence of PCOS in 2014 was ~2.27%. There was a considerable variation in the type of drug prescribed on the day of, or in the 24 months after, a PCOS diagnosis and prescribing differed between diagnosed and probable cases.

Strengths and limitations

To the best of our knowledge, this study is the first to investigate the diagnosis and management of PCOS in the primary care setting in the UK. As THIN contains over 10 million patient records, our study is robust in terms of sample size. The longitudinal nature of the database also allowed us to examine trends over a 10-year study period, which has not been captured by previous epidemiological studies where individuals were often sampled at a single time point.

As our data were collected in routine clinical practice, our results reflect the true burden of PCOS on the healthcare system. However, this also means that only data considered relevant at the time of a consultation are recorded by clinicians. Consequently, it is unsurprising that only 8% of diagnosed cases had two or more PCOS features recorded as, while the initial feature

prompting referral is likely to be noted by the general practitioner (GP), once a PCOS diagnosis has been made by a specialist a GP is unlikely to record anything other than the confirmed diagnosis in the coded record. The routine nature of data collection also meant that underdiagnosis was a concern in the current study and underestimation of PCOS rates was anticipated. We attempted to address under-reporting by allowing women with two or more features of PCOS (interfeature period within 3 years) to count as a PCOS case. However, the inclusion of probable cases may introduce case misclassification as some probable cases may not be true PCOS cases. For example, while we considered women with a raised testosterone level to have hyperandrogenism, there are concerns surrounding the accuracy of testosterone testing.¹⁹ On the contrary, it is also possible that many probable cases are true cases but do not have a diagnosis recorded in their medical records for some reason.

Incomplete patient history is a concern as women with prevalent PCOS diagnoses at the time of registration with a practice may not be identified, resulting in the underestimation of prevalence rates and the overestimation of incidence rates. Additionally, the lack of information on ethnicity is also an issue as the trends in incidence observed over age, deprivation and calendar year categories may be influenced by unobserved differences in ethnicity distributions across these covariates.

As we lack information on the indication for prescriptions, we cannot be certain that prescriptions issued after, or even on, the date of a PCOS record were prescribed for the treatment of PCOS. For example, ~30% of the PCOS cases prescribed metformin had a prior diagnosis of type 2 diabetes, the approved indication for this drug. However, by excluding those ever prescribed metformin prior to their PCOS diagnosis from our calculations, we can be relatively confident that prescriptions for

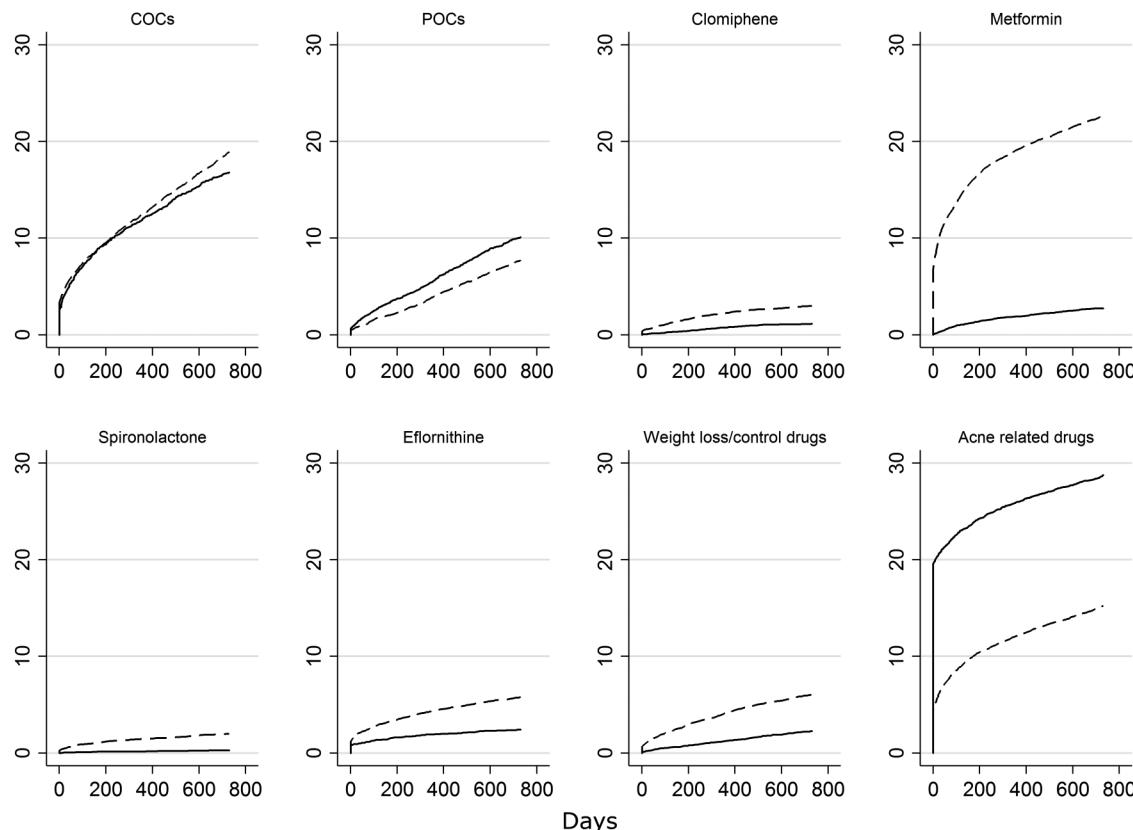


Figure 2 Plots describing the cumulative incidence of women with a prescription for each drug type over the 24 months following their index date stratified according to whether the case was diagnosed (dashed line) or probable (solid line). Results shown for the eight most commonly prescribed drugs. COC, combined oral contraceptive; POC, progestin oral contraceptive.

metformin issued on the date of a PCOS diagnosis are likely to be at least partly for the treatment of PCOS. Our confidence that the drug was prescribed for PCOS then decreases with increasing time after the PCOS diagnosis such that we expect the proportion of diagnosed cases prescribed metformin for PCOS to lie somewhere between the 8% with a prescription on the date of diagnosis and the 20% with a prescription on or in the 24 months after the date of diagnosis.

While we lacked information on prescribing outside primary care, the responsibility for prescribing treatments which have been initiated by specialists is likely to be transferred to an individual's GP a number of months after diagnosis. The use of a 24-month window to assess prescribing therefore allowed us to capture initiation of drugs prescribed in secondary care. This is reflected in the cumulative incidence curves shown in online supplementary figure S1 where the drugs that are commonly initiated outside primary care (eg, spironolactone and clomiphene) are initiated further after the index date than the drugs typically initiated in primary care (eg, COCs and acne drugs). However, prescribing rates may be underestimated if care is not transferred to the GP within 24 months (eg, for budgetary reasons).

The proportion of women with PCOS who had been prescribed COCs before their PCOS diagnosis is similar to that reported by other studies.^{20 21} The proportion of

women with PCOS who initiated metformin after their diagnosis in our study (over 10%) is comparable to that of a Danish study where 11.8% of the women with PCOS were identified as having received metformin.²¹ These comparisons support the validity of our prescribing data.

Interpretation

The prevalence of recorded PCOS in UK primary care in 2014 is comparable to that obtained from studies using databases in the USA (0.56–2.22%).^{22–24} However, the rates are significantly lower than those from epidemiological surveys in the Europe where systematic screening was often provided to identify cases from selected populations.^{25–28} This gap highlights the importance for improving public and GPs' awareness of PCOS.

The incidence of PCOS increased slightly over the study period; however, no significant changes in yearly rates were observed. This might reflect the increasing awareness of the syndrome after the establishment of the Rotterdam and Androgen Excess Society criteria during the study period. However, it could also be due to the improvement of the database, that is, the completeness of medical recordings has improved over time.

It should be noted that the Townsend score represents the deprivation level of the area in which a woman lives. Women who lived in more deprived areas had a higher

incidence of PCOS than those living in the less deprived areas. A possible explanation is that obesity (a factor strongly associated with PCOS) is more prevalent among women living in more deprived areas. Alternatively, these women may consult their GP more frequently than those in less deprived areas, for other morbidities (ie, type 2 diabetes), and therefore have more opportunity for PCOS to be diagnosed and recorded.

The fact that the incidence of probable PCOS cases was as high as the incidence of diagnosed cases indicates that there is a large group of women who present in primary care exhibiting two features of PCOS within a 3-year period but who do not have a subsequent PCOS diagnosis. While for some of these probable cases a PCOS diagnosis may not be relevant, it is likely that a considerable proportion of the women may meet the diagnostic criteria for PCOS and should therefore be referred for further assessment. Failure to refer such women may mean that they are not offered the lifestyle advice or medications that could reduce their risk of long-term PCOS-related complications.

Variation was observed in the treatments prescribed to diagnosed and probable PCOS cases; in particular, a greater proportion of diagnosed women received metformin prescriptions, while a greater proportion of the probable cases received treatment for the PCOS feature they presented with. This suggests that the diagnosed and probable cases are indeed receiving different care for their condition, with some probable cases not receiving potentially effective treatments such as metformin. The wide variation in prescribing patterns may also be due to the varied nature of clinical presentations of PCOS not only by individuals and also by age. For example, young women consulting their GPs are more likely to ask for drugs to regulate their menses or to treat acne, whereas more elderly women may initiate antidiabetic drugs to prevent rapid conversion to diabetes.

Metformin and oral contraceptives were the two drugs most commonly initiated in women with diagnosed PCOS, possibly reflecting the major concerns of long-term metabolic risks of this syndrome stated by the three PCOS consensuses. However, it is notable that even among the diagnosed PCOS cases, there is some variation in treatments prescribed following a diagnosis. This suggests that there may be a lack of consensus on the ideal treatment for the condition. This is supported by a recent survey of European endocrinologists which found variation in the treatments most commonly prescribed for PCOS.²⁹ Further research into the comparative efficacy and effectiveness of the various PCOS treatment options may therefore be warranted.

Conclusions

In conclusion, compared to rates estimated in community samples, the incidence of women presenting in primary care with PCOS diagnoses and features is low compared with most epidemiological surveys. Among

the women who present, only 50% were observed to have a PCOS diagnosis recorded. Further work is therefore needed to inform women and healthcare professionals about the condition to avoid any worsening of the disease or rapid conversion into other metabolic disorders considering the relatively low cost of diagnosis and high cost of care for the associated diseases suggested by Azziz *et al.*³⁰ There is much potential for these treatments to prove cost-effective alternatives, which should be carefully considered by public healthcare providers, such as the National Health Service in the UK.

Although there is much variation in the treatments prescribed following a PCOS diagnosis, the widespread prescribing of oral contraceptives and metformin generally reflects the prognostic concerns raised in PCOS consensuses, aiming to reduce the future metabolic risks of patients with PCOS or patients who are undergoing treatment for PCOS and may already have developed metabolic disorders. Further work is needed to identify the most effective treatment for the condition.

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Diagnosis and management of polycystic ovary syndrome in the UK (2004–2014): a retrospective cohort study

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Diagnosis and management of polycystic ovarian syndrome

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Polycystic ovarian syndrome (PCOS) causes irregular menstrual cycles and symptoms of hyperandrogenism and affects 10% of females (Figure 1).¹ Symptoms most often begin between the ages of 18 and 39 years, but diagnosis and treatment of PCOS are often delayed or patients remain undiagnosed.^{1,2} People with PCOS are more likely to be overweight or obese (53%–74%) than those without the condition, and higher body mass index (BMI) is associated with more severe symptoms of PCOS.^{3–5} Patients with PCOS also have higher rates of adverse reproductive, cardiovascular, psychological, metabolic and neoplastic outcomes than the general female population.^{3,6} Early diagnosis of PCOS allows for identification and treatment of associated conditions such as hypertension, diabetes, obstructive sleep apnea, depression and anxiety. We review evidence on the pathophysiology, diagnosis and management of PCOS from guidelines and other relevant articles (Box 1).

What is the pathophysiology of PCOS?

The pathophysiology of PCOS is complex and poorly understood. Hyperandrogenism and hyperinsulinemia underpin the clinical symptoms, diagnosis and treatment targets of PCOS. Clinical phenotypes vary widely. Whether the presence of immature ovarian follicles, characteristic of PCOS, precedes hyperandrogenism, hyperinsulinemia and their associated clinical symptoms or vice versa remains unclear (Figure 2).⁸

Two theories for why hyperandrogenism occurs in PCOS have been proposed.⁸ The first theory, called the altered gonadotropin secretion theory, postulates that increased gonadotropin-releasing hormone (GnRH) pulse frequency leads to excessive levels of luteinizing hormone (LH) and slightly elevated levels of follicle-stimulating hormone (FSH).^{9–11} Elevated LH stimulates androgen production from theca cells, while elevated FSH stimulates follicular development and excess estrogen production.^{10,11} The second theory, called the functional ovarian or adrenal hyperandrogenism theory, postulates that hyperandrogenism originates from dysregulated steroidogenesis at the level of the ovary or adrenal gland.⁸

Elevated androgens support follicular recruitment while also inducing follicular atresia.^{8,10,12} This ultimately leads to the classic appearance of multifollicular ovaries (or polycystic ovaries) on transvaginal ultrasonography.

Key points

- Polycystic ovarian syndrome (PCOS) is a chronic disorder associated with infertility; miscarriage; adverse pregnancy outcomes; and cardiovascular, metabolic, psychological and neoplastic risks.
- Diagnosis of PCOS can be made based on the presence of any 2 of menstrual irregularities, clinical or biochemical hyperandrogenism or polycystic ovarian morphology on transvaginal ultrasonography.
- Treatment of PCOS may target anovulation, androgen excess, hyperinsulinemia and weight management.
- Patients with PCOS should have regular monitoring of their body mass index, blood pressure and metabolic parameters, and should be regularly screened for depression, anxiety and obstructive sleep apnea.

Hyperinsulinemia is thought to have multiple effects including elevating LH, decreasing sex hormone-binding globulin (SHBG), increasing conversion of androstenedione to testosterone and reducing LH desensitization at the level of the ovary.^{9,10} Hyperinsulinemia leads to an increase in visceral adipose tissue deposition and hypertrophy. Hyperandrogenism may also lead to increased visceral adiposity. Obesity worsens symptoms of PCOS but the prevalence of PCOS rises only slightly with increasing BMI, suggesting it is not the main cause of PCOS.^{5,10,13}

What symptoms do patients with PCOS describe?

Patients with PCOS often have menstrual cycle irregularities with or without features of hyperandrogenism, which include hirsutism, acne and female-pattern alopecia (overall thinning with maintenance of hairline).¹ Before a diagnosis of PCOS can be made, other causes for these phenomena must be excluded. These alternative causes include hyperprolactinemia, thyroid dysfunction, non-classic congenital adrenal hyperplasia, Cushing syndrome, ovarian tumours or adrenal tumours. A detailed history is the first step to differentiating among potential causes of a patient's symptoms.

Symptoms suggestive of PCOS

Patients with PCOS typically present with irregularities in the frequency of their menstrual cycle, suggestive of anovulation.

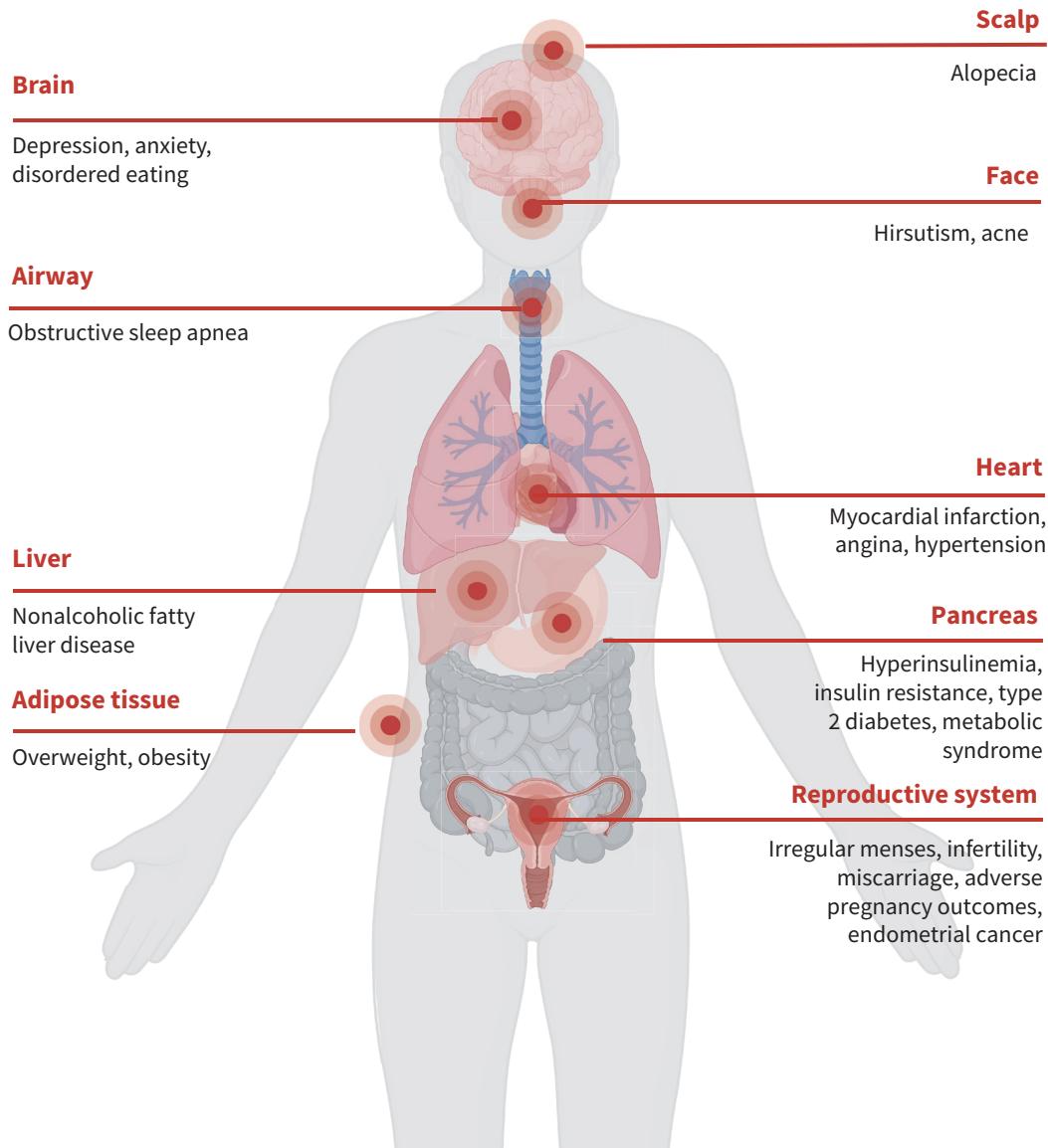


Figure 1: Health impacts associated with polycystic ovarian syndrome. Created with BioRender.com.

Box 1: Evidence used in this review

We drew on the international guideline on the management of polycystic ovarian syndrome (PCOS) published by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine in 2023 and the hirsutism guideline published by the Endocrine Society in 2018.^{1,3,7} We also searched articles in PubMed from 2018–2023 using the terms “PCOS,” and “polycystic ovarian syndrome.” We considered all articles and further searched reference lists of relevant articles to find other articles of interest.

Menstrual cycle patterns among patients with PCOS can fluctuate through a patient’s lifetime, ranging from amenorrhea to regular

ovulatory cycles. Clinicians should determine whether the patient has a family history of PCOS, dyslipidemia, hypertension or diabetes, as PCOS has a heritable component.³

The androgenic symptoms of PCOS — such as acne, hirsutism and female-pattern alopecia — develop gradually. Hirsutism, which is the symptom most predictive of biochemical hyperandrogenism, can be assessed objectively using the Ferriman-Gallwey score, although the clinical utility of this scoring system is limited as patients will often engage in hair removal before assessment.¹ Thus, subjectively distressing hair growth can be adequate to consider treatment.¹

Clinical features suggestive of other diagnoses

Other causes of both hyperandrogenism and menstrual cycle irregularities that can mimic PCOS include non-classic congenital adrenal hyperplasia and Cushing syndrome. Although non-classic congenital adrenal hyperplasia is clinically indistinguishable

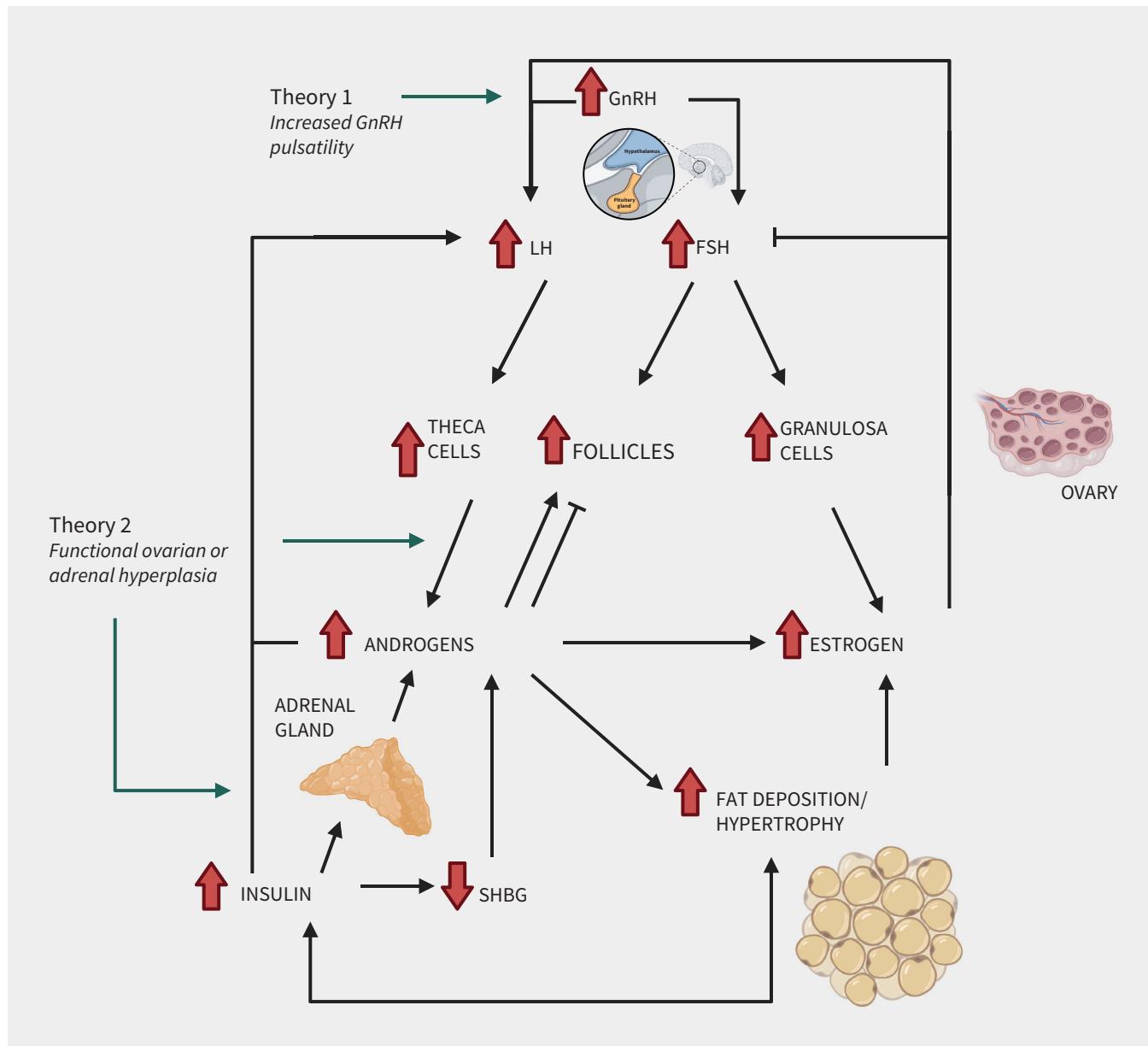


Figure 2: Two theories of the pathophysiology of polycystic ovarian syndrome (PCOS). The 2 main defining pathophysiological mechanisms of PCOS are hyperandrogenism and hyperinsulinemia; this relationship has been described and one perpetuates the other, but the exact mechanisms are not fully elucidated. The 2 main theories that are postulated include increased gonadotropin-releasing hormone (GnRH) pulse frequency (theory 1) and functional ovarian or adrenal hyperandrogenism (theory 2). Gonadotropin-releasing hormone stimulates release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. At the ovary, LH acts on theca cells to produce androgens; FSH acts on granulosa to produce estrogens. Estrogen has negative feedback mechanisms to FSH production. Both androgens and estrogen stimulate LH production. Ovarian release of androgens may also be functional. Hyperandrogenism, as well as FSH and LH stimulation, stimulates both follicular development and atresia leading to the classic multifollicular appearance of the ovaries on ultrasonography. Androgens may also be overproduced by the adrenal glands, which may be further driven by insulin. Both hyperinsulinemia and hyperandrogenism are postulated to be worsened by and drive adipose tissue deposition. Created with BioRender.com.

from PCOS, many patients with Cushing syndrome will have other features such as violaceous striae, weight gain with central fat deposition and dorsal fat pad, easy bruising and proximal muscle weakness.

Intermenstrual bleeding and heavy regular menstrual bleeding are not usually associated with PCOS; infectious or structural causes of heavy bleeding such as fibroids, polyps or adenomyosis should be considered. Associated symptoms, such as hot

flashes presenting in the context of new menstrual cycle irregularities, are more suggestive of premature ovarian insufficiency.

Patients with thyroid dysfunction and hyperprolactinemia may have additional symptoms; skin or hair changes or hot or cold sensitivity often accompany thyroid dysfunction, and galactorrhea, headaches, visual changes are features of hyperprolactinemia. A thorough review of medications that may cause hyperprolactinemia or hyperandrogenism should also be undertaken. Severe, sudden onset of

Box 2: Rotterdam criteria¹

Polycystic ovarian syndrome is diagnosed when 2 out of 3 of the following criteria are met and other diagnoses are excluded:

- Irregular cycles (if > 3 yr post-menarche, > 35 d apart or < 21 d apart; < 8 menstrual cycles per year; or > 90 d for any 1 menstrual cycle)
- Clinical hyperandrogenism (acne, hirsutism, alopecia) or biochemical hyperandrogenism
- Polycystic ovarian morphology on transvaginal ultrasonography or high antimüllerian hormone*

*Only applicable if patient is at least 8 years from menarche.

Box 3: Suggested initial investigations for patients presenting with menstrual irregularities or clinical hyperandrogenism

Tests should be completed in early follicular phase (day 2–4) in non-amenorrheic patients

- Prolactin
- Thyroid-stimulating hormone
- Luteinizing hormone, follicle-stimulating hormone and estradiol
- β-human chorionic gonadotropin (β-hCG)
- 17-hydroxyprogesterone (17-OHP)
- Total testosterone, calculated free testosterone or free androgen index with or without androstenedione, dehydroepiandrosterone sulfate
- Transvaginal ultrasonography or antimüllerian hormone*

*Optional if clinical criteria are not met; antimüllerian hormone used as an alternative to transvaginal ultrasonography, but should not be used in adolescents.

virilizing symptoms (e.g., clitoromegaly, voice deepening, male-pattern balding) are more suggestive of an androgen-secreting tumour originating from the adrenal glands or ovaries.⁷

How is PCOS diagnosed?

The Rotterdam criteria are the most widely accepted criteria for diagnosis of PCOS (Box 2).¹ As PCOS is considered a diagnosis of exclusion, diagnostic testing is required for patients presenting with symptoms, although the results of this testing may be normal. Suggested investigations are included in Box 3. An interpretation of test findings can be found in Table 1. If a patient has a concomitant disorder, such as hypothyroidism, the concomitant disorder should be treated and the patient should be reassessed to determine whether the patient has PCOS.

Biochemical hyperandrogenism is found in 60% of patients with PCOS and can be assessed using total testosterone, calculated free testosterone, dehydroepiandrosterone sulfate (DHEA-S) and androstenedione.¹ If feasible, testing for these androgens should be done in a step-wise fashion, with total testosterone and calculated free testosterone or the free androgen index evaluated first. If these initial investigations are normal, then DHEA-S and androstenedione levels should be tested.¹ Androgen

levels are only marginally elevated in PCOS; marked elevations should prompt further investigation for androgen-secreting tumours.¹ Androgen levels cannot be measured reliably while a patient is on combined hormonal contraceptives (CHCs) because of the elevation in SHBG and altered gonadotropin-dependent androgen production, resulting in falsely lowered values.¹ If a patient meets 2 of 3 Rotterdam criteria, this satisfies criteria for PCOS diagnosis without need for laboratory confirmation of elevated androgens. If laboratory confirmation is necessary, CHCs must be stopped for 3 months before measuring androgens.¹⁶

Polycystic ovarian morphology on transvaginal ultrasonography (≥ 20 follicles or an ovarian volume ≥ 10 mL in at least 1 ovary) may be an additional criterion if clinical or laboratory criteria are not met.^{1,12,17} Transabdominal ultrasonography can be used as an alternative with different thresholds (≥ 10 follicles or an ovarian volume ≥ 10 mL in at least 1 ovary).¹ The requisition should indicate the clinical concern for PCOS so that an antral follicle count is performed. Normal follicle numbers per ovary can overlap based on age and polycystic ovarian morphology; the normal mean follicle number is 8 among reproductive-aged females, with a mean volume of 6.1 mL.^{1,18} Polycystic ovarian morphology may be present in as many as 25% of healthy females and is considered a variant of normal.¹⁹ Patients should be counselled that cysts are immature follicles, which is a normal finding in all ovaries; the number of follicles is what indicates polycystic ovarian morphology. An incidental finding of polycystic ovarian morphology should prompt the clinician to inquire about irregular menstruation, acne, hirsutism and alopecia, and targeted laboratory evaluation for biochemical hyperandrogenism can also be considered.

The serum anti-müllerian hormone level is also a marker of follicle number. A recent meta-analysis suggests an appropriate threshold for PCOS diagnosis may be an anti-müllerian level of 34.2 pmol/L.¹⁵ Values and thresholds are highly dependent on age and laboratory measurement.¹ Although the anti-müllerian hormone level can be used as an alternative to transvaginal ultrasonography, it is not widely available in laboratories in Canada and is not covered by most provincial health plans.

How are the clinical manifestations of PCOS managed?

Patients with PCOS often request treatment for cycle irregularity, heavy bleeding, acne or hirsutism, and weight management (Table 2).

Weight loss

Among patients who are overweight or obese, weight loss of 5%–10% can help to reduce the severity of symptoms, including menstrual cycle irregularity, acne, hirsutism and alopecia.^{16,22} No specific diet or exercise recommendations for PCOS are available, and clinicians should be particularly sensitive to weight stigma as patients with PCOS are at risk of dysmorphic body image and disordered eating.¹

Combined hormonal contraceptives

Combined hormonal contraceptives are first-line medical treatment options for cycle regulation and hirsutism or acne. No evidence

Table 1: Initial investigations and differential diagnoses for polycystic ovarian syndrome

Test	Results				Next steps
	Expected results for patient with PCOS	Results for a patient with an alternative diagnosis	Alternative diagnoses		
Prolactin	Normal	Markedly elevated	Pituitary tumour	<ul style="list-style-type: none"> Repeat early morning, fasting prolactin Test macroprolactin Consider pituitary MRI Referral to endocrinology 	
TSH	Normal	Elevated	Hypothyroidism	<ul style="list-style-type: none"> Repeat TSH Test free T4 Consider levothyroxine supplementation Consider referral to endocrinology 	
		Depressed	Hyperthyroidism	<ul style="list-style-type: none"> Repeat TSH Measure T3/T4, refer to endocrinology 	
FSH, LH and estradiol	Normal–high LH and normal FSH in the context of low follicular phase estradiol	High FSH and LH in the context of low follicular phase estradiol	POI	<ul style="list-style-type: none"> Repeat test in 4 wk Refer to gynecology or endocrinology 	
		Low FSH, LH and estradiol	Hypogonadotropic hypogonadism		
β-hCG	Negative	Positive	Pregnancy		
17-OHP	Normal	Elevated	Non-classic adrenal hyperplasia	<ul style="list-style-type: none"> Refer to endocrinology 	
Calculated free testosterone, total testosterone and free androgen index	Normal–mildly elevated	Markedly elevated total testosterone (> 5.2 nmol/L) ¹⁴	Ovarian or adrenal tumour	<ul style="list-style-type: none"> Transvaginal ultrasonography Adrenal CT or MRI Refer to endocrinology or gynecologic oncology 	
Androstenedione	Normal–mildly elevated	Markedly elevated	Non-classic adrenal hyperplasia or possible adrenal tumour	<ul style="list-style-type: none"> Refer to endocrinology 	
Dehydroepiandrosterone sulfate	Normal–mildly elevated	Elevated (> 18.9 nmol/L) ¹⁴	Adrenal tumour	<ul style="list-style-type: none"> Adrenal CT or MRI Refer to endocrinology 	
Transvaginal ultrasonography	PCOM (\geq 10 mL ovarian volume or \geq 20 follicles in either ovary)	Ovarian tumour		<ul style="list-style-type: none"> Refer to gynecology 	
Anti-müllerian hormone	Typically greater than 34 pmol/L ¹⁵	Undetectable	POI (if age < 40 yr)	<ul style="list-style-type: none"> Refer to gynecology or endocrinology 	
		Low	Age-related decline in ovarian reserve		

Note: CT = computed tomography, FSH = follicle-stimulating hormone, LH = luteinizing hormone, MRI = magnetic resonance imaging, PCOM = polycystic ovarian morphology, PCOS = polycystic ovarian syndrome, POI = premature ovarian insufficiency, TSH = thyroid-stimulating hormone, 17-OHP = 17-hydroxyprogesterone, β-hcg = β-human chorionic gonadotropin.

demonstrates the superiority of 1 form of CHC over another in minimizing symptoms and, thus, guidelines cannot recommend which to choose.^{1,7} Several mechanisms are involved when treating hyperandrogenism with CHCs; the estrogenic component increases SHBG, which decreases the amount of free testosterone, and both the estrogen and progestin provide nega-

tive feedback mechanisms to pituitary LH production and thus decrease production of LH-induced ovarian androgen.²³

Many patients specifically desire cycle regularity, although this is not medically necessary provided cycles are fewer than 90 days apart. Cycle irregularity may be associated with heavy bleeding. Combined hormonal contraceptives are first-line

Table 2 (part 1 of 2): Management options for polycystic ovarian syndrome according to symptoms^{1,20}

Symptom	Treatment	Dosing or recommendation	Clinical considerations
Menstrual irregularity, heavy bleeding	First-line		
	Lifestyle interventions	Diet and exercise aimed at weight reduction by 5%–10% or prevention of excess weight gain	<ul style="list-style-type: none"> Be aware of weight stigma and increased risk for disordered eating
	CHCs	Any form	
	Progestins		
	Oral medroxyprogesterone	5–10 mg for 5–10 d every 30–90 d	
	Oral norethindrone acetate	5 mg daily for 7 d every 30–90 d or 5 mg daily for 3 wk on, 1 wk off	
	Oral drospirenone	4 mg 24 d, 4 d placebo	
	Oral dienogest	2 mg daily	<ul style="list-style-type: none"> May cause breakthrough bleeding
	Levonorgestrel intrauterine device	52 mg released over 5 yr	<ul style="list-style-type: none"> Patients may continue to have irregular, although lighter, bleeding
	Etonogestrel subdermal implant	68 mg released over 3 yr	<ul style="list-style-type: none"> Patients may continue to have irregular, although lighter, bleeding
	Intramuscular medroxyprogesterone acetate	150 mg intramuscularly every 3 mo	
Acne, hirsutism or alopecia	Alternative options		
	Metformin	1500–2000 mg daily in divided doses	<ul style="list-style-type: none"> Start at 500 mg and increase by 500 mg every 1–2 wk Cannot be used for endometrial protection in the event of amenorrhea but may help induce regular ovulation
	Inositol	Dosing varies 4 g of myo-inositol with a 40:1 ratio between myo-inositol and D-chiro-inositol daily ²¹	<ul style="list-style-type: none"> Cannot be used for endometrial protection in the event of amenorrhea but may help induce regular ovulation
Acne, hirsutism or alopecia	First-line		
	CHCs	Any form	
	Topical hirsutism treatment	13.0% eflornithine	<ul style="list-style-type: none"> Can be used during or before external hair removal methods
	Minoxidil (for alopecia)	2% twice daily	
	Topical or oral acne treatments	According to general guidelines	
	External hair removal methods	Mechanical laser and light therapy	
	Alternative options		
	Spironolactone	50–100 mg twice daily	<ul style="list-style-type: none"> Must be used with effective contraception given teratogenicity (i.e., CHCs or progestin-based contraception if CHCs are contraindicated) Do not use in combination with CHC containing drospirenone Requires monitoring with electrolytes 3 mo after starting and then annually and with dose adjustments
	Finasteride	5 mg daily	<ul style="list-style-type: none"> Must be used with effective contraception given teratogenicity (i.e., CHCs or progestin-based contraception if CHCs contraindicated)

agents that provide predictable bleeding patterns. When estrogen is contraindicated or not tolerated, progestin-only methods include oral and injectable progestins, the levonorgestrel intrauterine device and the etonogestrel subdermal implant.

Oral progestins can be used cyclically (i.e., 3 wk on and 1 wk off) or in rescue fashion (i.e., short course taken after > 90 d amenorrhea) to induce regular withdrawal bleeding. Continuous use of progestins will likely result in amenorrhea. Patients should

Table 2 (part 2 of 2): Management options for polycystic ovarian syndrome according to symptoms^{1,20}

Symptom	Treatment	Dosing or recommendation	Clinical considerations
Overweight or obesity	First-line		
	Lifestyle interventions	Diet and exercise aimed at weight reduction by 5%–10% or prevention of excess weight gain	<ul style="list-style-type: none"> Be aware of weight stigma and increased risk for disordered eating
	Metformin	1500–2000 mg daily in divided doses	<ul style="list-style-type: none"> Start at 500 mg and increase by 500 mg every 1–2 wk
	Alternative options		
	Inositol	Dosing varies 4 g of MI with a 40:1 ratio between myo-inositol and D-chiro-inositol daily ²¹	
	Anti-obesity medications or surgery		<ul style="list-style-type: none"> According to general guidelines
Ovulation induction	First-line		
	Lifestyle interventions	Diet and exercise aimed at weight reduction by 5%–10% or prevention of excess weight gain	<ul style="list-style-type: none"> Be aware of weight stigma and increased risk for disordered eating
	Metformin	1500–2000 mg daily in divided doses	<ul style="list-style-type: none"> Start at 500 mg and increase by 500 mg every 1–2 wk
	Letrozole	2.5 mg–7.5 mg for 5 d	<ul style="list-style-type: none"> Although considered first-line by many guidelines, still considered as off-label use in Canada If cycling regularly, start on day 2–5 If irregular cycles, can start randomly after negative home pregnancy test or medroxyprogesterone-induced withdrawal bleed Consider measuring serum progesterone level 3 wk after starting letrozole to confirm ovulation
	Alternative options		
	Inositol	Dosing varies; 4 g of myo-inositol with a 40:1 ratio between myo-inositol and D-chiro-inositol daily ²¹	
	Referral to gynecologist or reproductive endocrinologist and infertility specialist		

Note: CHC = combined hormonal contraceptive.

be reassured that this is a normal outcome with this medication and should not be confused with oligomenorrhea in untreated PCOS. The levonorgestrel intrauterine device and the etonogestrel subdermal implant may provide patients with endometrial protection, as well as less menstrual pain and bleeding, but may not allow for predictability in menstrual bleeding. Many progestins have high androgenic activity and may worsen clinical hyperandrogenism.⁷

When amenorrhea exceeds 90 days, endometrial protection is critical. The risk of endometrial cancer is 2–6 times higher among people with PCOS than the general population and often presents before menopause.¹ Patients with prolonged amenorrhea should be offered CHCs or progestins to maintain a nonproliferative endometrial lining (Table 2). An endometrial biopsy should

be considered for all patients with amenorrhea exceeding 90 days, especially if this occurs frequently.²⁴

Nonhormonal medications

Some patients are not candidates for CHCs or prefer not to be on a hormonal medication. Metformin, an insulin sensitizer, can be used as a nonhormonal alternative for PCOS by promoting modest weight loss and reducing insulin levels, which may subsequently have an impact on cycle regularity and hyperandrogenism.¹ A meta-analysis of 22 randomized control trials (RCTs) of metformin for treatment of PCOS found a reduction in BMI (-0.53), testosterone (-13.36 ng/dL) and fasting glucose (-2.39 mg/dL).¹ Subgroup analyses demonstrated that metformin lowered BMI, fasting glucose and total and low-density lipoprotein cholesterol

among patients with BMI greater than 25, while the free androgen index and fasting insulin were lowered among patients with a BMI less than or equal to 25.¹ The efficacy of metformin in reducing clinical features of PCOS remains uncertain. However, given the improvements in metabolic markers, metformin should be considered in patients with PCOS and a BMI greater than 25.¹

Metformin has been compared with CHCs in 22 RCTs.¹ Between the 2 treatments, no statistically significant differences were shown for weight, BMI or hirsutism, with very low certainty of evidence. Compared with metformin, CHCs did significantly improve menstrual irregularities, with moderate certainty of evidence. Compared with CHCs, insulin and cholesterol levels were improved with metformin with low to very low certainty of evidence.¹ The addition of metformin to CHCs can be considered in patients with PCOS in high metabolic risk groups, which includes those with a BMI greater than 30, those with impaired glucose tolerance, ethnic groups with high metabolic risk factors and those with other diabetes risk factors.¹

Inositol is an over-the-counter supplement that can be considered in management of PCOS. It belongs to the vitamin B complex group and is involved in many signalling cascades, including downstream of FSH and insulin. It may have a role in improving insulin sensitivity.^{1,20} A recent meta-analysis showed that inositol, in particular myo-inositol, reduced BMI (mean difference 0.45 kg/m²) compared with placebo.²⁰ Cycle normalization was higher in the inositol group (relative risk [RR] 1.79). Myo-inositol has minimal adverse effects, although more studies are needed to further support this. Furthermore, as inositol is a supplement, there is no regulation of what is commercially available to consumers and thus it must be used with caution.^{1,20}

Anti-androgen agents

Anti-androgen agents can be considered for patients with clinical hyperandrogenism after 6 months of CHCs with no improvement or in those with contraindications for CHCs. Medical treatment of hirsutism can reduce new hair growth but cannot reverse hair growth that was previously established.⁷ Only external hair removal techniques such as mechanical laser and light therapy (i.e., laser removal) can be used for previous hair growth. Addition of topical eflornithine may improve outcomes of mechanical laser and light therapy.⁷

Metformin and inositol may also indirectly reduce androgen levels, although their specific effect on the clinical reduction of hirsutism and acne has not been shown.¹ Anti-androgen agents such as spironolactone, cyproterone acetate and finasteride must be used with effective contraception given their teratogenicity; evidence also supports the reduction of hirsutism with the addition of an anti-androgen to CHCs.¹

What are the fertility and pregnancy considerations for patients with PCOS?

If a patient intends to conceive, clinicians should communicate that irregular or prolonged (> 35 d) cycles may still be sporadically ovulatory.²⁵ Conversely, contraception is needed if pregnancy is not desired. Time to pregnancy is longer on average; a

large population-based study in Sweden observed that spontaneous conception took an average of 2 years longer among patients with PCOS.²⁶ Ovulatory function and, thus, cycle regularity tend to improve as patients age, although all patients are subject to age-related fertility decline regardless of PCOS.²⁷

In the population-based study from Sweden, the cumulative probability of childbirth after spontaneous conception was 55% among patients with PCOS, compared with 73.8% among women without PCOS.²⁶ With assisted reproduction, the cumulative probability of childbirth was the same among both patients with PCOS (80%) and those without (78%).²⁶ First-line options for management of return of ovulatory cycles that can be initiated by primary care physicians include weight loss of 5%–10% for patients with overweight or obesity, metformin, inositol or letrozole.¹ It is reasonable to trial these methods for 6–12 months in patients younger than 35 years. Metformin and inositol are safe in pregnancy; however, unless the patient has concurrent type 2 diabetes, no convincing evidence supports continuing these medications in pregnancy. Referral to a fertility specialist for ovulation induction with letrozole, gonadotropins or laparoscopic ovarian drilling (i.e., use of a monopolar needle to puncture the ovarian cortex) can be considered at any time.¹

Pregnant patients with PCOS are at increased risk of miscarriage, gestational weight gain, gestational diabetes, hypertension, preeclampsia, intrauterine growth restriction, preterm delivery and cesarean delivery; some of the risks may be mitigated by maintenance of a normal BMI.¹ Given the known contribution of PCOS to impaired glycemic status, screening for impaired fasting glucose or impaired glucose tolerance with a 75-g oral glucose tolerance test should be considered before conception.³ When not completed before conception, it should be performed at the first prenatal visit before 20 weeks' gestation and again at 24–28 weeks' gestation.¹ Although the quality of evidence is low, an oral glucose tolerance test is the preferred method for identification of insulin resistance among patients with PCOS.¹

What are the long-term health complications associated with PCOS?

Long-term complications such as hypertension, impaired glucose tolerance, type 2 diabetes, metabolic syndrome, non-alcoholic fatty liver disease, depression, anxiety, obstructive sleep apnea and cardiovascular disease (i.e., ischemic heart disease, myocardial infarction and cardiovascular mortality) have all been associated with PCOS.¹⁶ These conditions tend to present earlier among people with PCOS than age-matched controls.²⁷ People with PCOS and a BMI greater than 25 are at higher risk of long-term health complications than patients with PCOS and a BMI of 25 or less. Ongoing care for patients can often be fragmented as the emphasis in PCOS can be overly focused on reproduction rather than long-term sequelae.²⁸ Baseline and follow-up assessments, as outlined in Box 4, should be performed for all patients with PCOS.

Polycystic ovarian syndrome may be associated with hypertension. A recent meta-analysis showed that the risk of hypertension was increased only among patients of reproductive age (pooled RR 1.72, 95% confidence interval [CI] 1.43–2.07) but not

Box 4: Baseline and annual health assessment in all patients with PCOS

- Measurement of height, weight and body mass index
- Measurement of blood pressure
- Cardiovascular risk assessment including cigarette smoking, physical activity and family history of premature cardiovascular disease.
- Assessment of lipid profile (cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides)
- Assessment of glycemic status, ideally with oral glucose tolerance test
- Assessment for obstructive sleep apnea symptoms (i.e., snoring with waking unrefreshed, daytime sleepiness or fatigue)
- Screening for depression and anxiety
- Screening for amenorrhea exceeding 90 d

among menopausal patients who had PCOS during their reproductive years (pooled RR 1.26, 95% CI 0.95–1.67).²⁹ As such, patients with PCOS should have blood pressure measurements annually and at any time when fertility is desired since patients are at increased risk of hypertensive disorders in pregnancy.¹

Data on cardiovascular risk outcomes show inconsistent findings, although this is likely owing to the low event rate of major adverse cardiovascular events among premenopausal women.²⁸ Recently, several meta-analyses have suggested with very low to low certainty that females with PCOS have higher ORs or incidence rate ratios for composite cardiovascular disease, composite ischemic heart disease, myocardial infarction, stroke and cardiovascular mortality.¹ Thus, monitoring of cardiovascular risk profiles, including lipid profiles, should be undertaken both at baseline and on an ongoing basis for all patients with PCOS.¹

Polycystic ovarian syndrome is also related to hyperinsulinemia, impaired glucose intolerance and type 2 diabetes.^{9,16,22} A meta-analysis of 41 studies indicated an increased risk of type 2 diabetes among patients with PCOS compared with those without PCOS (OR 2.87, 95% CI 1.37–6.01).¹ Hyperinsulinemia is present in 75% of patients with PCOS and a BMI of 25 or less and 95% of patients with a BMI greater than 25.¹

Polycystic ovarian syndrome is associated with a higher risk of obstructive sleep apnea, independent of BMI. In a recent meta-analysis of 8 studies, those with PCOS had a 10 times higher chance of obstructive sleep apnea than those without PCOS, with an odds ratio (OR) of 9.52 (95% CI 3.90–23.26).³ Patients with PCOS should be assessed for symptoms of obstructive sleep apnea, screened using appropriate tools (e.g., Berlin Questionnaire) and directed for a sleep study and treatment if obstructive sleep apnea is identified.³

Patients with PCOS also have a high prevalence of depression and anxiety. In a meta-analysis of 47 studies, depression was more likely among patients with PCOS than those without PCOS (OR 2.59, 95% CI 2.11–3.16).¹ In a meta-analysis of 27 studies reporting on anxiety, patients with PCOS had a higher risk of anxiety than those without, with an OR of 2.68 (95% CI 2.08–3.44).¹ Polycystic ovarian syndrome can have a negative impact

on body image and self-esteem, and is also associated with a higher rate of disordered eating.¹

Conclusion

Polycystic ovarian syndrome, a common endocrinological disorder among reproductive-aged females, presents with menstrual irregularities, hyperandrogenism and polycystic ovarian morphology. It is associated with important long-term health consequences such as hypertension, neoplastic risks, metabolic consequences, adverse cardiovascular outcomes, psychological impacts and adverse reproductive outcomes. Early diagnosis can allow for improvement in symptoms and mitigation of long-term health complications.

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Abstract

Polycystic ovary syndrome (PCOS) is a complex multisystem condition associated with life-long reproductive, metabolic, and psychological symptoms. Individuals with PCOS are at an increased risk of cardiovascular disease and type 2 diabetes, with approximately 70% of all PCOS cases presenting with insulin resistance. Lifestyle interventions have historically been recommended as first-line therapies for the management of PCOS-related cardiometabolic disorders. The term “lifestyle management” incorporates a multifaceted approach to dietary, exercise, and behavioral strategies, aiming to promote a healthy lifestyle. This approach has been commonly employed in practice, in particular through exercise and dietary modulation, due to its effect on cardiometabolic outcomes as well as its tolerability. Furthermore, there is evidence to suggest that combining dietary change with exercise may yield the greatest improvements in clinical outcomes. However, such practices require careful consideration and coordination, as there are instances where certain exercise and/or dietary prescriptions may compromise the effectiveness of the respective interventions. Thus, this review aims to provide practical guidance on diet and exercise planning in the routine care of PCOS. Such recommendations include emphasizing realistic and achievable goals, as well as minimizing barriers to lifestyle changes in order to increase the long-term sustainability of this treatment strategy.

Keywords

- polycystic ovary syndrome
- exercise
- diet
- lifestyle medicine
- realistic medicine

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in females during reproductive years, affecting 2 to 20% of this population.^{1,2} This condition is associated with life-long metabolic (impaired glucose tolerance, insulin resistance, type 2 diabetes mellitus, cardiovascular disease risk), reproductive (infertility, hirsutism,

hyperandrogenism), and psychological symptoms (anxiety, depression, and worse health-related quality of life).³ The updated 2023 International Evidence-based Guideline for the assessment and management of PCOS recommends the use of the revised Rotterdam criteria for the diagnosis of PCOS in adults: the presence of two of (1) clinical/

biochemical hyperandrogenism, (2) ovulatory dysfunction, and (3) polycystic ovaries on ultrasound or elevated anti-mullerian hormone (AMH) levels.^{4,5} In adolescents, the diagnosis is made in the presence of hyperandrogenism and ovulatory dysfunction, with ultrasound and AMH levels not recommended.^{4,5} A key characteristic of PCOS is insulin resistance, which affects 60 to 95% of individuals with the condition.⁶ Beyond pathogenesis related to excess adiposity, it is thought that insulin resistance is exacerbated through interactions with hyperandrogenism.^{7,8} In fact, hyperandrogenic PCOS phenotypes have the highest prevalence of insulin resistance: 80% in PCOS phenotypes with hyperandrogenism and oligomenorrhea and 65% in phenotypes with hyperandrogenism and polycystic ovaries, compared to 38% in normoandrogenic PCOS phenotypes.⁹

Lifestyle interventions, including dietary modulation and exercise, have historically been considered first-line therapies for the management of cardiometabolic risk factors in PCOS.^{10,11} In this narrative review, we aim to provide practical guidance on nutrition and exercise planning in the routine care of PCOS, with an emphasis on realistic and achievable goals. While examining the evidence base underlying these management strategies, we present practical considerations for person-centered care, including identifying and minimizing barriers to lifestyle changes in order to increase the long-term sustainability of this treatment strategy.

Lifestyle Intervention: An Overview

Among the general population and those with metabolic disorders, exercise is critical for the prevention and treatment of chronic disease,¹² as well as for improving in quality of life.¹³ In individuals with PCOS, exercise improves cardiorespiratory fitness, lowers central obesity,¹⁴ increases insulin sensitivity,^{10,15,16} and ameliorates psychological distress.¹⁷ While intricately connected to the condition itself, insulin resistance, hyperinsulinemia, and central obesity have been shown to exacerbate the clinical manifestations of PCOS.^{3,18} As a result, the current international evidence-based guidelines for exercise intervention in the management of PCOS specifically

recommend a minimum of two sessions of muscle-strengthening activities and 150 to 300 minutes of moderate-intensity exercise per week or 75 to 150 minutes of vigorous exercise per week, aiming for 30 active minutes daily, for the prevention of weight gain and maintenance of overall well-being.^{4,5} When aiming for weight loss or central obesity reduction, the guidelines recommend a minimum of 250 minutes per week of moderate-intensity exercise or 150 minutes per week of vigorous exercise, in addition to muscle-strengthening activities.^{4,5} Additionally, limiting sedentary time is advised.^{4,5} Given the lack of available evidence, the guidelines were unable to recommend one form of exercise training over another (►Table 1).^{4,5,19} Furthermore, it is important to consider that these recommendations act as benchmarks and clinicians should consider an individualized exercise prescription, rather than a “one-size-fits-most” approach.

Currently, there is no evidence that a specific dietary composition is superior to others in individuals with PCOS.^{4,5} The International Evidence-based Guideline for the assessment and management of PCOS recommends general healthy eating principles that tailor dietary recommendations to the individual in order to meet personal goals and PCOS presentation.^{4,5} Although not highlighted in the guidelines, the evidence does show an anti-inflammatory nutrition pattern such as the Mediterranean diet may be effective in reducing chronic low-grade inflammation and the health problems that this induces in PCOS.²⁰ For instance, diets that follow anti-inflammatory principles are mostly plants and limit processed foods. Nevertheless, dietary modifications should be personalized to the individual according to personal goals and PCOS presentation. In some instances, an energy deficit of 30% or 500 to 750 kcal/day may be beneficial in individuals who are wanting to achieve weight loss (body mass index [BMI] $\geq 25 \text{ kg/m}^2$). Clinicians should consider the appropriateness of the prescription as patients with a history or risk of disordered eating and an unhealthy relationship with self and body may require a focus on behaviour-change goals as an alternative to a weight loss focus.^{4,5,21,22} The input of a registered or accredited practicing dietitian, as part of the multidisciplinary team, may be helpful for the implementation of dietary changes.

Table 1 General exercise recommendations based on the 2023 International Guideline for all people with PCOS^{4,5}

Recommendation	Frequency and duration	Examples
Moderate intensity exercise	For the prevention of weight gain and maintenance of health: 150–300 min/wk	A brisk walk, cycling with light effort, playing tennis, mowing the lawn
	For modest weight loss and the prevention of weight re-gain: >250 min/wk	
Vigorous intensity exercise	For the prevention of weight gain and maintenance of health: 75–150 min/wk	Jogging, cycling fast, an exercise class at your local gym (e.g., circuits, spinning), playing soccer/basketball
	For modest weight loss and the prevention of weight re-gain: >150 min/wk	
Resistance training	Twice weekly	Bodyweight exercises (e.g., squats, lunges, push-ups, plank), free weights, pilates, plyometrics

Abbreviation: PCOS, polycystic ovary syndrome.

As a complex and multifaceted condition, the management of PCOS often relies on the multidisciplinary team.²³ While many healthcare professionals play an important role in the multidisciplinary management of PCOS, primary care providers are the first point of contact for an individual with PCOS,²⁴ and may take on a leadership role, particularly in contexts with limited resources, where balancing perspectives regarding allied health involvement could be considered.

Evidence-based practice involves considering the latest available evidence, the capacity and expertise of the clinician, and the individual desires and preferences to achieve optimal goals.²⁵ This approach will often involve using SMART goals (Specific, Measurable, Achievable, Relevant, and Time-Bound),²⁶ self-monitoring, problem-solving, and focusing on stimulus control, among other interventions.¹¹ However, it is important to note that while evidence-based practice involves using the guidelines and recommendations as a structured and evidence-based treatment framework, individual preferences should be taken into account to create a personalized and sustainable approach that leads to long-term behavior change.¹¹

Body Composition in PCOS

Individuals with PCOS are at higher risk of weight gain compared to the general population, as demonstrated in multiple longitudinal studies.^{27–29} Indeed, 40 to 60% of individuals with PCOS are classified as overweight or obese.³⁰ Despite adjusting for lifestyle and psychosocial factors, participants in a 19-year longitudinal study gained an excess of 4.62 kg compared to controls, suggesting an underlying cause of weight gain unrelated to these factors.²⁸ The driver of this disproportionate weight gain is unclear, but a greater daily energy intake and lower physical activity in individuals with PCOS may contribute.³¹ Whether the weight gain results from physiological or psychological consequences of the conditions remains unclear. However, there is some evidence to suggest that postprandial thermogenesis, a reduced resting metabolic rate, and increased subjective hunger levels may contribute to this finding.^{32–34}

Appetite regulation may be affected by PCOS, as previous reports have shown impaired levels of appetite hormones, including cholecystokinin and ghrelin, in people with this condition.^{35,36} Other intrinsic hormonal abnormalities, including insulin resistance and hyperandrogenism, may contribute to the increased levels of adiposity in this group, as evidenced by a large population-based cohort study that found that these features were not related to adverse lifestyle behaviors such as poor dietary quality or a lack of physical exercise.³¹

Lifestyle Intervention: Important with or without Medical Therapy

The term “lifestyle management” incorporates a multifaceted approach to dietary, exercise, and behavioral strategies, aiming to promote a healthy lifestyle. This approach is recommended for all individuals diagnosed with PCOS due to its positive effects on metabolic health, quality of life,

weight management, and body composition.^{4,5} Higher weight exacerbates clinical features of PCOS, while weight loss ameliorates symptoms.²⁹ A 5% reduction in body weight is considered clinically significant weight loss; however, there is a significant variation in weight between individuals with different anthropometric parameters.³⁷ For the average Australian woman who is 161.8 cm tall and weighs 71.1 kg,³⁸ a clinically significant weight loss would be 3.5 kg. It has been suggested that this modest initial loss provides the greatest effect on the restoration of ovulation and fertility in obese individuals with PCOS,³⁹ and allows achievable and realistic goals to be set. Furthermore, the initial amount of weight lost by individuals does not affect the maintenance of weight loss long-term; the mean percentage of weight loss maintenance 1 year post-intervention was found to be 54% regardless of the initial weight loss.⁴⁰ Therefore, an approach balancing dietary modulation and exercise, perhaps at the expense of a greater initial weight loss, is beneficial in the long term. The approach to weight management should be determined in partnership with the individual, discussing whether they are interested in weight loss and avoiding weight stigma in the clinical setting.

The available evidence suggests that in the pursuit of weight loss, the greatest results are from the synergistic effects of dietary changes combined with exercise intervention.^{10,12} A period of intense exercise is followed by a perceived decrease in appetite, and the energy expended by physical activity is not compensated by a change in dietary intake.⁴¹ While exercise alone can elicit weight loss, this is seldom achieved without high volumes of exercise which may be unattainable for the average person⁴²; however, when added to a low-calorie diet, it induces greater fat loss while preserving lean body mass.⁴³ Due to its weight loss-independent effects on metabolic health, physical capacity,^{12,44–46} and psychological outcomes,¹⁷ exercise is considered a cornerstone therapy for PCOS management. Among individuals with PCOS, exercise has been reported to improve cardiometabolic outcomes, including lipid profile,^{47,48} fasting glucose levels,⁴⁷ systolic blood pressure,⁴⁷ and insulin sensitivity.^{12,18,48} Body composition is also improved, with reduced waist circumference,^{12,14,47,48} body fat percentage,⁴⁸ and improved cardiorespiratory fitness,^{12,14,48} a clinical vital sign⁴⁹ associated with cardiometabolic health.⁵⁰ The greatest improvement in these anthropometric and metabolic outcomes is seen in individuals with PCOS who have a higher weight, compared to individuals with a BMI below 25 kg/m².^{18,48} Exercise may also be beneficial for reproductive outcomes, including hormone profiles,^{12,18,47} but the evidence on this is limited to a few small studies with heterogeneous methodologies and varying magnitudes of effect.

When considering dietary interventions, no one dietary composition is superior to another for the management of PCOS.¹¹ However, a range of dietary patterns underpinned by general healthy eating principles are beneficial for PCOS management, independent of weight change.^{51,52} The benefits are potentially due to the effects on the chronic low-grade inflammatory environment of PCOS, which is mediated by higher fat mass, insulin resistance, and high androgen concentration.⁵³ For example, the Mediterranean Diet (MedDiet) has

been found to be beneficial in PCOS populations,^{20,54,55} as it reduces inflammatory markers, testosterone, and Ferriman-Gallwey score and improves insulin resistance and hyperandrogenemia.⁵⁶ Furthermore, adequate intake of omega-3 fatty acids may reduce liver fat concentrations and oxidative stress, and optimize lipid profiles and overall metabolic measures,^{57–59} although not specifically recommended by the International Evidence-based Guideline for the assessment and management of PCOS.^{4,5} Similarly, the use of probiotics for 8 to 12 weeks has been shown to decrease weight, improve insulin markers and lipid profiles, reduce inflammatory markers, and favor hormone changes and hirsutism scores in individuals diagnosed with PCOS,^{60–62} but the evidence is limited to studies with small numbers of participants and therefore should be interpreted with caution.

Apart from their efficacy, lifestyle interventions are recommended for PCOS because of their tolerability. Increased physical activity has been demonstrated to not cause serious adverse effects or injuries over 1- to 2-year interventions.⁶³ Despite concerns that caloric restriction could lead to an increase in eating disorder symptoms, this hypothesis was not supported by a randomized controlled trial that demonstrated this intervention had benign or beneficial psychological and behavioral effects,⁶⁴ although screening for disordered eating or eating disorders using the SCOFF or EDE-Q 21 item is recommended early on in therapy to best guide appropriate care.¹¹ Furthermore, a consensus panel of experts agreed that the benefits of dieting for weight management outweigh potential negative side effects such as an increased risk of gallstone formation, loss of lean muscle mass, or electrolyte imbalance^{65,66}; however, further empirical evidence is needed to confirm such statements. Additional benefits of lifestyle changes for PCOS management that are not specific to this condition include a reduced risk of cardiovascular disease and type 2 diabetes mellitus.⁴⁸ Lifestyle interventions have been demonstrated to decrease all-cause mortality in a population with impaired glucose tolerance,⁶⁷ which is highly prevalent in individuals with PCOS.⁶⁸ Improvements in cardiorespiratory fitness, measured using VO₂ max as a proxy, have been shown to reduce cardiovascular risk,⁶⁹ and are achievable through exercise in a PCOS population.^{12,14,48}

Dietary Specifications in PCOS

An accredited practicing dietitian can contribute significantly to the management of all women with PCOS and should be offered if resources are available, independent of PCOS phenotype or presenting weight. Dietary management should focus on the immediate presenting needs and prevention of conditions associated with PCOS.^{4,5} In doing so, dietary interventions should incorporate person-centered care to minimize attrition and promote long-term motivation and behavior change.⁷⁰ However, the evidence regarding specific dietary interventions is limited to studies with a small number of participants and moderate-to-high risk of bias; therefore, these specific recommendations serve as a guide but should be adapted to individual preference (**Table 3**).

Overall, individuals with PCOS exhibit poorer intake of grains, fruits, vegetables, proteins, nuts, seeds, and dairy when compared to those without PCOS.⁷¹ Plant-based diets are rich in dietary fiber and abundant in phytochemicals that promote glycemic control, reduce hyperglycemia, and enhance acute insulin response and sensitivity.^{72,73} Plant-based eating patterns such as the MedDiet are primarily based on sufficient intake of wholefoods, particularly green leafy vegetables, fruits, whole grains, legumes, lentils, and seafood, with moderate amounts of poultry and dairy, and limited red meat consumption (**Table 3**).

The MedDiet emphasizes 60 mL/day of extra virgin olive oil, incorporates full fat or low-fat dairy, and limits alcohol to no more than 2 glasses per day of wine.⁵⁶ Interestingly, individuals with PCOS report lower consumption of extra virgin olive oil, legumes, fish, and nuts when compared to those without PCOS.⁵⁶ Greater emphasis on these food groups may elicit improvements in various cardiometabolic risk factors among individuals with PCOS. For people with minimal improvements in insulin sensitivity after following traditional MedDiet principles over 12 weeks, a low carbohydrate (<100 g/day) MedDiet may be beneficial to help reduce anthropometric measures, LH to FSH ratios, insulin resistance, and lipid profiles.⁷⁴ Clinicians may find it useful to use the PREDIMED 14-item questionnaire as a tool to monitor adherence to the MedDiet and highlight dietary recommendations.⁷⁵

Table 2 Recommended nutrition behaviors for the general population, applicable to PCOS

1. Eat small more frequent meals (3 main meals, 1–2 snacks per day)
2. Couple protein with carbohydrate sources in each meal and snack
3. Consume the majority of energy during the day and less at night time, particularly after 8 pm
4. Aim for a 12–16-h fasting window between finishing dinner and having breakfast
5. Incorporate vegetables in each main meal
6. Incorporate green leafy vegetables in main meals, when possible
7. Aim for at least 3 different vegetable colors in each meal
8. Enjoy all vegetables, with greater emphasis on those with lower glycemic index (e.g., artichokes, Brussels sprouts, asparagus, bean sprouts, celery, cucumber, eggplant, mushrooms, onions, leafy greens, spinach, tomato, turnips, zucchini, cauliflower, cabbage, broccoli, capsicums, and tomato).
9. Enjoy all fruit, with particular emphasis on lower glycemic index varieties (e.g., berries, strawberries, raspberries, blackberries, citrus fruits—tangerines, oranges, lemons, grapefruit, cherries, pears, plums, peaches).
10. Enjoy a variety of nuts and seeds—almonds, walnuts, pumpkin seeds, sunflower seeds, sesame seeds, poppy seeds
11. Recommended to limit alcohol and avoidance is best if taking metformin¹⁴²

Abbreviation: PCOS, polycystic ovary syndrome.

Table 3 General dietary recommendations based on the Mediterranean Diet

Recommendation	Serve	Additional information
EVOO	(60 mL or ≥ 4 T/d)	Add when cooking, to salad dressings and cooked vegetables
Nuts	3–5 serves/wk	Particularly include walnuts and almonds. 1 serve = 30 g
Fresh fruit	2–4 serves/d	
Vegetables	5 serves/d	Consume with every meal—particular focus on green leafy vegetables and tomatoes
Fish or seafood	2–3 serves/wk	Fatty fish best, e.g., salmon, sardines, mackerel, tuna
Legumes	≥ 3 serves/wk	E.g., soups, casseroles, vegetarian burgers, falafels, curries
Whole grains	6–8/d	
Dairy	2–4/d	Reduced fat
Tomato-based meals	≥ 3 serves/wk	Sauce made from tomatoes, onions, garlic, and herbs simmered in EVOO
White meat	2 serves/wk	e.g., chicken, turkey, pork, or rabbit without skin
Limit		
Red and processed meats	<1 serving/d	Lean and small portions
Carbonated beverages and sugary drinks	<1/d	
Commercial bakery products, sweets, pastries, biscuits, processed savory snacks	<2/wk	
Fat spreads and cream	<1 serving/d	

Abbreviation: EVOO, extra virgin olive oil.

Source: Adapted from Estruch et al.¹⁴³

An important consideration for dietary therapies is the overall intake and type of protein, with emphasis on both plant (e.g., tofu, tempeh, beans and legumes, and nuts) and animal-based (e.g., lean red meats, chickens, pork, turkey, fish, and dairy) sources, contributing 20 to 30% of total daily energy intake.⁷⁶ Individuals wishing to increase lean muscle mass may combine resistance training with higher protein intake at 2.2 g per kg of body weight per day.⁷⁷ Attention should also be placed on adequate omega-3 fatty acid intake, aiming for 2 g/day of supplemented or at least 400 mg/day of omega-3 through food for a minimum of 6 months, in order to meet daily requirements.⁷¹ Other nutrients of focus are calcium,⁷⁸ selenium,⁷⁹ chromium,⁸⁰ zinc,⁸¹ carotenoids, vitamin D,⁸² vitamin E,⁸³ and magnesium,⁸⁴ due to their positive effects on PCOS management. This is imperative in individuals with PCOS and metabolic syndrome who consume lower amounts of these nutrients when compared to leaner people with PCOS.⁸⁵ While all dietary recommendations should meet macronutrient reference values (protein 20–30%, carbohydrates 45–65%, fat 20%, saturated fat <20% total daily energy intake), an individualized person-centered approach will likely allow for greater long-term sustainability and health,⁸⁶ while correcting nutrient deficiencies, in particular those often deficient in individuals with PCOS.

Gastrointestinal dysbiosis is hypothesized to play a significant role in the pathogenesis of PCOS due to less microbial diversity, changed microbiota composition, and damaged mucosal barrier when compared to individuals

without PCOS.⁸⁷ Interestingly, changes in structure and composition of gut microflora occur irrespective of insulin resistance in people with PCOS,⁸⁸ contributing to the manifestations of hyperandrogenism, insulin resistance, chronic inflammation, and abnormal levels of brain-gut peptides.^{89–91} As dysbiosis is associated with irritable bowel syndrome (IBS),⁹² and IBS is reported to impact the quality of life in 21 to 27% of those diagnosed with PCOS,⁹³ focusing on interventions to treat dysbiosis through prebiotics, probiotics, and synbiotics is an important part of PCOS nutritional care. Probiotics are thought to stabilize the hormonal imbalance through the gut-brain axis, leading to a reduction in the LH/FSH ratio in PCOS populations.⁹⁴ Beneficial probiotics over 8 to 12 weeks include *Lactobacillus rhamnosus GGs*, *Bacillus coagulans*, *Bacillus indicus*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Bifidobacterium breve*, and *Streptococcus thermophilus*, commonly coupled with inulin as a probiotic.^{60–62,95} To partner with probiotics, nutrition recommendations include a high-fiber diet (incorporating 28–30 g of soluble and insoluble fiber per day), reduced saturated fat intake, meeting hydration needs, and limiting gastrointestinal irritants such as spicy, deep-fried foods, carbonated beverages, caffeine, and alcohol.⁹⁶ If these dietary recommendations lead to unsatisfactory results, following the three phases of the low fermentable oligosaccharides, disaccharides, and monosaccharides and polyols (FODMAP) diet can be beneficial in reducing IBS symptoms.⁹⁷

Weight Loss, a Byproduct but Not Goal of Lifestyle Intervention

As higher weight, which is highly prevalent in PCOS, exacerbates PCOS symptoms, it is natural to focus on weight loss as a therapeutic goal. However, the benefits of lifestyle changes in managing PCOS have been shown to be independent of weight loss.^{12,44–46} Given that sustained weight loss is seldom achieved, shifting the focus from weight loss, particularly when trying to commence healthy lifestyle behaviors, may be beneficial. Concentrating instead on the outcomes recognized to improve with exercise, such as cardiorespiratory fitness and physical capacity, may allow these individuals to appreciate the effects of lifestyle intervention notwithstanding the absence of weight loss.^{12,14} Beyond physical changes, individuals with PCOS who undertake healthy behaviors will likely see improvements in psychological and patient-reported outcomes such as quality of life.⁹⁸

"Diet failure" is often accompanied by weight cycling or "yo-yo dieting" in which periods of weight loss and regain occur.⁹⁹ Weight cycling leads to excess fat and decreased muscle mass. During the period of intentional weight loss, muscle mass is lost along with fat, and in the subsequent period of weight gain, the muscle mass is not recovered while fat mass increases.^{100,101} This pattern increases all-cause mortality by 41% and cardiovascular mortality risk by 36%, due to reduced resting metabolic rate¹⁰² and lean muscle mass, and changes in the use of brown adipose tissue.¹⁰³ Each weight cycle results in 20 to 25% of loss in brown fat and lean muscle mass,¹⁰⁴ contributing to insulin resistance,¹⁰⁵ increased abdominal fat,¹⁰⁶ elevated triglycerides,¹⁰⁷ chronic inflammation,¹⁰⁸ and overall sarcopenic obesity over multiple weight cycles.¹⁰⁹ Adaptive thermogenesis makes maintaining newly suppressed weight highly difficult, needing to employ rigid dietary habits so as to not exceed lower daily energy requirements (e.g., $\leq 1,500$ cal/day) compared to 2,000 cal/day in those without weight cycling behaviors.¹⁰⁹

Body recompensation, a concomitant increase in skeletal muscle mass and decrease in fat mass, is a strategy that can address this phenomenon in weight cycling and is a goal in clinical and nonclinical settings.^{110,111} Maintenance of skeletal muscle is an important consideration in PCOS patients, as it is associated with improvements in insulin resistance.¹¹² Muscle is one of the main targets of insulin, and the metabolic effects of insulin and insulin resistance partially depend on the quality and quantity of muscle mass.¹¹³ Resistance training and dietary strategies, such as whey protein supplementation, can preserve muscle mass during a weight loss program,^{114,115} but also increase the relative proportion of protein intake to fat and carbohydrates. Rather than aiming for overall weight loss, lifestyle intervention in individuals with PCOS may focus on body recompensation, which can occur without a change in BMI.¹¹⁴

Continuously restricting dietary intake and linking thinness as a value of self-worth leads to greater psychological distress,¹¹⁶ increases weight over time, reduces physical activity, and increases binge eating¹¹⁷ in those who weight

cycle. There is an overall increased risk of eating disorders when compared to people who remain weight stable.¹¹⁸ Individuals with PCOS are at increased risk of cardiovascular disease,¹¹⁹ disordered eating, eating disorders,^{120,121} low self-esteem, and overall psychological distress.¹²² Therefore, coupled with the weight stigma commonly experienced from patients when seeking help to manage PCOS,¹²³ weight management should be one of, but not the central treatment goal in cases where it has the capacity to worsen PCOS psychopathology. In such instances, focusing on other outcomes such as insulin sensitivity, cardiorespiratory fitness, and behavioral goals such as increased physical activity may lead to greater long-term effects.

Barriers to Lifestyle Intervention

Lifestyle changes are most effective if they are realistic and adapted to meet the health goals of the individual. Unfortunately, many people with PCOS experience barriers to sustained lifestyle change due to feeling discouraged by a lack of results, lack of time, feeling embarrassed, and financial costs,¹²⁴ resulting in an average attrition rate of 47.1%.¹²⁵ These findings coincide with other metabolic conditions affecting women such as gestational diabetes mellitus,¹²⁶ for which PCOS is a significant risk factor.¹²⁷ Therefore, part of realistic lifestyle intervention is identifying and minimizing the barriers to change. An important barrier to lifestyle intervention includes patients' perception that they are not achieving their health goals through diet and exercise changes, and this remains a common theme when considering dietary intervention.¹²⁴ A study found that more than 82% of participants had modified their diet for health reasons; however, a third of participants did not achieve their health goals or any positive effect from dietary changes.¹²⁸ A lack of adequate information may be a contributor. Individuals with PCOS report dissatisfaction with the information provided at the time of diagnosis, including details on lifestyle interventions.¹²⁹

Weight stigmatization is an often overlooked contributor to negative health outcomes and behaviors.¹³⁰ The phenomenon of weight stigma and the associated negative stereotyping of obese individuals has been documented by multiple studies.^{131,132} The resulting stress leads to depleted self-regulation and low self-esteem.¹³³ Weight stigma extends to healthcare settings, with a patient's weight affecting how they are viewed and treated by physicians.¹³⁴ The negative attitudes toward higher weight displayed by healthcare providers can act as a barrier to the management of medical conditions.^{135,136} Even the language utilized can be detrimental; using person-first language, an evidence-based terminology that puts the person in front of the condition can help address the stigma.¹³⁷ While it is well established that higher weight leads to adverse health outcomes⁶⁵ and exacerbates PCOS symptoms,²⁹ and therefore weight loss plays a role in the management of this condition, it can be counterproductive and stigmatizing to focus on weight reduction as the main pillar of PCOS management. Instead, adopting a balanced and individualized approach

that focuses on the specific goals of treatment relevant to the individual, uses person-first language, and shifts the focus of management from weight loss to behavioral change and body recomposition may be a more appropriate therapeutic strategy.¹³⁸

The management of PCOS should be practical through positive psychology, motivational interviewing, open-ended questions, active listening, tools for behavior change, and positive communication, with the responsibility of self-care and behavior change falling on the individual.¹³⁹ Providing a non-judgmental, shame-free space, and being aware of weight stigmatizing beliefs and attitudes which may unconsciously drive lifestyle suggestions is the duty of health practitioners. Individual preferences, including not wishing to discuss weight as part of therapy, should be respected.¹³⁹ Identifying weight stigmatizing beliefs in the individual and working through these is also important. The use of weight-neutral approaches such as basic nutritional therapy information, mindful eating, body image work, hunger-fullness work, building self-esteem, and understanding diet cycles have the same weight loss outcomes as prescribed dietary therapies over 12 months¹⁴⁰ while motivating sustainable healthy behaviors.

Conclusion

Lifestyle interventions in PCOS lead to improvements in anthropometric, metabolic, reproductive, and psychological outcomes,^{12,14,31} and should incorporate psychology, nutrition, and movement, using person-centered approaches to facilitate self-determined health goals and empower long-term change.¹⁴¹ A personalized approach, focusing on the individual's specific goals rather than a one-size-fits-most approach, is essential in the management of this condition. Another key element in the management of PCOS through lifestyle changes is shifting the focus from weight loss to behavioral change and body recomposition. Setting realistic goals and minimizing barriers to lifestyle intervention will increase the long-term sustainability of this management strategy.

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Conflict of Interest

The authors report no conflict of interest.

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Dietary intake, body composition and energy expenditure in women with polycystic ovary syndrome (PCOS) compared with healthy controls: an observational study

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PCOS affects $\leq 10\%$ of women of reproductive age in the UK. Obesity is a common feature of the syndrome, with approximately 33% of UK women with PCOS (wPCOS) being obese⁽¹⁾ compared with 20% of women in the general population⁽²⁾. The present study aims to compare the diet and energy expenditure of wPCOS with matched controls to further elucidate the complex relationship between weight and PCOS presentation.

A 7 d food diary and a medical questionnaire were completed by thirty-seven wPCOS and thirty-one age- and weight-matched controls. A pedometer was also provided to record physical activity levels on the same 7 d. Anthropometric data (BMI, waist:hip ratio (WHR) and percentage body fat (%BF), using bioelectrical impedance) were measured. Energy expenditure was estimated in a subset (sixteen wPCOS, seventeen controls); values derived from BMR, which was measured by indirect calorimetry, were used to calculate metabolic equivalent intensity levels for activities⁽³⁾ from the 7 d activity diary.

The mean age of the sample as a whole was 31 (sd 6) years, with 97% of the sample being white British women. Mean BMI (kg/m^2) were 24.4 (sd 4.1) and 24.2 (sd 4.5) for wPCOS and control women respectively (NS). Mean WHR and %BF for wPCOS were 0.77 (sd 0.07) and 30 (sd 7) respectively, compared with 0.7 (sd 0.06) and 29 (sd 7) respectively for controls (NS). A similar percentage of women reported their weight as being stable (wPCOS 62, controls 72) and a similar percentage reported their weight to be increasing (wPCOS 19, controls 13). Mean energy intake for wPCOS was 7980 (sd 1516) kJ (1906 (sd 362) kcal)/d, not significantly different from that reported by controls (7624 (sd 175) kJ (1821 (sd 418) kcal)/d). However, percentage energy (%E) from fat was significantly higher for wPCOS (40 (sd 6)) compared with controls (35 (sd 5); $P=0.001$). %E from carbohydrate for wPCOS was significantly lower (41 (sd 8)) compared with controls (46 (sd 5); $P=0.003$) with no differences in %E from protein. The mean number of steps per d was 9308 (sd 2672) for the whole sample, with no significant difference between wPCOS and controls (9240 (sd 2699) and 9392 (sd 2682) respectively). Mean energy expenditure for wPCOS (n 16) was 9772 (sd 2010) kJ (2334 (sd 480) kcal)/d, which was not significantly different from that reported by controls (n 17; 9010 (sd 1369) kJ (2152 (sd 327) kcal)/d).

Results indicate qualitative differences in the dietary intakes of wPCOS compared with age- and weight-matched controls. However, no significant differences in activity levels or body composition have been identified. Analysis of biochemical data, including lipid profiles and insulin resistance would help to further elucidate the relationship between behaviour, weight and risk factor profile in wPCOS. The present study is the first to report the habitual dietary intake of UK wPCOS compared with matched controls, and results are similar to US findings⁽⁴⁾. Identification of suboptimal dietary patterns in wPCOS in the UK will allow dietary information for this population to be more effectively tailored to help maximise the success of lifestyle interventions.

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PCOS Detection using Machine Learning Algorithms

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ABSTRACT

Polycystic Ovary Syndrome (PCOS), is a hormonal disorder that occurs among women in their reproductive age. It has effective conflicts throughout this gynecological disorder, as it affects one in ten women at a nearly age. There are certain symptoms such as irregular menstrual cycles, missed periods, heavy bleeding during the menstruation period, excess of androgen hormones, obesity, acne or oily skin, hair growth on the face, and a typical weight gain. The exact cause of PCOS is not yet properly defined, but it could involve genetic causes and a metabolic balance in the diet. Due to certain effectiveness like the risk of heart attack, and type two diabetes, it is necessary to get detected and diagnosed as early as possible and start the possible treatments which include a healthy diet and exercises, with medications like birth control pills that control the level of hormones. Certain Machine Learning algorithms are used to detect this disorder. The data set consists of 541 patients, and out of 44 features, 10 potential features were identified using the filter method. This paper includes a detection model of PCOS using various machine learning algorithms like Random Forest, Logistic Regression, Support Vector Classifier, and Decision Tree. Among all these algorithms, Random Forest has 83.48% accuracy for the model.

Keywords: Polycystic Ovary Syndrome, Machine Learning, Random Forest, Logistic Regression, Support Vector Classifier, Decision Tree.

INTRODUCTION

Technology is boosting its measure every single time which makes every transformation very flexible whether it is in the gadgets or the health care industry and services. Machine Learning plays a paramount role in all health-related domains as it is a constituent subset of artificial intelligence. There are distinct application areas of it such as image recognition, health monitoring, robotic perception, anomaly detection, and many more. It predominantly focuses on the development of algorithms that can be easily accessible from the data sets that are provided for detecting and predicting the required information. Thus, Machine Learning algorithms are utilized efficiently for the detection of PCOS. PCOS is a common hormonal disorder observed in women of childbearing age. Few symptoms indicate the





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hormonal balance, and it results in obesity associated with an enlarged polycystic ovary. In the productive age of 15-40, women experience their regular trend of their menstruation with hormonal effects, which shows that PCOS can affect individuals at any age. There are certain health risks due to this disorder including cardiovascular diseases which generally increase blood pressure and cholesterol levels, and uterine cancer occurs because the least ovulation leads to the build up of the uterine lining, mental health issues affect physiological conditions such as depression and anxiety, and type two diabetes happens due to insulin resistance and high blood sugar levels increase the risks of circumstances. The significant element in this heterogeneous condition is hormones. Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), and Anti-Mullerian Hormone (AMH) affect follicles and the development of the eggs, creating issues in ovulation, and FSH levels might be normal or lower than the usual values. Estrogens and Progesterone are essential for balancing the level of hormones to get the regular menstrual cycle. Among every suffering patient, 70% are undiagnosed. Hence, the prediction and detection of PCOS is necessary at the preliminary phase as it sustains the life of an individual by reducing lifelong health risks and creating a healthy life style.

The certain work focused in this paper is:

- I. Selection of the influential components affecting the patients of PCOS with the help of feature selection.
- II. Implementation of various machine learning algorithms on the selected features of the dataset. Comparing the accuracy of the different algorithms to fit the best model

LITERATURE REVIEW

PCOS detection has become a hot topic for researchers in the last decade. Few individuals have implemented the various methodologies in this field to achieve the desired outcome for the health benefit to all women.

This section consists of the distinct literature works done previously based on various implemented methods such as follicles detection, feature extraction, and classification, Cross Validation, Support Vector Machine (SVM), Logistic Regression, k nearest neighbors (kNN), and many more [4].

METHODOLOGY

Data Collection

Data collection is a crucial step. For this, various platforms are available example for Kaggle, UCI Repository etc. In this paper, we have used a dataset from Kaggle [1]. This dataset is composed of 44 different features with more than 500 records. Such features include pimples, hair growth, cycles, vitamin d3, etc.

Data Preprocessing

Data Preprocessing is a step that takes raw data and transforms it into a format that can be understood and analyzed. Unprocessed data must contain some Missing values, Outliers, Unstructured manner, and Categorical data. Missing values can be corrected in many ways but the most common methods are Delete Rows with Missing Values and replace the missing value with some arbitrary value using `fillna()`. Missing values can also be imputed using 'interpolation'. Here we have also dropped unnecessary features. Furthermore, the dataset should only contain a value that is float or integer so that algorithms can process the data. The next step is Exploratory data analysis. This process involves summarizing, visualizing, and getting deeply acquainted with the important traits of a dataset. It examines a correlation matrix of all the features, and how all the features correlate with the PCOS, having a look at features bearing significant correlation.[4].

Feature Selection

The feature selection method intends to select the most useful feature for a model to predict the output. Feature selection is performed to improve predictivity, reduce the dimensionality of feature space, and get rid of noisy data.





Some favored techniques for feature selection are Filter Methods, Wrapper Methods, and Embedded methods. In this paper, we have used the filter method to rank each feature based on some univariate metric and then select the highest-ranking features and we have also referred to previous research to select the highest-ranking features [5].

Fitting into models

After the Data preprocessing, it is now ready to be handled by the models. Selected sets of features are used to study the algorithm. Among countless ML algorithms available, we have applied Logistic Regression (LR), Decision Tree Classifier, Random Forest Classifier, Gradient Boosting Classifier, and Support Vector Machine.

Logistic Regression (LR)

Logistic Regression, a supervised learning algorithm, uncovers its preliminary application in classification tasks by assessing the probability of a sample belonging to a distinct class. It is specifically fitted for binary classification, where the output variable is categorical. This algorithm operates the logistic function, also known as the sigmoid function, to convert the result of a linear equation into a value within the range of 0 to 1. This altered value represents the likelihood or probability of a data point being associated with a certain class. [11]. The accuracy of this algorithm was 82.56% here

Decision Tree Classifier

The Decision Tree classifier is a supervised algorithm principally operated for classification tasks. This technique operates by iteratively splitting the dataset into subsets according to the attribute values, resulting in a tree-like configuration. In this structure, individual inner node exemplifies a conclusion based on a distinctive characteristic, and each leaf node corresponds to a class label. Here, the accuracy of this algorithm was 77.98%. [12]

Gradient Boosting Classifier

Gradient Boosting is a significant boosting approach that assembles numerous weak learners into vital learners. This methodology involves training individually unique samples to minimize the loss function, such as mean squared error or cross-entropy, based on the performance of the previous model employing gradient descent. In each iteration, the algorithm computes the gradient of the loss function regarding the predictions assembled by the current ensemble. Thereafter, a unique weak representative is trained to minimize this gradient. The predictions yielded by the new model are incorporated into the ensemble, and this iterative approach persists until a predefined stopping criterion is satisfied. The accuracy here was 82.56% [12].

Random Forest Classifier

The Random Forest Algorithm is a supervised machine learning technique employed for addressing both classification and regression challenges in the realm of machine learning. It can be considered as an ensemble of decision trees. Instead of depending on a single decision tree, the random forest contains multiple decision trees, each prepared on distinct subsets of the delivered dataset. To enhance predictive accuracy, the algorithm computes the intermediate prediction from these trees. Instead of just depending on one tree's outcome, the absolute prediction is determined by a majority vote among the predictions from the ensemble of trees. The accuracy for this algorithm was 83.48%. [13]

Support Vector Machine

The Support Vector Machine (SVM) is a supervised learning algorithm appropriate for both classification and regression tasks, although it is primarily employed in classification problems in the field of machine learning. The primary objective of SVM is to establish an optimal conclusion limitation, usually directed to as a hyperplane, within an n-dimensional distance to effectively distinguish between different classes. This hyperplane relieves the proper categorization of further data attributes in the future. SVM identifies the critical data points that play a major role in determining this hyperplane; these pivotal representatives are known as support vectors, giving rise to the name "Support Vector Machine". The accuracy was 70% here. [14]



**Evaluation and Comparison of Models**

The comparison of these models is done based on accuracy. Various classification algorithms are used to find the most acceptable models. As shown in the table and plot the best accuracy is given by Random Forest Classifier, Gradient Boosting classifier, and Logistic Regression

RESULT

The dataset contained 541 samples with 44 features. Out of these 44 parameters, only ten parameters are considered. Parameters that are more important for the diagnosis of PCOS are shown in Table III, after analyzing the performance of all five models, we can conclude Random Forest is most Suitable.

CONCLUSION

This paper exhibits the different Machine Learning algorithms and a model to detect the early phase of PCOS, as it is essential for women's health. This hormonal disorder impacts the regular condition of women and disturbs the psychological, physical, and metabolic components. Day-to-day exercise and a regular healthy diet are initialized to decrease the effect and maintain a nourishing lifestyle. The model in this paper ventures the comfortable system to detect the disorder at an early stage, with a definitive set of parameters. Among all the various algorithms used, the Random Forest Classifier possesses the foremost result in its performance with 83.48% by considering the relevant 10 features. This model is flexible such that it can be utilized by doctors for the early detection of PCOS. Hence, we have built the model with different machine-learning techniques to detect PCOS at an early stage

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Table 1. Research Methodology

AUTHORS	OBJECTIVES	RESEARCH METHODOLOGY	RESULTS
Rihana et.al. [2013] [2]	classificationn in ovary and Cysts detection, ultrasound images with geometricalfeatures of the cyst.	Image pre-processing,Feature extraction, SVM classifier, andValidation were used byROC.	Accuracy of 90% was achieved and cysts were detected inovary ultrasound images.
Purnama et al. [2015][3]	Detecting follicles via ultrasound (USG) pictures through a process involving binary follicle images, feature extraction, and segmentationn.	Multiple classification methods were developed suchas SVM – RBF kernel, Neural Network – LVQ, and KNN – Euclidean distance.	At K=5,KNN attained an accuracy of 78%, and on C=40, 82% accuracy was achieved in the SVM-RBF kernel.
Denny et al. [2019][4]	Diagnosis of PCOS based on dataset available on Kaggle.	Attributes of PCOS are transformed with PCA by various machine learning algorithms such as Decision Trees, Random Forest, SVM, KNN, etc.	Random Forest was the best model for PCOS detection with an accuracyof 89%.
Subrato et al. [2020][5]	Diagnosis of PCOS using Kaggle dataset.	Algorithm used for classification are gradient boosting, Random Forest , Logistic regression, RFLR and used holdout and cross validation methods	RFLR gave highest accuracy of 91.01% with 90% recall value
Madhumita ha et al. [2021][6]	Used image segmentation to get details of the ovary for example follicle size, type of cysts.	SVM, KNN and Logistic Regression were used as per pre- processing and morphological operations.	With the combination of all three algorithm, the hybrid model gave 0.98 accuracy.
Pijush et al. [2021] [7]	Detection and prevention of PCOS.	The algorithm used were SMOTE and five other algorithms Logistic Regression, Random Forest, Support vector machine and K- NN, and Random Forest together for early detection of PCOS.	The best model achieved, Recall: 98%, Precision: 98% and AUROC: 95.6%.





Shamik Tiwari et al. [2022] [8]	To diagnose PCOS using Machine Learning	The algorithms used for classification are SVM, DT, RF, LR, GB, AB, XB, AND CB for correlation coefficients of various levels.	Random Forest (RF) gave highest accuracy of 93.25%
Samia Ahmed et al. [2023] [9]	A review on the PCOS using the Machine Learning	A study on various dataset used for PCOS diagnosis was conducted. In quantitative and Qualitative approaches, the performance of algorithms are compared.	The shortcomings like insufficient dataset, lack of clustering approach, not were detected in this paper.

Table 2. Accuracy of all Models

Models	Accuracy
Logistic Regression	82.56%
Decision Tree Classifier	77.98%
Gradient BoostingClassifier	82.56%
Support Vector Machine	70%
Random Forest Classifier	83.48%

Table 3. Selected Features

Ranking	Features name	Value
1	FSH/LH	Between 1 and 2 (normal),2 or 3(abnormal)
2	FSH (mIU/mL)	4-8(abnormal)
3	AMH (ng/mL)	1-4 (normal), >4 (abnormal)
4	BMI	<24 (normal), >24 (abnormal)
5	Weight gain (Y/N)	Yes(y)/No(n)
6	Follicle No. (L)	<12(normal) >=12(abnormal)
7	Follicle No. (R)	20-30(abnormal)
8	Avg. F size (L) (mm)	2–9 mm in diameter
9	Cycle	(Regular/Irregular)
10	Cycle Length	Number of days





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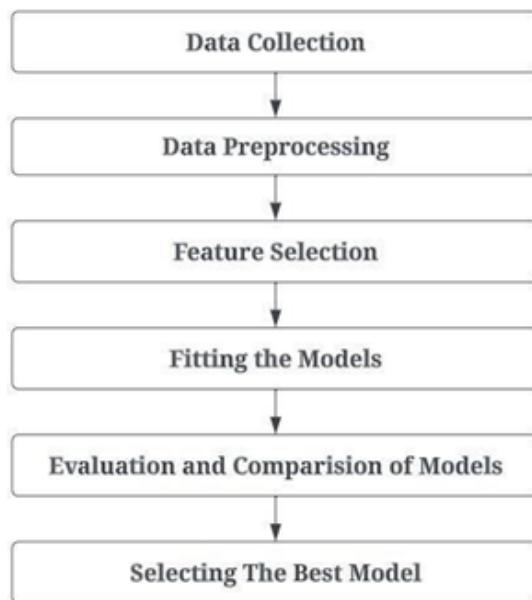


Fig I: System Flow of the Model

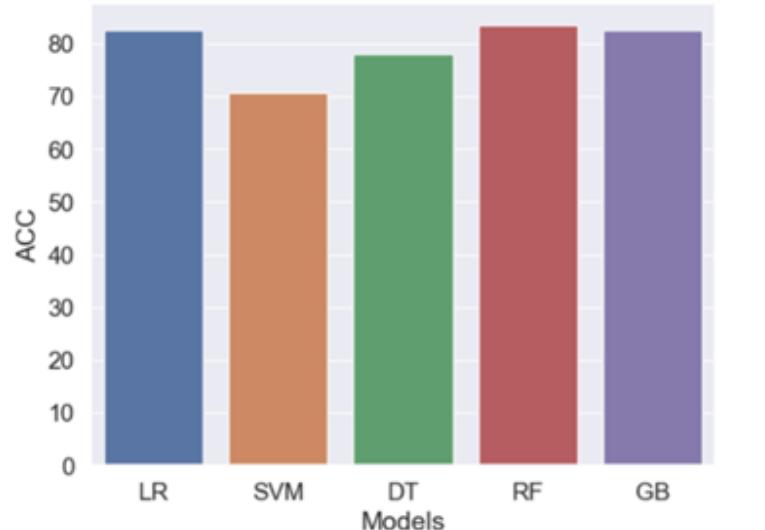


Fig 2.: Accuracy of all Models



Eating habits among women with insulin resistance (IR) on a vegetarian vs non-vegetarian diet

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A – Study Design, B – Data Collection, C – Statistical Analysis, D – Data Interpretation, E – Manuscript Preparation, F – Literature Search, G – Funds Collection

Summary **Background.** Insulin resistance is one of the major metabolic disorders. The composition of one's diet has a crucial effect on the risk of developing this disorder and is a key component of treatment. Following a vegetarian diet seems to be promising for health benefits.

Objectives. The aim of the study is to assess the eating habits of women suffering from insulin resistance following vegetarian and non-vegetarian diets.

Material and methods. The survey was conducted among 248 women between the age of 18 to 64 in Poland from January to March 2022. The research tool was a website survey questionnaire. The analysis was performed using the Statistica 10 program. The data obtained was subjected to statistical analysis using the chi-square test. Results were considered significant at $p \leq 0.05$.

Results. Women on a vegetarian diet had the correct body weight more often (47.4%) compared to those following a traditional diet (40.5%) or not following any diet (38.5%). 69.3% of vegetarians assessed their nutritional knowledge as better than good. Women on a plant-based diet included legumes in their diet and consumed vegetables much more often than others. Attitudes towards plant-based meat substitutes and plant-based dairy substitutes were significantly more positive among vegetarians than others.

Conclusions. Women with insulin resistance on a vegetarian diet often have better nutritional choices compared to women on a traditional diet or those not following any diet. These promising findings may be helpful in preventing and treating this disorder. However, the amount of research and results is insufficient and requires further analyses on a larger group of subjects.

Key words: insulin resistance, feeding behavior, diet, vegetarians.

Rokicka G, Wiśniewska K, Okręglicka K. Eating habits among women with insulin resistance (IR) on a vegetarian vs non-vegetarian diet. *Fam Med Prim Care Rev* 2022; 24(4): 336–340, doi: <https://doi.org/10.5114/fmpcr.2022.120858>.

Background

Insulin resistance is one of the major metabolic disorders on which a lot of research is being carried out. Detection of this disorder has increased significantly in recent years. The prevalence among people shown in studies depends on population, but it is reported to be 10% to 30% [1]. Insulin resistance is highly correlated with obesity, but it has been proven that people with a healthy body weight can also struggle with it. If they are left untreated, it can also have serious health consequences, despite being non-obese [2].

Insulin resistance is defined as the lack of ability of insulin-target tissues to dispose glucose from blood and inhibition of endogenous glucose production and lipolysis. At the same time, inability of stimulating glycogen synthesis at high plasma insulin concentrations occurs. An imbalance of energy intake and expenditure is the main reason for common insulin resistance. Genetic predispositions are also important issues [3].

The frequency of this condition is associated with age, body weight, gender, physical activity, as well as genetic and lifestyle issues. Moreover, scientific research has shown that insulin resistance can be related to stress and overstimulation of the sympathetic nervous system. This condition is also correlated with the occurrence of inflammation in the body [1].

The composition of one's diet has a major effect on the risk of developing this condition and is a key component of treatment for insulin resistance. This is why the assessment of the

nutritional habits of patients is very important [1]. Diet models most suitable for patients with insulin resistance have also been investigated. The Third National Health and Nutrition Examination Survey (NHANES III) found that people who follow a diet very similar to the Mediterranean diet had lower BMI and waist circumference. These indicators correlated with lower glycated haemoglobin levels, fasting insulin levels and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index values [4].

Referring to the individual components of the diet, lower insulin sensitivity was associated with high consumption of animal products and low intake of vegetable food. It has been shown that this is correlated with type 2 diabetes and cardiovascular disease [5]. Eating habits, physical activity and lifestyle are extremely important but also modifiable factors on which the risk of insulin resistance depends [1]. Since 1935, when Hinsworth and Marshall [6] investigated and noted that a diet high in animal products and low consumption of plant-based foods increased the risk of type 2 diabetes, it has been proven that we should focus on prevention through proper and healthy eating habits.

A lot of research has been done, and now we have evidence that a nutrition model based on high consumption of animal and low-vegetable proteins promotes insulin resistance in patients with diabetes and in healthy people [7–9]. This is caused by glucagon secretion activated by amino acids, like arginine and alanine from animal protein. In the liver, glucagon is opposite to insulin and interferes with its action. High plasma glu-



cagon is maintained for at least four hours after a meal which is high in animal protein. This mechanism is very well observed in diabetic patients. Hyperglucagonemia that lasts a long time may induce insulin resistance [5].

A meta-analysis that included 19 trials showed that a diet rich in fruits, vegetables, whole grains, nuts, legumes, fat-free/low-fat dairy and a diet low in saturated fat, cholesterol, red and processed meats, refined grains and sweets had a good effect in improving insulin sensitivity. It is also important that a diet should be based on products with a low glycaemic index (GI) as low GI diets have been reported to improve insulin sensitivity and lower blood glucose. Foods rich in dietary fibre and micro-nutrients are essential in diet for insulin resistance. It has also been found that a calorie-restricted diet may have positive effect for glycaemic control by improving insulin sensitivity and β -cell function. Moreover, treatment and following a diet duration also had an important influence on the positive effects for glycaemic control by improving insulin sensitivity and β -cell function [10].

Objectives

The aim of the study is to assess the eating habits of people suffering from insulin resistance following vegetarian and non-vegetarian diets.

Material and methods

The survey was carried out in Poland from January to March 2022. The questionnaire was completed by 356 individuals. Incomplete data was rejected, and 248 participants aged 18–64 were enrolled in the study.

A survey was prepared by the authors. The questions concerned one's behaviours and eating habits, the frequency of meals, the subjective frequency of eating snacks, the consumption of vegetable, meat and dairy substitutes, the frequency of meat consumption and stimulants used, the type and amount of physical activity. Besides these, the KomPAN® questionnaire was used to assess the frequency of food consumption [11]. Moreover, there were questions concerning anthropometric parameters (body weight and height, waist circumference), as well as questions related to socio-demographic characteristics. There were 97 questions in the survey, 11 of which concerned anthropometric and socio-demographic data, and the rest concerned the frequency of food consumption and eating behaviours. The percentage of analysed questions with a $p < 0.05$ level was 45.3.

The exclusion criteria were being under 18 years of age, body mass index (BMI) below or equal to 18, anorexia, bulimia, malnutrition, as well as severe diseases (alcoholism, severe and extensive surgery, kidney failure), cancer in the last 5 years and the use of enteral and parenteral nutrition. Inclusion criteria were age and BMI over 18 and being diagnosed with insulin resistance, which the respondents declared in the survey. The study participants were people that voluntarily consented to take part in the study, which was announced on social media.

Statistical analysis was carried out with the use of the Statistica 10 program. The division of people into three groups was introduced due to type of diet (traditional, vegetarian and non-diet) and was verified using the chi-square independence test. In all analyses, a significance level of $\alpha = 0.05$ was assumed.

Results

248 women aged 18–64 suffering from insulin resistance participated in the study. More than a half of them were on a traditional diet, while 31.5% were on a vegetarian diet, and 15.7% declared to be non-dieters. BMI (body mass index) range was 18.0–46.4 kg/m². A large majority of participants (68.5%) had high education. The exact population data is presented in Table 1.

Table 1. General description of the studied population

Number of participants	n = 248
Age (year) (age range)	18–64
BMI (kg/m ²) (BMI range)	18.0–46.4
Smoking (%)	21.8
Age groups (%)	
18–20 years	4.3
21–40 years	85.0
41–60 years	10.7
Physical activity (%)	
low level	44.8
middle level	43.5
high level	11.7
Commune size (%)	
< 10,000 inhabitants	14.9
10,000–20,000 inhabitants	6.0
20,001–100,000 inhabitants	13.7
> 100,000 inhabitants	65.3
Level of education (%)	
under middle	1.6
middle	28.2
high	68.5
vocational	1.6
Type of diet (%)	
traditional	52.8
vegetarian	31.5
non-diet	15.7

Nutritional habits

Women on a vegetarian diet were much more likely to not consume milk and milk drinks (53.8%) than those on a traditional diet (19.1%) and those who do not follow any diet (10.3%). 52.7% of the respondents on a traditional diet chose low-fat dairy products compared to 26.9% of vegetarian women and 51.3% of non-dieters ($p < 0.01$). In contrast, 77.0% of the respondents on a vegetarian diet consumed dairy alternatives (e.g. drinks, yoghurts, vegetable spreads) once a week or more often ($p < 0.01$). The data is presented in Tables 2 and 3.

Regarding the frequency of eating alternatives to meat products, such as vegetable sausages, burgers, meatballs, nuggets, etc., 68.0% of the surveyed women on a vegetarian diet consumed those products more often than once a week. Compared to them, this was 16.0% of the respondents on a traditional diet and 23.1% of the women who do not follow any diet ($p < 0.01$). The data is presented in Table 4.

Table 2. Type of milk

Type of diet	Traditional (n = 131)	Vegetarian (n = 78)	Non-diet (n = 39)	p
I do not consume milk or milk drinks	25 (19.1%)	42 (53.8%)	4 (10.3%)	$p < 0.01$
Fat-free milk	3 (2.3%)	2 (2.6%)	2 (5.1%)	$p < 0.01$
Low-fat milk	69 (52.7%)	21 (26.9%)	20 (51.3%)	$p < 0.01$
Full-fat milk	34 (26.0%)	13 (16.7%)	13 (33.3%)	$p < 0.01$

Table 3. Frequency of consumption of dairy alternatives (e.g. plant-based soy and coconut yogurts, plant-based drinks, vegetable spreads)

Type of diet	Traditional (n = 131)	Vegetarian (n = 78)	Non-diet (n = 39)	p
Never	35 (26.7%)	2 (2.6%)	18 (46.2%)	p < 0.01
1–3 times a month	37 (28.2%)	16 (20.5%)	7 (17.9%)	p < 0.01
Once a week	19 (14.5%)	6 (7.7%)	4 (10.3%)	p < 0.01
A few times a week	31 (23.7%)	24 (30.8%)	7 (17.9%)	p < 0.01
Once a day	6 (4.6%)	13 (16.7%)	2 (5.1%)	p < 0.01
A few times a day	3 (2.3%)	17 (21.8%)	1 (2.6%)	p < 0.01

Table 4. Frequency of consumption of meat alternatives (e.g. vegetable cutlets, sausages, burgers, meatballs, schnitzels, nuggets)

Type of diet	Traditional (n = 131)	Vegetarian (n = 78)	Non-diet (n = 39)	p
Never	61 (46.6%)	7 (9.0%)	22 (56.4%)	p < 0.01
1–3 times a month	49 (37.4%)	18 (23.1%)	8 (20.5%)	p < 0.01
Once a week	11 (8.4%)	20 (25.6%)	6 (15.4%)	p < 0.01
A few times a week	10 (7.6%)	30 (38.5%)	3 (7.7%)	p < 0.01
Once a day	0 (0%)	1 (2.6%)	0 (0%)	p < 0.01
A few times a day	0 (0%)	1 (1.3%)	0 (0%)	p < 0.01

Table 5. Frequency of consumption of legumes, e.g. beans, peas, soybeans, lentils

Type of diet	Traditional (n = 131)	Vegetarian (n = 78)	Non-diet (n = 39)	p
Never	18 (13.7%)	1 (1.3%)	2 (5.1%)	p < 0.01
1–3 times a month	46 (35.1%)	6 (7.7%)	11 (28.2%)	p < 0.01
Once a week	25 (19.1%)	23 (29.5%)	14 (35.9%)	p < 0.01
A few times a week	31 (23.7%)	30 (38.5%)	10 (25.6%)	p < 0.01
Once a day	8 (6.1%)	14 (17.9%)	2 (5.1%)	p < 0.01
A few times a day	3 (2.3%)	4 (5.1%)	0 (0%)	p < 0.01

Table 6. Self-assessment of nutritional knowledge

Type of diet	Traditional (n = 131)	Vegetarian (n = 78)	Non-diet (n = 39)	p
Very Good	15 (11.5%)	19 (24.4%)	1 (2.6%)	p < 0.01
Good	42 (32.1%)	35 (44.9%)	12 (30.8%)	p < 0.01
Bad	50 (38.2%)	18 (23.1%)	16 (41.0%)	p < 0.01
Very bad	24 (18.3%)	6 (7.7%)	10 (25.6%)	p < 0.01

Another point is that more of the surveyed women on a vegetarian diet (25.6%) stated that they never eat fried foods (meat or flour) compared to those on a traditional diet (10.7%) and non-diet (12.8%) ($p < 0.01$).

A large majority of participants (89.7%) on a vegetarian diet declared that they include legumes in their diet at least once a week. In the case of people following a traditional diet, this was 51.9%, while those not following any diet – 46.2%. Among the respondents on a vegetarian diet, there was not a single person who declared to never consume legumes ($p < 0.01$). The data is presented in Table 5.

Regarding the frequency of eating vegetables, most people on a plant-based diet consumed vegetables several times a day (75.6%) compared to those on a traditional diet, with less than half of the respondents – 49.6%, and people not following any diet – 51.3% ($p < 0.02$).

Attitude to plant-based products

We examined the association between the type of diet and attitudes towards plant-based meat substitutes and plant-based dairy substitutes. A large majority of participants on a vegetar-

ian diet (82.1%) declared that plant-based meat substitutes are for them a wholesome alternative to meat products. However, the same was stated only by 36.6% of respondents on a traditional diet and 28.2% of women not following any diet ($p < 0.01$).

As for the same claim regarding plant-based dairy alternatives, the results were similar. 76.9% of vegetarians declared that plant-based substitutes for dairy products were a full-fledged alternative. Only 42.0% of non-vegetarians and 38.5% of non-dieters agreed with this statement.

Self-assessment of nutritional knowledge and nutrition, well-being, physical activity, sleep habits

Additionally, we examined the respondents' opinion on their nutritional knowledge. 69.3% of vegetarians defined it as good or very good, only 43.6% of women following a traditional diet had the same opinion about their own knowledge, and this was even less (33.4%) for respondents who did not follow any diet ($p < 0.01$). The data is presented in Table 6.

The results related to the amount of sleep, physical activity, well-being and self-assessment of nutrition were not statistically significant ($p > 0.05$).

Body Mass Index

Body mass index (BMI) was calculated based on the data concerning the height and weight of the surveyed women. Correct BMI was within the range of 18.5–24.99 kg/m². The results showed that 47.4% of the women on a vegetarian diet had the correct body weight compared to those following a traditional diet (40.5%) and those not following any diet (38.5%). BMI over 24.9 kg/m² (overweight or obesity) amounted to 55.0% of the respondents on a traditional model of nutrition, 44.9% of women eating plant-based foods and 61.5% of non-dieters ($p < 0.02$).

Discussion

As far as we know, there is no other study comparing the eating habits of women suffering from insulin resistance on a vegetarian or non-vegetarian diet. From the results that we were able to collect, we obtained data confirming our research hypothesis that the eating habits of women on a non-vegetarian diet differ from those on a plant-based diet, and this has further consequences.

The respondents on a plant-based diet displayed healthier eating habits by consuming more legumes and vegetables and more often chose low-fat milk or plant-based substitutes for meat and dairy products. Similar results were obtained in a study among Argentinean vegetarians and non-vegetarians. In this survey, the respondents on a plant-based diet were also more likely to eat legumes and vegetables more often, as well as fruit, whole grains, seeds and nuts. Researchers compared adherence to healthy vegan lifestyle habits according to the vegetarian diet pattern category and presented results that indicated that non-vegetarians scored significantly lower than the vegetarian groups [12]. On this basis, we can assume that vegetarians may have better eating habits.

In our research, we discovered that women following a plant-based diet had normal BMI more often than non-vegetarians. The same results were found in the Rotterdam Study [13], which also examined this relationship. In this study, they constructed an overall plant-based dietary index measured by the food frequency questionnaires (FFQs) divided into 23 food categories. A higher score on the plant-based dietary index was related to lower longitudinal HOMA-IR and BMI. Referring to our results and those of the the Rotterdam Study, it can be assumed that a plant-based model of eating probably has a positive effect on the occurrence and course of the disease.

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Review Article

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Epidemiology, pathogenesis, genetics & management of polycystic ovary syndrome in India

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder predominantly affecting women of reproductive age. Clinical manifestations are diverse including hyperandrogenism, anovulation, infertility and increased risk of metabolic diseases besides psychosocial dysfunction. This review provides information on the problem of PCOS in India, its pathophysiology, genetics and an overview of current management options to instigate further research in this field. Prevalence of PCOS in India ranges from 3.7 to 22.5 per cent depending on the population studied and the criteria used for diagnosis. Abnormalities in leptin-adiponectin (adipocyte biology), oxidative stress and autoimmunity are among the mechanisms studied regarding pathogenesis of PCOS. Many candidate gene studies have shown associations with PCOS in various studies. Studies have consistently demonstrated the relationship between the well-known manifestation of hyperandrogenism among Indian PCOS women and the metabolic morbidities including insulin resistance, glucose intolerance and cardiovascular risk. Management of individual components of PCOS can be achieved by medications or surgical methods, though further clarification regarding pathogenesis of PCOS is needed to sharpen our therapeutic armamentarium.

Key words Epidemiology - genetics - India - management - pathogenesis - pathophysiology - polycystic ovary syndrome - prevalence

Introduction

Polycystic ovary syndrome (PCOS) is considered to be a multifaceted disease with a spectrum of manifestations affecting not only women of childbearing age, but also adolescents and postmenopausal women¹. PCOS, by the nature of the disease, adversely influences the fertility and reproductive health of the affected women²; moreover, with its association with other lifestyle diseases, it is also

the cause of significant cardiovascular and metabolic morbidity³. The exact aetiology and pathogenesis of PCOS are still an area of active research, although multiple hypotheses have been postulated, ranging from genetic susceptibility to environmental exposure, both *in utero* and in the postnatal life⁴. Data on the genetics, metabolic parameters and clinical aspects of PCOS in Indian women are available. This article was aimed at reviewing the literature related to the

pathogenesis, epidemiology and genetics of PCOS in India, and biochemical and hormonal abnormalities in this disorder besides providing a brief overview of the management options.

Evolution of PCOS as a distinct syndrome - A historical overview

PCOS, discovered by Stein and Leventhal⁵, earned its name based on the ovarian morphology. The authors described seven women who shared the common features of menstrual disturbances, hirsutism and enlarged ovaries with many small follicles⁵. They also suspected that bilateral cystic ovaries were the result of abnormal hormonal stimulation, which was confirmed by the later investigators. Medical treatment became the preferred treatment over surgical resection of the ovaries when options such as clomiphene and follicle-stimulating hormone (FSH) became available⁶. There was a renewed interest in the surgical treatment of PCOS when laparoscopic treatment became popular. Newer technologies such as ultrasound to image ovaries were a breakthrough in the history of PCOS, and the ease of this technique made the diagnosis of PCOS simpler. However, this had the unexpected result that many women were diagnosed with mild or no other features of PCOS, but had polycystic ovaries⁷. This led to the term of polycystic ovarian morphology, the significance of which is still a subject of debate. It has been argued that the widespread acceptance of the Rotterdam criteria⁸, which included oligo-anovulatory women with polycystic ovarian morphology without clinical or biochemical evidence of hyperandrogenism, is premature and will lead to unnecessary diagnosis, laboratory evaluation and probably lifelong implications in these women⁹. Even after so many years of the recognition, the exact aetiology of this syndrome remains elusive and is now considered to be multifactorial, with a strong genetic component. Although insulin resistance (IR) is consistently found in women with PCOS, yet it is not included in any diagnostic criteria.

Clinical features, comorbidities and diagnostic criteria of PCOS

The clinical manifestations of PCOS include oligomenorrhoea, hirsutism, excessive acne and hair loss. In adolescence, it causes significant psychiatric disturbances such as anxiety and depression. PCOS is the leading cause of anovulatory infertility in women. The metabolic consequences include impaired glucose tolerance, type 2 diabetes, obesity and increased risk of cardiovascular diseases. Metabolic complications and increased cardiovascular morbidity were found to be more in the classic PCOS compared to other phenotypes, even after adjustment for obesity¹⁰. Clinicians now have these three sets of criteria (Table I) to choose from, though the Rotterdam criteria⁸ are found to be more preferred. The National Institutes of Health (NIH) Evidence-based Methodology Workshop in 2012 published the final report¹³ which stated that the following specific phenotypes (Table II) should be reported explicitly in all research studies.

Epidemiology of PCOS in India

Only a few researchers have studied the prevalence of PCOS in India and among those, most of the sampling was convenience based, which might not reflect the true status of PCOS prevalence in the community. A pilot cross-sectional study conducted in Tamil Nadu assessed young adolescent females and found a prevalence of 18 per cent for PCOS¹⁴. They also concluded that the proportion of PCOS was higher in urban women in comparison to the rural women. A similar study conducted in Mumbai, which was an urban community-based study, found that the prevalence of PCOS was 22.5 per cent by the Rotterdam criteria and 10.7 per cent by the Androgen Excess Society criteria¹⁵. A study conducted among medical students at a private medical college in south India using the modified Cronin questionnaire¹⁶, which included 10 items, found that PCOS was a common disorder among the participants and reported a high

Table I. Diagnostic criteria of polycystic ovary syndrome (1990-2009)

PCOS definition	Clinical hyperandrogenism or biochemical hyperandrogenism (elevated total/free testosterone)	Oligomenorrhoea or oligo-anovulation	Polycystic ovaries on ultrasound
NIH (1990) ¹¹	Yes	Yes	Not included
ESHRE/ASRM Rotterdam (2003) ⁸ 2 of 3 criteria	Yes/no	Yes/no	Yes/no
AE-PCOS Society (2006) ¹²	Yes	Yes/no	Yes/no

PCOS, polycystic ovary syndrome; AE, androgen excess; NIH, National Institutes of Health; ASRM, American Society for Reproductive Medicine; ESHRE, European Society of Human Reproduction and Embryology

incidence of mood disorders among them¹⁶. A study from Lucknow was published, in which college-going women with menstrual irregularity and hirsutism, in the age range of 18-25 yr, were studied, and it was reported that the calculated prevalence using the NIH criteria, among the participants, was only 3.7 per cent¹⁷. Another study from Andhra Pradesh studied young women from a residential college and found that 9.13 per cent of them satisfied the Rotterdam criteria for PCOS¹⁸. Vidya Bharathi *et al*¹⁹ showed that the prevalence of PCOS diagnosed by the Rotterdam criteria in community-dwelling women from rural and urban areas of Chennai was 6 per cent. International studies report the prevalence of PCOS to be in the range of 4-10 per cent of women of reproductive age²⁰. As the prevalence of PCOS has been found to be higher or lower depending on the criteria used in these studies, which might be the obvious reason for the discrepancy in the prevalence rates among the studies from India, it is difficult to draw a clear conclusion. Hence, from the limited data available, it can be said that the prevalence

of PCOS in India ranges from 3.7 to 22.5 per cent (Table III).

Pathophysiology and genetics of PCOS

PCOS is a disease with a complex multipronged pathogenesis which is still under investigation (Figure). The various pathogenetic mechanisms of PCOS include abnormal gonadotropin-releasing hormone (GnRH) regulation leading to increased luteinizing hormone (LH) and decreased FSH; decreased response of ovarian follicles to FSH; increased anti-Mullerian hormone (AMH); follicular arrest and increased secretion of testosterone, estradiol and dehydroepiandrosterone (DHEA). Obesity, especially abdominal fat deposition, is the major predisposing factor for the expression of IR and metabolic phenotype in PCOS²². Thus, IR at post-receptor level and adipocyte dysfunction are responsible for the metabolic consequences of

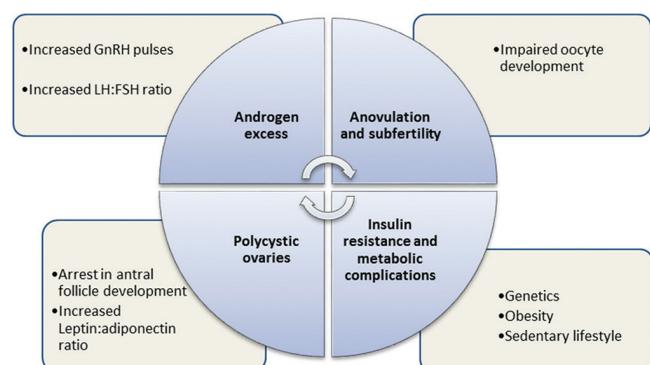


Figure. Current concept of pathophysiology of polycystic ovary syndrome. LH, luteinizing hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone.

Source: Ref 21.

Table III. Prevalence studies on polycystic ovary syndrome in Indian women/girls

Study	n	Place/yr	Population/sampling	Prevalence per cent (criteria)
Balaji <i>et al</i> ¹⁴	126	Tamil Nadu/2015	Young adolescents (12-19 yr) Urban and rural	18 (Rotterdam) ⁸
Joshi <i>et al</i> ¹⁵	600	Mumbai/2014	Adolescents and young adolescents (15-24 yr) Community based	22.5 (Rotterdam) ⁸ 10.7 (AES) ¹²
Joseph <i>et al</i> ¹⁶	441	Karnataka/2016	Medical and dental college students (20.4 ± 1.5 yr) with either menstrual irregularity or hirsutism	9.1 (modified version of Cronin questionnaire) ¹⁶
Gill <i>et al</i> ¹⁷	1520	Lucknow/2012	College girls (18-25 yr) with menstrual irregularity and hirsutism	3.7 (NIH criteria) ¹¹
Nidhi <i>et al</i> ¹⁸	460	Bengaluru/2011	College girls (15-18 yr) Oligomenorrhoea and/or hirsutism	9.13 (Rotterdam) ⁸
Vidya Bharathi <i>et al</i> ¹⁹		Chennai/2017	Random general rural and urban population	6 (Rotterdam) ⁸

PCOS²¹⁻²⁵. Many other biochemical and hormonal aspects apart from the widely known pathophysiological mechanisms underlying PCOS have been studied by Indian researchers and are reviewed in detail below.

Studies on PCOS pathogenesis from India

Role of leptin and adiponectin in PCOS pathogenesis

Leptin is a major intermediary between nutritional status and reproductive health of women. High levels of leptin have been found to be associated with the markers of IR in PCOS patients^{24,26}. After adjusting for potential confounders such as obesity status, PCOS women had higher leptin levels as compared to controls and leptin also was positively correlated with the serum testosterone levels²⁷. Another study also demonstrated that high leptin in PCOS women was independent of the obesity status, but this study did not find a significant correlation between leptin levels and serum testosterone²⁷. From these case-control studies, it is difficult to ascertain the cause and effect relationship between leptin levels and hyperandrogenemia or PCOS phenotype, though it is imperative that the complex nature of the same needs further exploration. Singh *et al*²⁸ in a case-control study demonstrated lower serum adiponectin levels in women with PCOS as compared to controls. The adiponectin levels were lowest in obese women with PCOS and even non-obese PCOS women had low adiponectin, which improved with metformin treatment. Independent of obesity status, hypoadiponectinemia correlated with IR and hyperandrogenemia; this may be because lean PCOS women also may have intra-abdominal fat and thus unhealthy metabolic profile. Reiterating the role of adiponectin in PCOS pathogenesis, animal studies showed that adiponectin treatment reduced androgen synthesis in DHEA-treated PCOS mice in an *in vitro* study²⁹. In another case-control study, plasma leptin:adiponectin ratio (L:A ratio) seemed to be positively associated with markers of metabolic syndrome and IR, thus reconfirming the lower adiponectin levels to be a potential biomarker of metabolic risk and IR in PCOS women³⁰.

Evidence from proteomics and metabolomics studies

In large case-control study on the proteomics of follicular fluid from women with PCOS and controls undergoing *in vitro* fertilization (IVF) treatment found altered levels of proteins involved in extracellular matrix remodelling, complement coagulation cascade, fibrinolysis, vasculature development, angiogenesis, lipid transport and metabolism, and the authors

postulated that it might reflect the molecular defects in folliculogenesis³¹. A study of the serum metabolomics of Indian women with PCOS during day 3 to 5 of their menstrual cycle using proton nuclear magnetic resonance and pattern recognition approach showed dysregulation in the expression of various metabolites in the serum of PCOS women, which indicated involvement of multiple pathways in amino acid metabolism, carbohydrate/lipid metabolism, purine and pyrimidine metabolism and protein synthesis³².

Role of oxidative stress and autoimmunity in PCOS pathogenesis

The role of oxidative stress in the pathogenesis of various reproductive diseases and conditions including infertility, recurrent abortions and pre-eclampsia has been postulated, and PCOS is no exception. Plasma amino acid levels were found to be significantly deranged (lower levels of methionine, cystine, isoleucine, phenylalanine, valine, tyrosine, proline, glycine, lysine and histidine and higher arginine and alanine levels) in PCOS women as compared to controls³³, and the authors suggested this to be a marker of higher metabolic and oxidative stress in PCOS women. Reduced arginine bioavailability was found in PCOS women, which correlated with low nitric oxide levels, increased oxidative stress and thus lowered regulatory T cells (Treg cells) in patients with PCOS³⁴. Krishna *et al*³⁵ demonstrated for the first time that the immunosuppressive action of CD4+CD25+CD 127-Treg cells was reduced in PCOS, and this might influence the reproductive function of these women adversely. Sumithra *et al*³⁶ studied the markers of oxidative stress and high sensitivity C-reactive protein levels (marker of cardiovascular risk), in patients with PCOS compared to controls, and found that both are significantly elevated in the PCOS cases. Deepika *et al*³⁷ studied genomic instability and cytotoxicity due to oxidative stress, assessed by estimating the frequency of micronucleated cells in epithelial samples and serum malondialdehyde levels, respectively, and found a positive correlation in patients of PCOS as compared to controls, which suggested high oxidative stress in PCOS women. Other investigators have specifically demonstrated elevated oxidative stress markers in lean PCOS patients³⁸. In oral contraceptive pill (OCP)-treated women, plasma intercellular adhesion molecule-1 (ICAM-1) and tumour necrosis factor- α (TNF- α) levels were significantly higher, compared to drug-naïve PCOS women, which suggested a pro-

inflammatory state in the OCP-treated women, despite reduced androgen and regularized menstrual cycles³⁹.

PCOS has long been suspected to have a component of autoimmune origin. Arora *et al*⁴⁰ from New Delhi found higher prevalence of antithyroglobulin antibodies in PCOS women and suggested a possible role of autoimmunity in the pathogenesis of PCOS. A small case series of patients with both PCOS and Grave's disease also suggested a possible autoimmune aetiology of PCOS⁴¹.

Other mechanisms proposed to have a role in PCOS pathogenesis

Some studies have suggested a role of vitamin D deficiency in metabolic abnormalities seen in PCOS women, but many authors have opined that hypovitaminosis D is ubiquitous in India, and this does not seem to alter the metabolic phenotype in women with PCOS^{42,43}. Altered mineral status in the form of hypercalcaemia and very low manganese levels in addition to higher levels of zinc and copper was demonstrated in women with PCOS compared to controls⁴⁴, which led the authors to propose that altered trace mineral milieu might play a significant role in the pathogenesis of PCOS. The various metabolic, inflammatory and autoimmune components including the obesity-related cytokines and oxidative stress markers evaluated in relation to the pathogenesis of PCOS highlight the multifaceted nature of this disorder and the need for further research to better delineate the contribution of each of these markers and mediators in the final expression of the syndrome of PCOS.

Genetics in PCOS

The evidence that PCOS may be genetically determined initially came from twin studies, where the incidence of PCOS was twice as high in women with an affected twin as compared to the rest of population⁴⁵. Candidate gene approach worldwide has identified many susceptibility genes including cytochrome P1A1 (*CYP1A1*), *CYP11A*, *CYP17A1*, *CYP19*, 17 β -hydroxysteroid dehydrogenase (*HSD17B6*), androgen receptor (*AR*), sex hormone-binding globulin (*SHBG*), insulin receptor (*INSR*), insulin receptor substrate 1 (*IRSI*), peroxisome proliferator-activated receptor gamma (*PPAR- γ*), follicle stimulating hormone receptor (*FSHR*), luteinizing hormone/chorionic gonadotropin receptor (*LHCGR*), anti-Mullerian hormone receptor type 2 (*AMHR2*), interleukin (*IL*) IL-1A, IL-1B and IL-6⁴⁵, whereas genome-wide association studies have identified many susceptibility

loci including THADA, DENND1A, LHCGR, FSHR, C9orf3, YAP1, GATA4,-NEIL2 and ERBB4^{23,46}.

Studies in the genetics of PCOS from India

Diabetes and metabolic syndrome-related genes

In a small study from Hyderabad, 15 single-nucleotide polymorphisms (SNPs) from nine type 2 diabetes-related genes (such as *TCF7L2*, *IGF2BP2*, *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A*, *IRSI*, *CAPN10* and *PPAR- γ*) were studied in PCOS women and controls; no significant association was found; the authors cited studies from other ethnic populations and suggested that the non-association might be universal⁴⁷. Gly972Arg SNP of IRS1 was found to have a positive association with PCOS in a south Indian study population, whereas *INS*, *IRS2*, *PPAR- γ* and *CAPN10* failed to show any association in the same study from Chennai⁴⁸. Insulin receptor gene polymorphism was studied later⁴⁹, for its association with IR in Indian women with PCOS; the study suggested that CC genotype (C1085T) might be developed as a marker for IR and metabolic complications in Indian women⁴⁸. Pro12Ala polymorphism of *PPAR- γ* showed significant association with reduced susceptibility for PCOS in a study published from Mumbai⁵⁰. The Calpain-10 (*CAPN10*) SNPs showed variable association with PCOS in the obese subgroup of patients⁵¹; the authors highlighted the importance of this gene in PCOS pathophysiology. The *IRSI* and *PPAR- γ* gene polymorphisms were found to have a probable protective role against the development of certain specific PCOS sub-phenotypes⁵². Angiotensin-converting enzyme (ACE) I/D polymorphism was found to be associated with an early age at onset of PCOS symptoms in a case-control study from Hyderabad⁵³. A preliminary study on vitamin D receptor polymorphisms in PCOS patients and controls found no significant association, though some of the SNPs suggested a possible functional significance with regard to PCOS-specific clinical/biochemical traits⁵⁴. In a study conducted by Yousuf *et al*⁵⁵ among Kashmiri women with PCOS and controls, it was found that the *ICAM 1* gene polymorphism was not significantly associated with PCOS women compared to controls.

Ovarian function-related gene polymorphisms

In a study to investigate the association of Connexin37/Gap junction alpha 4 gene C1019T SNP with the susceptibility to PCOS among south Indian women⁵⁶, cases of PCOS were found to be significantly more associated with C/C and C alleles of the C1019T

SNP, compared to the controls. Another study⁵⁷ conducted among two ethnically different PCOS case-control groups has shown that 5,10 methylene tetrahydrofolate reductase (*MTHFR*) gene 677 CT polymorphism does not affect PCOS susceptibility in Indian women. The *LHCGR* gene polymorphism rs-2293275 was found to be significantly associated with PCOS compared to controls in a study⁵⁸ from Hyderabad. Another study from Hyderabad⁵⁹ suggested that vascular endothelial growth factor +405G/C polymorphism might constitute an inheritable risk factor for PCOS in south Indian women. Insulin-like factor 3 gene polymorphisms were studied among women from Mumbai⁶⁰, and the authors showed a significant association between rs6523 polymorphism and increased risk of PCOS. Follistatin gene exons were amplified and studied⁶¹ for mutations in a large cohort of PCOS women and controls from south India; the authors found no significant role of follistatin gene variants in PCOS susceptibility. Androgen receptor CAG repeat length polymorphism was reported to have no significant association with PCOS in a case-control study⁶².

Oxidative stress and cytokine-related gene polymorphisms

Two polymorphisms (L55M and Q192R) of paraoxonase 1 (*PON1*) gene were studied for their association with PCOS susceptibility and related traits in Indian women from Mumbai⁶³, and the authors found that one of those SNPs (L55M) was associated with reduced PCOS susceptibility only in lean women and that it also impacted features such as hyperandrogenemia, lipid parameters and glucose metabolism in these women. This led the authors to suggest that the genetic pathophysiology of PCOS was different in lean and obese women. In another study from south India⁶⁴, *IL* 6174 G/C SNP was found to be significantly associated with PCOS risk. A case-control study from south India on the polymorphisms of *TNF-α* gene and found that the distribution of genotypes for rs1799964 was significantly different between the groups⁶⁵. *IL-β*, *IL-1Ra* and *FABP1* gene variants were found to be significantly associated with many metabolic features of PCOS⁶⁶. Adiponectin and resistin gene polymorphisms were studied in south Indian women⁶⁷; while it showed no association of the former with PCOS, the authors suggested that resistin gene variants might have a role in PCOS susceptibility. Another study from Hyderabad has shown that carriers of PPAR-γ coactivator 1α (PGC-1α) rs8192678 'Ser' allele have increased risk of developing PCOS⁶⁸.

Miscellaneous genes associated with PCOS

In a study from Hyderabad, *CYP11A1* microsatellite (ttta)n repeat polymorphism was found to be more common in PCOS patients as compared to controls⁶⁹, and the authors opined that because this cholesterol side-chain cleavage enzyme-encoding gene was instrumental in the synthesis of sex hormones, this could be a genetic marker of susceptibility to PCOS in the south Indian population studied. Lutinizing hormone β-subunit gene variants were studied among women⁷⁰ with PCOS from south India; although the ones found to have significant correlation were silent in nature, the authors suggested exploration of other significant polymorphisms in the hypothalamic-pituitary-gonadal axis⁷⁰. Plasminogen activator inhibitor 1 (PAI-1) 4G/5G polymorphism was found to be associated with risk for recurrent pregnancy loss and implantation failure²⁵. Sagvekar *et al*⁷¹ showed that altered global DNA hypomethylation in peripheral blood lymphocytes and granulosa cells was strongly associated with PCOS and recommended larger studies to shed light on such epigenetic modifications in the PCOS susceptibility.

Candidate gene polymorphism studies involving genes related to diabetes, metabolic syndrome, oxidative stress, cytokines, ovarian function *etc.*, have been conducted in the area of PCOS related genetic research in India. The limitations of candidate gene polymorphism studies in proving the association and the strength of the association need to be acknowledged. Genome-wide studies need to be planned in the future.

Clinical features and co-morbidities of PCOS

A clinical study⁷² reported that in PCOS subgroups, the phenotype with hyperandrogenism and regular menstrual cycles had higher IR and gonadotropic hormonal abnormalities compared to the subgroup which had patients with irregular menstruation. Another study demonstrated that hyperandrogenism, in the form of high testosterone values, correlated well with obesity and sleep-disordered breathing in PCOS women, and this might be one of the reasons for high cardiovascular morbidity in the PCOS patients⁷³. Hyperandrogenic phenotypes of PCOS were found to be more prone to metabolic complications as compared to the phenotypes with normal androgen levels⁷⁴.

PCOS occurs in both obese and non-obese women equally, although markers of IR are more common in obese women⁷⁵. Acanthosis nigricans (AN) was found to be present in more than half of the PCOS women examined in a study conducted at Manipal,

south India⁷⁶. The authors described an association of AN with a family history of diabetes in first-degree relatives in all of these patients. Cardiovascular autonomic function was tested in women with PCOS in a study from south India, which showed an imbalance in the sympathovagal output in patients as compared to controls, and the authors suggested that the altered autonomic function might predispose these patients to cardiovascular morbidity⁷⁷. The prevalence of abnormal glucose tolerance (AGT) detected by oral glucose tolerance test (OGTT) was found to be high (around 35%) in a large number of young Indian women with PCOS, and it was found that family history of diabetes was not a predictor of AGT in these women⁷⁸. Thus, studies from India have consistently demonstrated the relationship between the well-known manifestation of hyperandrogenism among Indian PCOS women and the metabolic morbidities including IR, glucose intolerance and cardiovascular risk in this population.

Management of PCOS

The management of PCOS is as complex as the condition itself. The management and treatment of PCOS include a healthy diet, regular physical activity, and medications, which address the associated manifestations and co-morbidities. PCOS management strategies mainly aim at resolving the four major components of PCOS including regularity of menstrual periods, control of hyperandrogenism (acne and hirsutism), management of infertility and IR along with its associated risk factors (type 2 diabetes mellitus, hyperlipidaemia, and obesity). Both non-pharmacological and pharmacological management strategies are important in the overall management of PCOS.

Non-pharmacological measures

Studies on non-pharmacological measures to treat PCOS are very limited in the Indian literature. In a study on reproductive-age women with PCOS, improvement in novel inflammatory cardiac risk markers such as hs-CRP was reported with lifestyle modification, although metformin was also given to the study participants⁷⁹.

Pharmacological treatment

In a randomized, single-blinded, dose-comparison study, Bhattacharya *et al*⁸⁰ reported that OCP containing 20 µg ethinyl estradiol (EE) with drospirenone had similar effects on free androgen index in PCOS women

as that containing 30 µg EE with drospirenone. The same authors had earlier studied⁸¹ a combination of EE with desogestrel and found significant improvement in hyperandrogenic parameters only during the first six months of treatment and further continuation was useless. A six-month, open-label, randomized trial by Ganie *et al*⁸², of low-dose spironolactone and metformin combination than either drug alone, showed the superiority of the former in terms of improved clinical parameters and compliance to treatment. A comparison of metformin and OCP (EE plus drospirenone) was done as a prospective observational study (n=46) over one year by Suvarna *et al*⁸³, and metformin alone was found to be equally effective in regularizing menstrual cycles and treating hyperandrogenism in Indian women with PCOS. Use of non-hormonal options *i.e.*, metformin and spironolactone, after a period of oral contraceptive use, was retrospectively studied by Kulshreshtha *et al*⁸⁴, in a small group of women with PCOS for regularization of their menstrual cycles. They concluded that 75 per cent of women achieved regular cycles with non-hormonal treatment within one year of stopping OCPs. Saini *et al*⁸⁵ have tried to develop metformin-loaded cationic niosomes amalgamated with thermosensitive gel for intravaginal use in PCOS patients.

Treatment of complications

Infertility

Meenakumari *et al*⁸⁶ studied the use of metformin in PCOS women with luteal-phase progesterone deficiency and reported improvement in the same after four weeks of treatment with metformin 500 mg thrice a day. A prospective randomized trial was conducted where letrozole and clomiphene citrate (CC) were compared in patients with PCOS and anovulatory infertility. After three cycles of treatment, both letrozole and clomiphene showed comparable ovulation rates, but endometrial response and pregnancy rates were better in the former group⁸⁷. In a randomized trial comparing metformin and CC, where the primary outcome was live birth rate (LBR), Kar and Sanchita⁸⁸ reported that the efficacy of metformin was similar to clomiphene in terms of LBR, and their combination gave the highest ovulation rate and LBR. Yanamandra and Gundabattula⁸⁹ conducted a retrospective study of women who failed ovulation induction for primary infertility and hence underwent diagnostic laparoscopy and hysteroscopy followed by ovarian drilling. They showed an enhanced conception rate (around 50%)

with laparoscopic ovarian drilling (LOD). In a small prospective cohort study, the author opined that LOD had no significant effect on AMH levels and thus ovarian reserve⁹⁰. However, as Mitra *et al*⁹¹ pointed out, use of this treatment in unselected cases of PCOS was not prudent owing to its potential risks such as iatrogenic adhesions and ovarian insufficiency. Moreover, many authorities have questioned⁹² the utility of LOD in infertility treatment citing lack of significant rates of clinical pregnancy in evidence-based reviews. Considering the adverse effects of LOD, medical treatment with rosiglitazone and CC was compared with LOD and CC in women with PCOS suffering from infertility in a prospective randomized trial⁹³, and the authors concluded that there was no significant difference in ovulation rate or pregnancy rate between the two groups. A retrospective analysis of four-year data at a tertiary care centre in north India was reported by Singh *et al*⁹⁴ where PCOS patients undergoing IVF cycle with long GnRH agonist protocol were compared with those on fixed GnRH antagonist protocol, and there was no significant difference in pregnancy rate or incidence of ovarian hyperstimulation syndrome between the two groups.

Obesity, diabetes and other co-morbidities

Kumar and Arora⁹⁵ reported the results of a randomized controlled trial (RCT) where they studied orlistat versus metformin for weight reduction and ovulation rates in obese PCOS women. Orlistat was equal to metformin in terms of achieving the outcomes of weight reduction and ovulation. They also noted that orlistat had a better side effect profile and was better tolerated than metformin in this trial population. In a retrospective study, the authors⁹⁶ reported that in women with PCOS with AGT measured by OGTT, six-month therapy with spironolactone and metformin had similar effects in reducing the glucose levels.

Use of unconventional and supplemental pharmacological treatment in PCOS and its complications

Supplementation of vitamin D on insulin sensitivity/resistance parameters in PCOS women was studied by Garg *et al*⁹⁷ in a double-blinded RCT, and they concluded that vitamin D at a dose of 4000 IU daily for six months had no significant effect on these parameters.

Conclusion

PCOS is a heterogeneous clinical syndrome with a multifaceted pathogenesis and is associated with

lifelong morbidity. The clinical manifestations of PCOS include oligomenorrhea, hirsutism, excessive acne and hair loss. The estimated prevalence in India ranged from 3.7 to 22.5 per cent. The prevalence of PCOS was found to be higher or lower depending on the criteria used, which might be the obvious reason for the discrepancy in the prevalence rates among the studies. Considering the vast diversity in the population of India, large-scale community-based studies using internationally accepted criteria, in various geographic regions, are necessary to shed light on the actual prevalence of this disorder. The various metabolic, inflammatory and autoimmune components including the obesity-related cytokines and oxidative stress markers in relation to the pathogenesis of PCOS highlight the multifaceted nature of the disorder and the need for further research into the subject to better delineate the contribution of each of these markers and mediators in the final expression of PCOS. Management and treatment of PCOS included healthy diet, regular physical activity, and medications, which address the associated manifestations and co-morbidities. More randomized trials are needed to find the best treatment options for Indian women suffering from this condition.

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Family history of PCOS, obesity, low fiber diet, and low physical activity increase the risk of PCOS

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ABSTRACT

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Background: Polycystic ovarian syndrome (PCOS) is a common endocrine disorder and leading cause of prolonged anovulation. PCOS has been linked to a variety of long-term health problems, including: heart disease; metabolic syndrome; and diabetes. It is interesting to know the risk factors for PCOS in local settings.

Objective: The aim of this research is to identify PCOS risk factors in our own settings (Asri Medical Center in Yogyakarta), so that we could identify the specific preparation to avoid having disorders personalized in local characteristics.

Methods: This is a descriptive-analytic cross-sectional study. The research was carried out at Asri Medical Center in Yogyakarta, Indonesia, with a total sample size of 92 people who met the inclusion and exclusion criteria. They were divided into two groups: non-PCOS and PCOS. Data were retrieved using the questionnaire. The variables evaluated were nutritional status, physical activity, carbohydrate diet, fiber diet, family history of diabetes, family history of PCOS, and age of menarche. The data was analyzed using the Chi-square test.

Results: Family history of PCOS, obesity, low physical activity and a low-fiber diet proved to differ significantly between the two groups ($p<0.05$).

Conclusion: Family history of PCOS, obesity, low physical activity, low fiber diet had a substantial impact on the occurrence of PCOS.

Latar Belakang: Polycystic ovary syndrome (PCOS) adalah gangguan endokrin umum dan merupakan penyebab penting anovulasi kronis pada wanita. PCOS terkait dengan banyak masalah kesehatan jangka panjang seperti penyakit kardiovaskular, penyakit sindrom metabolik, dan diabetes. Penting untuk menyelidiki faktor-faktor yang meningkatkan risiko PCOS.

Tujuan: Tujuan dari penelitian ini adalah untuk mengetahui faktor risiko PCOS sehingga wanita yang memiliki faktor risiko dapat mengantisipasi untuk menghindari PCOS.

Metode: Penelitian ini merupakan penelitian deskriptif analitik dengan desain penelitian cross sectional. Pengambilan sampel dilakukan di Asri Medical Center Yogyakarta, dengan jumlah sampel sebanyak 92 orang yang memenuhi kriteria inklusi dan eksklusi. Sampel dibagi menjadi 2 yaitu kelompok kontrol (non PCOS) dan kelompok PCOS. Kueisioner digunakan untuk pengambilan data. Variabel yang diamati adalah status nutrisi, aktivitas olahraga, diet karbohidrat, diet serat, riwayat keluarga DM, riwayat keluarga dengan PCOS

dan usia menarche. Analisis data menggunakan uji Chi square.

Hasil: Riwayat keluarga PCOS, obesity, aktivitas fisik rendah dan diet rendah serat terbukti berbeda secara signifikan antara kedua kelompok ($p<0,05$).

Kesimpulan: Ada hubungan yang bermakna antara riwayat keluarga PCOS, obesitas, kurang aktivitas fisik dan diet rendah serat dengan kejadian PCOS.

INTRODUCTION

PCOS is one of the most frequent type of endocrine disorder that affects women of childbearing age. Depending on the diagnostic criteria used in different parts of the world, the prevalence varies significantly. PCOS affects 5–10% of the world's reproductive-age population.^{1,3} Several studies have lately documented an increase in PCOS prevalence due to higher calorie intake, high carbohydrate intake, high fiber intake, and rarely exercise, as well as the tendency to gain weight, which promotes insulin resistance.⁴

The Rotterdam criteria are widely used to establish the diagnosis of PCOS. These criteria include 2 of the following 3 symptoms; anovulation, clinical and/or laboratory hyperandrogenism and ultrasound features typical of PCOS.¹ Approximately 50–70% of women with PCOS exhibit hyperandrogen-related clinical symptoms⁵, and 65–95% have increased insulin resistance.⁶ Genetic factors can influence the occurrence of PCOS but the association between its variables, on the other hand, is still uncertain. Consumption of junk food and a high-carbohydrate diet raises the risk of insulin resistance, which can lead to PCOS.⁷ Due to the hyperinsulinemia and insulin resistance caused by PCOS, one of the hazards is a lack of physical exercise.⁸ Obesity is the next most common risk factor.⁴ The sensitivity of pancreatic beta cells to elevated blood sugar is reduced as the result of obesity.⁹ The tissue's sensitivity to insulin will decrease as a result of this condition, and the pancreas' beta cells will instantly compensate by boosting insulin synthesis, resulting hyperinsulinemia.¹⁰ By complex processes, hyperinsulinemia increases androgen production.^{11,12} The age of menarche is

another factor that may influence the occurrence of PCOS. The early maturation of the adrenal cortex reticular zone promotes an increase in androgen production, resulting in a younger age of menarche. Increased androgen levels, also known as hyperandrogenism, are thought to have a role in the development of PCOS.¹³ Those factors that are described above could be different in our local setting in Yogyakarta. As the term of personalized medicine is increasingly prominent, it is necessary to find out the evidence of the specific characteristics in our own local settings.

METHODS

Design and subjects

This is a cross-sectional research with an analytic observational design. This study undertaken from May to August 2019 at the Asri Medical Center Hospital in Yogyakarta, Indonesia.

Data Collection

In this study, a purposive sample method was adopted. The inclusion criteria were all women who had menstruation issues and were willing to participate in the study. Whereas women with menstrual issues who also had liver disease, diabetes, kidney disease, or other causes of anovulatory infertility were excluded. The study included 46 women with PCOS diagnosed using the Rotterdam criteria, as well as 46 women with other menstrual problems. The data was gathered from the patient's medical records and also questionnaire. Diabetes mellitus (DM) in the family, PCOS in the family, age of menarche, nutritional status, physical activity, carbohydrate diet, and fiber diet are some of the questions asked. Nutritional status is measured by BMI (Obesity: >30; Overweight: 25-30, normal :<25). Physical activity is assessed by frequency of doing exercise in a week (high ≥ 3 times/week; low: < 3 times/week). Carbohydrate diet is assessed by the frequency of consuming high-carbohydrate foods beyond large meals (high: >3 times/week; low: <3 times/week), a high-fiber diet is assessed with frequency

consuming high-fiber foods (high: >3 times/week; low: <3 times/week).

The Health Research Ethics Committee of the Faculty of Medicine and Health Science, University of Muhammadiyah Yogyakarta, Indonesia has given its approval to this study (150/EP-FKIK-UMY/IV/2019).

Statistical analysis

Bivariate data analysis was done using the Chi-square test with a significance threshold of $p<0.05$ and Confidence Interval=95%.

RESULTS

Group characteristics

A total of 46 PCOS patients and 46 non-PCOS individuals participated in the study. The existence of a family history of PCOS, obesity, low physical activity, and a low-fiber diet were all linked with the incidence of PCOS. Based on the research that has been conducted, the following results were obtained using the Chi square test. Family history of PCOS, obesity, low physical activity and a low-fiber diet proved to differ significantly between the two groups ($p<0.05$, Table 1).

Table 1. Risk factor of PCOS

Variable	Group		p
	PCOS	non-PCOS	
Family history of Diabetes Mellitus			
Yes	9	13	0.328
No	37	33	
Family history of PCOS			
Yes	9	1	0.007*
No	37	45	
Age of menarche			
<12 years old (early)	12	12	
12-16 years old (normal)	31	32	0.898
>16 years old (late)	3	2	
Nutritional status			
Obesity	12	4	
Overweight	9	1	0.001*
Normal	24	42	
Physical activities			
High	10	16	0.003*
Low	36	30	
Carbohydrate diet			
High	36	33	0.375
Low	10	13	
Fiber diet			
High	1	11	0.000*
Low	45	36	

* $p<0.05$

DISCUSSION

There was a relationship between PCOS incidence and a family history of PCOS in this study, however it was not associated to a family history of diabetes mellitus. Genetic factors have a role in the pathophysiology of PCOS. Although this genetic explanation has not been verified, various theories suggest that PCOS is inherited by an autosomal dominant gene and several candidate genes that may impact PCOS occurrence.

The pathophysiology of PCOS is linked to an inherited genetic component; genetic factors influence the PCOS phenotype in at least 10% of cases. Several chromosomal locations and potential genes for PCOS have been found through genome-wide association studies (GWAS).¹⁴ According to a meta-analysis, polymorphisms in the steroidogenic acute regulatory gene (StAR), gonadotropin-releasing hormone receptor (GnRHR), follicle stimulating hormone receptor (FSHR), fat mass and associated obesity, insulin receptor (IR), IR substrate (IRS), vitamin D receptor (VDR) are all involved in the pathophysiology of PCOS.^{14,15} Despite the fact that most women with PCOS have insulin resistance, pancreatic B cell dysfunction, poor glucose tolerance, and/or type 2 diabetes, PCOS does not appear to be associated with genetic changes that increase the risk of type 2 diabetes. Family history of DM, on the other hand, is linked to the phenotype of PCOS. Sex Hormone Binding Globulin (SHBG) and Free Androgen Index (FAI) are both associated with a family history of DM. PCOS individuals with a family history of diabetes have higher rates of Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and FAI. A family history of diabetes is associated with elevated hemoglobin A1c (HbA1c) levels in PCOS women.¹⁶

Our findings indicate a link between obesity and the occurrence of PCOS. Patients with a family history of obesity had a greater percentage of body fat than those who did not. PCOS individuals who are obese are more prone to have irregular menstrual cycles and maturation

of ovarian follicles.¹⁷ Obesity appears to trigger insulin resistance that causing PCOS, and women with PCOS appear to be more prone to obesity.¹⁸ Obese PCOS women were shown to have higher systolic and diastolic blood pressure, as well as fasting blood sugar, insulin, HOMA-IR, total cholesterol, and triglycerides.⁶ In roughly 50-70 percent of PCOS women, and 95 percent of obese PCOS women, IR occurs. Obesity causes changes in adipokine production, such as a decrease in adiponectin and an increase in leptin, which leads to an increase in proinflammatory cytokines.¹⁹ Obesity and insulin resistance enhance the release of inflammatory cytokines such as high-sensitivity CRP (hs-CRP), IL-6, IL-18, and tumor necrosis factor alpha (TNF- α) in PCOS women, which is one of the low-grade chronic inflammatory illnesses.^{20,21} This increase in proinflammatory cytokines regulates IR by boosting IRS-1 serine phosphorylation and reducing Akt substrate of 160 kDa (AS160) phosphorylation, resulting in a decrease in the expression of the glucose transporter type 4 (GLUT-4) and decreasing glucose transport into cells.²² Obesity reduces the ability of the body's cells to fight insulin. The sensitivity of pancreatic beta cells to elevated blood sugar is reduced as a result of obesity. Because the tissue's sensitivity to insulin reduced, pancreatic beta cells will be instantly adjusted by boosting insulin synthesis, resulting in hyperinsulinemia. By a variety of processes, hyperinsulinemia increases androgen production.^{19,24}

On the other hand, PCOS also linked to a poor diet. The diet in question involves the proportion, quantity, variety, or a mix of different drinks and meals, as well as the frequency with which they are typically consumed. A healthy diet consists of foods that meet the body's energy requirements. However, there are a few PCOS women who consume more food than their bodies require. Dietary habits such as overeating in junk food and consuming macronutrients in excess of the body's requirements can increase the risk of polycystic ovaries. Content high carbohydrate, high calorie, and low fiber content

in junk and fast food raises the risk of insulin resistance, which can lead to PCOS.²³ This study found no link between excessive carbohydrate consumption in the diet and the occurrence of polycystic ovarian syndrome. Previous research has suggested that a high-carbohydrate diet can raise the risk of polycystic ovarian syndrome in women.⁷ This disparity might be attributed to discrepancies in measuring methodologies. In this study, measures were taken solely through the completion of questionnaires, with no in-depth dietary assessment.

The findings of this study revealed that there was no statistically significant difference in menarche age between the PCOS and non-PCOS groups. In comparison to normal girls, PCOS girls have a wide range of menarche ages. Menarche onset is influenced by a number of factors, including BMI and genetic variance. PCOS women have a delayed beginning of menarche due to delayed follicular development in prepubertal, hormonal imbalances of estradiol, progesterone, and androgens, and hormonal imbalances of estradiol, progesterone, and androgens. Girls who are later diagnosed with PCOS may have primary amenorrhea as a consequence. Menarche may occur early in PCOS girls who have a history of deliveries with dysmaturity and smaller for gestational age newborns. Menarche appears earlier in PCOS girls with a high BMI. Furthermore, genetic variations can influence the age of menarche in women with PCOS.^{24,25}

This research discovered a link between low physical activity and the occurrence of PCOS. Low physical activity might contribute to the development of PCOS, which is characterized by hyperinsulinemia and insulin resistance. Physical activity that is sufficient and consistent is directly tied to the metabolism of stored glucose in the muscles for use as energy, and if the glucose level is low, the muscle will compensate by pulling glucose from the bloodstream. This is what causes blood glucose levels to drop, allowing for better blood glucose control.⁸ Insulin secretion and sensitivity are affected by physical exercise in patients with polycystic ovarian syndrome. Excessive fat accumulation occurs in the absence

of physical activity, resulting in an increase in the amount of free fatty acids (FFA) and triglyceride levels.²¹ In PCOS women, this low-density lipoproteins (LDL) saturated fat inhibits insulin action, resulting in hyperinsulinemia. Insulin resistance will diminish and insulin sensitivity will rise when you get enough exercise or physical activity. Long-term calorie restriction (5-6 months) and increased physical activity can result in weight loss of 5-10% of the original weight. IR and hyperandrogenism, as well as menstrual function and fertility, can all be affected by this disorder. Additionally, it has the potential to promote long-term metabolic health.²³

CONFLICT OF INTEREST

Family history of PCOS, obesity, low physical exercise, a low-fiber diet were major PCOS risk factors.

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REVIEW

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Genetic, hormonal and metabolic aspects of PCOS: an update

V. De Leo*, M. C. Musacchio, V. Cappelli, M. G. Massaro, G. Morgante and F. Petraglia

Abstract

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting 5–10 % of women of reproductive age. It generally manifests with oligo/anovulatory cycles, hirsutism and polycystic ovaries, together with a considerable prevalence of insulin resistance. Although the aetiology of the syndrome is not completely understood yet, PCOS is considered a multifactorial disorder with various genetic, endocrine and environmental abnormalities. Moreover, PCOS patients have a higher risk of metabolic and cardiovascular diseases and their related morbidity, if compared to the general population.

Keywords: PCOS, Genetic, Insulin-resistance, Hyperandrogenism, Infertility, Metformin, Oral contraceptives, Myo-inositol

Background

Definition and diagnostic criteria

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women and major cause of anovulatory infertility. PCOS patients can present a wide range of signs and symptoms, which make difficult the precise grading of the condition. Diagnosis of PCOS is currently based on the criteria of the ESHRE/ASRM Rotterdam consensus meeting in 2003 [1], which broadened the previous NIH classification of 1990 [2]. It based on at least two of the following features: oligo-anovulation, hyperandrogenism and polycystic ovaries by ultrasound [1]. In 2006, the Androgen Excess Society (AES) set up a committee of experts to review all the data published on PCOS for the purpose of simplifying diagnosis [3]. The AES criteria require clinical and/or biochemical hyperandrogenism simultaneously with oligo/anovulation and ultrasonographic evidence of polycystic ovaries.

Although the aetiology of PCOS is not completely understood yet, PCOS is considered a multifactorial disorder with various genetic, metabolic, endocrine and environmental abnormalities [4].

There is increasing evidence suggesting that PCOS affects the whole life of a woman, can begin *in utero* in

genetically predisposed subjects, it manifests clinically at puberty, continues during the reproductive years. It can also expose patients to increased risk of cardiovascular disease, hypertension, diabetes and other metabolic complications, especially after menopause [4]. During the fertile period it may cause anovulatory infertility and could be associated with increased prevalence of gestational complications, such as miscarriage, gestational diabetes and preeclampsia [5]. Early diagnosis is therefore crucial by enabling close follow-up and in an attempt to reduce the risk of such complications.

It is now widely recognised that insulin resistance, manifesting above all in obese or overweight women, but often also in lean PCOS women, is one of the key to this complex disorder. It determines hyperandrogenism by acting synergically with luteinising hormone (LH) on ovarian steroidogenic enzymes and on sex hormone-binding globulin (SHBG) production by the liver [5].

Diagnostic workup includes hormonal evaluation of androgen levels, clinical evaluation of hirsutism through Ferriman-Gallwey score and ultrasonographic examination of the number of antral follicles and ovarian volume. Insulin resistance should be evaluated by HOMA INDEX (product of fasting plasma insulin [μ U/L] and glucose [mmol/L] concentrations divided by 22.5). Future diagnostic approaches could be ultrasonographic 3D evaluation of follicles and is under discussion the role of anti-mullerian hormone (AMH) [6, 7].

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Etiopathogenesis and pathophysiology: role of genetic, environmental and endocrine factors

Genetic and endocrine factors, together with environmental influences. In the research of etiopathogenesis of the syndrome and in the subsequent pathophysiological expression play a role genetic and endocrine as well as environmental factors. The most interesting hypothesis was proposed by Franks et al. [4], who defined PCOS as a genetically determined ovarian pathology characterised by over-production of androgens and manifesting heterogeneously according to the interaction of this genetic "predisposition" with other genetic and environmental factors. This hypothesis is persistent by the finding of polycystic ovaries in pre-pubertal girls [4, 8]. Studies in rhesus monkeys have demonstrated that exposure of foetuses to high levels of androgens during intrauterine life determines the onset of clinical manifestations of PCOS during adolescence. Studies in sheep have shown that an excessive androgen exposure during foetal life influences early ovarian follicular activity and it may explain the typical altered folliculogenesis shown in PCOS [4, 8].

The aforementioned observations may suggest that exposure of the foetal hypothalamus-pituitary-ovarian axis to androgen excess may trigger a series of events that could determine PCOS onset at puberty.

The source of intra-uterine androgens excess is unlikely to be maternal, since the foetus is protected by placental aromatase activity and by high maternal SHBG concentrations.

The expression of aromatase in the placenta of PCOS women may be diminished [9] and this could potentially be unable to prevent foetal testosterone (T) excess in PCOS pregnancies [10]. It has been seen that the prevalence of decreased aromatase required to carry out T excess in female fetuses was reported to be extremely rare [11]. On the other hand, recent studies on hypertensive preeclamptic pregnancies have demonstrated a significant reduction in placental ability to synthesize oestrogens, indicating a gestational impairment of T aromatization that is more common than was previously considered [12, 13].

The source of androgens excess is more likely to be the foetal ovary, which is normally quiescent, but it could produce an excess of androgens in response to maternal hCG in subjects genetically predisposed to PCOS.

In newborn daughters of PCOS women, elevated T levels have been observed in the umbilical venous blood [14, 15]. This finding was not confirmed in other studies that demonstrated instead a reduced umbilical cord blood androstenedione levels [9, 16]. Hickey et al., showed no increase in T levels in umbilical cord blood of adolescent girls diagnosed with PCOS [17]. Taken the ovary as a key foetal site for gestational T excess, during

critical mid-gestational age for target organ differentiation [9], studies at the time of birth, are likely to be too late to detect any remaining hormonal differences [18, 19]. The mid-gestational T excess in human female foetuses can be accompanied by gestational hyperglycaemia and foetal hyperinsulinemia. Interestingly, elevated mid-gestation maternal T levels predict high AMH levels in adolescent daughters [20]. Since elevated AMH represents a characteristic of adolescents and women with PCOS [21] and daughters of PCOS women [22, 23], such associations might suggest a cross-generational relationship between the degree of maternal hyperandrogenism and the development of PCOS in their daughters.

Complete manifestation of the syndrome occurs at adolescence, when the hypothalamus-pituitary-ovarian access is activated. At this time, metabolic changes leading to modifications in the distribution of body fat also occur. In particular, at puberty there is a physiological increase in insulin levels, determining on one hand a reduction in SHBG levels with amplification of the effects of circulating androgens, and on the other hand, direct stimulation of ovarian steroidogenesis [24]. In women with PCOS, the physiologic hyperinsulinemia of adolescence may be a triggering factor for the development of hyperandrogenism and anovulation. Girls predisposed to insulin-resistance and overweight are even more at risk of developing early adrenarche and subsequent PCOS at adolescence [24] (Fig. 1).

Daughters of women with PCOS evaluated during early childhood (age 4–8 years) and early puberty (age 9–13 years) have exaggerated adrenarche compared with daughters of non-PCOS women of similar pubertal stage and body mass index (BMI) [25]. This is consistent with a role of obesity-related insulin-resistance in causing hyperandrogenemia in these girls through an effect of insulin on adrenal and ovarian steroidogenesis [26], manifesting as early adrenarche [27] and subsequent PCOS [28]. Such hyperandrogenemia appears to modulate gonadotropin levels, as has been demonstrated in obese peri-pubertal girls who were found to have increased LH frequency but low LH amplitude, and diminished overnight LH pulse amplitude compared with normal-weight girls [29]. These changes may reflect initial effect of obesity on LH pulses [30]. Subsequently, hyperandrogenemia reduces the inhibition of GnRH pulse frequency by progesterone, causing rapid LH pulse secretion and further increase in ovarian androgen production [30–32].

Epigenetics and PCOS

Since the development of other diseases in adulthood, induced by nutritional or environmental factors in utero, usually involves an epigenetic mechanism, it seems likely that the same mechanism may also occur in PCOS.

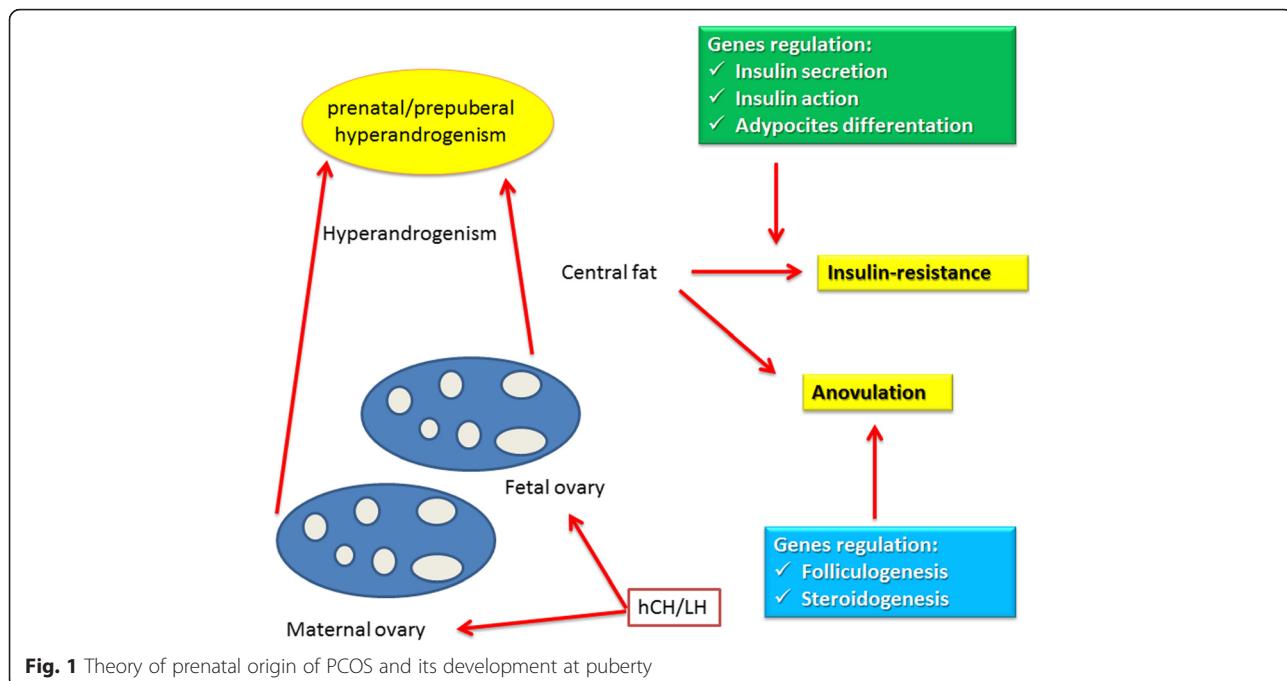


Fig. 1 Theory of prenatal origin of PCOS and its development at puberty

According to this hypothesis, exposure to hyperandrogenism *in utero* may lead to epigenetic reprogramming anomalies in foetal reproductive tissue, which is translated into the PCOS phenotype in adulthood. Moreover, if such epigenetic alterations persist in the germ cell line, transgenerational transmission of the PCOS phenotype is promoted. Clearly other genetic factors (i.e. linked to insulin resistance) and post-natal environmental factors (i.e. diet) may contribute to the development of PCOS phenotype, possibly in association with epigenetic anomalies.

In particular, epidemiologic and clinical studies conducted largely in adult human populations suggest a link between foetal growth restriction, and subsequent risk of type 2 Diabetes Mellitus (DM) and cardiovascular disease [33, 34]. The increased risk for these metabolic diseases has been linked to elevated insulin resistance in young individuals exposed to an adverse *in utero* environment and born small for gestational age (SGA) [35, 36]. These studies support an overall relationship between foetal growth restriction and increased adiposity and insulin resistance starting early in the childhood period. In addition to the *in utero* environmental factors, genetic polymorphisms may modulate insulin resistance parameters in SGA individuals. This may partially explain the variable degree of insulin resistance in subjects exposed to an adverse *in utero* environment [37]. At the other extreme, over-nutrition of these foetuses appears to have long-term effects on obesity, insulin resistance, and predisposition to disorders of glycemic regulation. Offspring of mothers with diabetes during pregnancy

have a higher frequency of childhood obesity and earlier onset of impaired glucose tolerance [38, 39] and type 2 DM [40]. Given the effect of insulin on modulating ovarian [41] and adrenal [42] steroidogenesis, a role of intrauterine adverse events which lead to insulin resistance and/or hyperinsulinemia may predispose adolescents to PCOS. Overall, these studies indicate that at least some metabolic components of the PCOS phenotype are programmed *in utero*, particularly the tendency for higher fat mass, visceral adiposity, and insulin resistance.

If further research verifies this hypothesis, new prospects for preventive treatment during the critical prenatal period will be mandatory.

Genetic factors

Increasing evidences over many years point to familial aggregation of women with PCOS, hyperandrogenism and metabolic alterations [43]. The model of inheritance of PCOS has not yet been defined. Some researchers have postulated autosomal dominant transmission linked to a single genetic defect, but most authors define PCOS as a polygenic pathology. It is also possible that a particular gene in a given family may have a predominant effect, influencing the phenotypic manifestations of the syndrome. The main candidate genes are those encoding for factors involved in the synthesis, transport, regulation and effects of androgens. Other candidate genes are those encoding for factors involved in insulin metabolism, such as insulin receptors, signalling cascade proteins responsible for binding of insulin to its receptor, IGF system, other growth factors and the gene encoding

for Calpain-10 enzyme, responsible for insulin secretion and action [43].

An association has also been found between “pro-inflammatory” genotypes and PCOS, linked to polymorphism of genes coding for TNF-alfa, IL-6 and IL-6 receptor [43]. Finally, recent evidence of altered early gonadotropin-independent folliculogenesis in women with PCOS suggests that genes involved in folliculogenesis may also be candidates in the etiopathogenesis of this syndrome [1].

However, only a few PCOS susceptibility genes have been repeatedly identified in studies of women with Chinese or European ancestry: allelic variants of fibrillin-3 (FBN3) [44–47], and variants of LH receptor (LHR) [44, 48, 49]. FBN3 encodes for an extracellular matrix protein that regulates transforming growth factor (TGF) signaling. Its PCOS associated allelic variant, A8, manifests a metabolically distinct phenotype, including insulin resistance [50]. FBN3 expression, is limited to early to mid-gestation in many organs and tissues, including the ovary [51, 52]. Such a gestational stage includes a period of foetal developmental at which T exposure induces altered DNA methylation of TGF-beta-regulating genes and subsequent PCOS-like traits [53]. Due to the degree and type of fibrillin expression contributes to differences in elasticity of cell extracellular matrix interactions and storage of TGF-beta, fibrillin may provide gestationally relevant [51] tissue-specific bases for cell mediated engagement of extracellular matrix-stored TGF-beta in proliferation, differentiation, and apoptosis [54, 55]. In the ovary, variants of LHR may diminish or enhance pituitary LH stimulation of ovarian theca and stroma cell T production, ovarian follicle development, LH surge-induced ovulation, and corpus luteum function [56], while in adipocytes, LHR variants may alter LH stimulation of adipogenesis [57]. Variants in these multi-organ system genes could contribute to genetically determination of PCOS phenotypes for reproductive and metabolic pathophysiology.

Environmental factors

Although the prevalence of PCOS is similar in all countries, ethnic factors influence the phenotypic manifestations of the syndrome. The prevalence of PCOS among Caucasian women, varies from 4.7 % in Alabama, to 6.5 % in Spain and 6.8 % in Greece [58]. In the United Kingdom, PCOS and type II diabetes are more frequent in women of Asian origin [58]. These observations suggest the existence of different environmental factors, such as diet, physical activity and life-style in general.

The increasing effects of metabolic disorders in economically developed countries has led authors to suggest that the pathogenic mechanisms of these disorders are associated with evolutionary advantages in terms of

survival [58]. On one hand, insulin resistance increases the availability of glucose for brain metabolism, while on the other, it increases blood pressure by mechanisms such as fluid retention and increase in the sympathetic tone. It also induces modifications in clotting factors (hypercoagulation) and a propensity for obesity characterised by a proinflammatory condition with increased secretion of cytokines and inflammatory factors. All the aforementioned alterations make the subject more resistant and favours survival when faced with stressors such as reduced availability of food, wounds and epidemics. The relative infertility of these women increases the interval between pregnancies and reduces the number of children, favouring survival of mothers and children. In the absence of stressors, as in the case of developed countries, these pathogenic mechanisms predispose to cardiovascular disease and atherosclerosis.

Endocrine factors

Ovarian folliculogenesis is regulated by a delicate equilibrium between extra- and intra-ovarian factors. Disturbance of this equilibrium may alter and compromise follicular development and the formation of mature oocytes, leading to infertility (Fig. 2).

Extraovarian factors

Extraovarian factors include a series of endocrine, paracrine and metabolic alterations, which by causing abnormalities in the follicular microenvironment, may alter folliculogenesis and oocyte development. These alterations include FSH deficit, hypersecretion of LH, hyperandrogenemia of ovarian or adrenal origin and hyperinsulinemia with insulin resistance [59]. Folliculogenesis and oogenesis also depend on intraovarian factors, especially follicular fluid factors (FFFs) [59] that are directly correlated with their levels in plasma. Recent studies suggest that FFFs implicated in folliculogenesis of polycystic ovaries belong to the family of growth factors including cytokines and inhibins [59].

Vitamin D is an essential regulator of bone and mineral homeostasis. Recent studies have demonstrated hypovitaminosis D is associated with an increased likelihood of developing metabolic disorders. [60]. Vit.D deficiency has also been demonstrated in patients with POCS [61]. Obese patients with PCOS have been shown to have lower serum levels of 25-OH-D than non obese women with PCOS and vitamin D deficiency has been suggested to have a role in the development of insulin resistance (IR) and impaired glucose tolerance in such patients [62].

Altered secretion of GnRH and gonadotropins

Although the etiopathogenesis of PCOS is still controversial, series of hypotheses have been proposed in the

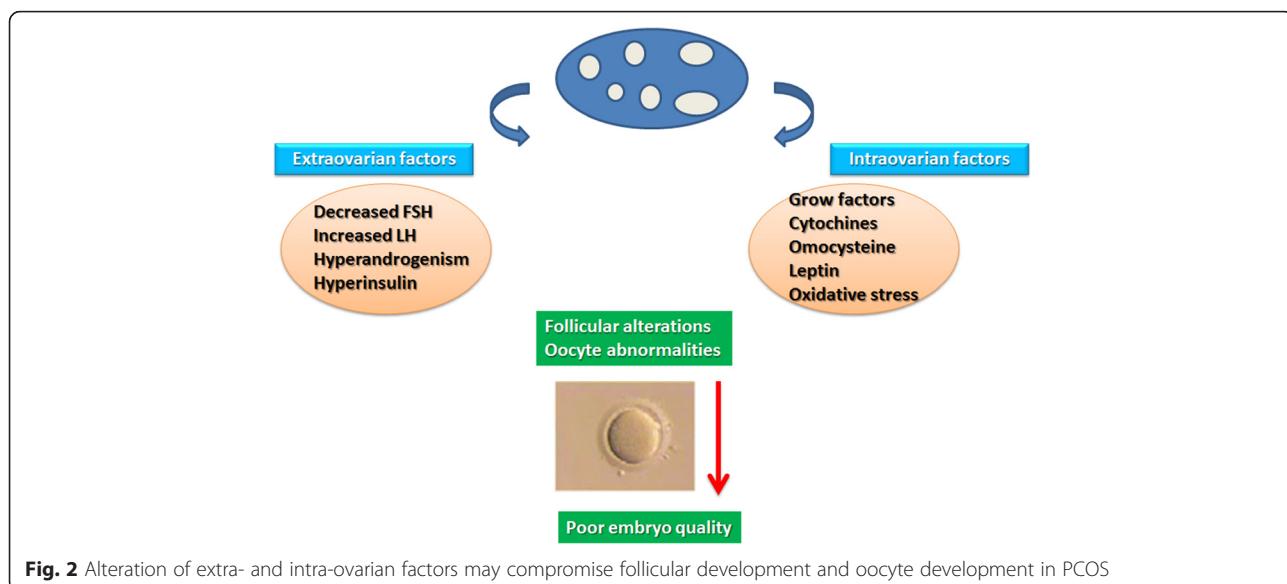


Fig. 2 Alteration of extra- and intra-ovarian factors may compromise follicular development and oocyte development in PCOS

recent decades. A high percentage (55–75 %) of women with PCOS have an elevated LH/FSH ratio presumably due to high levels of LH rather than reduced production of FSH. GnRH stimulation causes, indeed, excessive LH production [63] in those women. This condition may be determined by a higher frequency or amplitude of GnRH [60]. It is not yet clear whether alteration of the hypothalamo-pituitary axis in PCOS is primary or secondary to alterations in steroid hormones secretion. The role of FSH is to recruit ovarian follicles and stimulate their growth: 2–5 mm follicles are sensitive to FSH, whereas larger ones (6–8 mm) acquire aromatase activity and may increase oestradiol (E2) and inhibin B, reducing levels of FSH in late follicular stage. On the other hand, PCOS patients (having LH and FSH concentrations higher and lower than normal, respectively)

accumulate antral follicles (2–8 mm) that differentiate early and undergo premature growth arrest [63]. Hypersecretion of LH in these women may promote early luteinisation of granulosa cells and contribute to early growth arrest of antral follicles (Fig. 3). LH may also activate premature meiotic processes that damage oocyte quality and contribute to the formation of embryonic aneuploidies [64].

Altered dopaminergic and opioid tone has also been found in these patients. However, administration of opioid antagonists or dopaminergic agonists in PCOS patients have little influence on LH pulsatility [63].

Among the excitatory elements of the reproductive axis, kisspeptins have recently emerged as essential upstream regulators of GnRH neurons, with indispensable roles in key aspects of reproduction, such as brain sex

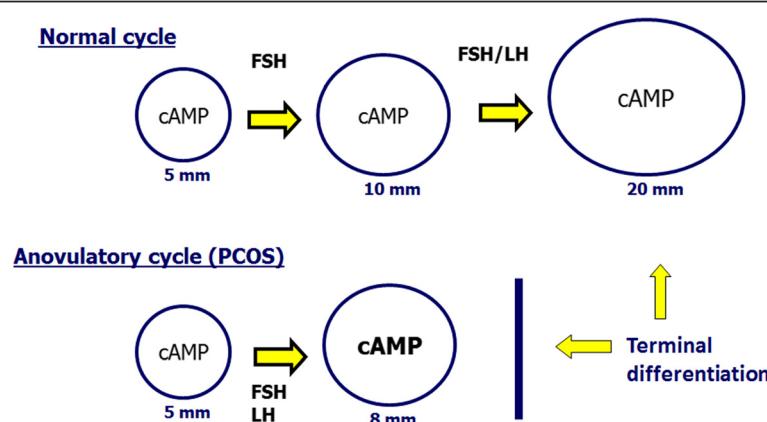


Fig. 3 In a normal cycle, only the dominant follicle responds to LH when it reaches 10 mm diameter. In PCOS the response to LH occurs inappropriately in smaller follicles and many antral follicles reach terminal differentiation before time, producing a greater quantity of steroids and inhibin B that exert negative feedback on FSH production

differentiation, puberty onset, gonadotropin secretion, ovulation, and the metabolic regulation of fertility [64–68]. Kisspeptins are a family of closely related peptides of different amino acid length (such as Kp-54 and Kp-10) that are encoded by the Kiss1 gene and operate through the G protein-coupled receptor Gpr54, also named kisspeptin receptor or Kiss1R [64, 65, 68]. Expression of the elements of the Kiss1 system in different ovarian compartments has been documented in human and rodent species [69, 70]. Ovarian expression of Kiss1 is under the positive control of gonadotropins [69]. On the other hand, local mediators also participate in the control of ovarian Kiss1 expression; inhibition of prostaglandin synthesis, which causes ovulatory dysfunction, evokes a marked suppression of ovarian Kiss1 mRNA levels during the periovulatory period. Moreover, inhibition of prostaglandin synthesis blocks the positive effect of gonadotropins on Kiss1 gene expression in the ovary [70].

Taken as a whole, these observations suggest a potential role of locally produced kisspeptins in the control of ovulation. Whether alterations of such local actions of kisspeptins might contribute to the ovulatory dysfunction seen in PCOS warrants specific investigation.

Ovarian and extraovarian hyperandrogenism

Hyperandrogenemia is the most typical hormonal alteration of PCOS. Biochemically, hyperandrogenism is usually assessed by assay of total testosterone (TT), free testosterone (fT), sex hormone binding globulin (SHBG), androstenedione (A), 17-hydroxy progesterone (17-OHP) and dehydroepiandrosterone sulphate (DHEAS) in serum and by calculation of the free androgen index ($FAI = (TT/SHBG)100$). Women with PCOS often have

higher than normal serum concentrations of all these androgens. Hyperandrogenism has a multifactorial origin attributed mostly to the ovaries with a substantial contribution from the adrenals and a minor contribution from fatty tissue.

Biosynthesis of androgens is mediated by microsomal P450c17 which catalyses 17–20 lyase activity. Alterations in P450c17 at transcriptional and post-transcriptional level have been implicated in the aetiology of PCOS [71]. These women show, indeed, relative inhibition of 17–20 lyase activity with respect to 17-hydroxylase, leading to an increased 17OHP/A ratio. Administration of GnRH or hCG in women with PCOS causes excessive production of 17OHP [68]. Low aromatase activity has also been demonstrated in women with PCOS. Aromatase is a granulosa cell enzyme that converts androgens into estrogens. It may be partly responsible for hyperandrogenism in this syndrome [70, 71] (Fig. 4).

Elevated levels of androgens may have a negative impact on follicular development, causing atresia, and on ovarian development, inhibiting meiotic maturation by decreasing oscillations of intracytoplasmic calcium levels [59].

Hyperinsulinemia and insulin resistance

Insulin resistance is defined as a pathological condition in which a cell, tissue or organism requires above-normal quantities of insulin to respond normally. It causes increased insulin secretion by pancreatic β cells and compensatory hyperinsulinemia, while blood glucose remains normal. When the response of pancreatic cells decreases, the patient develops glucose intolerance or type II diabetes [5].

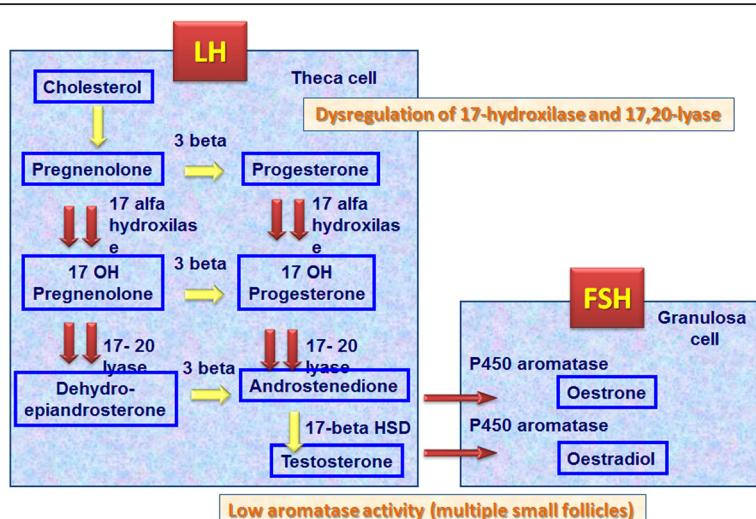


Fig. 4 Relative inhibition of 17–20 lyase activity with respect to 17-hydroxylase has been found in women with PCOS. This leads to an increase in the 17OHP/A ratio and reduction of aromatase activity, the enzyme of granulosa cells that converts androgens into estrogens

Since many women with PCOS seem to have insulin resistance, compensatory hyperinsulinemia is thought to contribute to hyperandrogenism [72, 73] by direct stimulation of ovarian production of androgens and by inhibition of liver synthesis of SHGB that increases testosterone availability. Insulin also increases ACTH-mediated adrenal androgen production and accentuates LH-stimulated ovarian steroidogenesis [73] (Fig. 5).

About 60–70 % of women with PCOS are obese or overweight, and obesity is associated with insulin resistance. However, many studies have shown that insulin resistance is also present in many lean women with PCOS [5, 73]. The mechanisms leading to insulin resistance consist of a defect in insulin binding to its receptor or to changes in insulin signal transmission [5, 74]. However, the ovaries of these women maintain approximately a normal response to insulin. A partial elucidation of this mechanism is explained by the action of insulin on the ovary through the IGF-1 receptor. This binding occurs when insulin reaches high concentrations, as compensatory hyperinsulinemia. Moreover, the action of insulin on the ovary uses the inositol glycan system as a signal mediator, a different mechanism from the system

activated by phosphorylation of the receptor at tyrosine level in other tissues [75]. An increase was observed in urinary clearance of inositol in some American and Greek women with PCOS. It reduces tissue availability of inositol. This mechanism could contribute to insulin resistance present in PCOS women [76]. Hyperinsulinemia directly stimulates ovarian steroidogenesis by acting on thecal and granulosa cells. *In vitro* studies have demonstrated that insulin stimulates thecal cell proliferation, increases secretion of androgens mediated by LH and increases cytochrome P450 expression of LH and IGF-1 receptor. Since the enzymes involved in ovarian steroidogenesis are similar to those of the adrenals, many studies have shown that insulin may act directly as stimulator adrenal steroidogenesis [5, 73]. The administration of metformin, an insulin-sensitising drug, significantly reduces production of 17OHP, T and A in response to ACTH in PCOS women [5].

In vitro data, obtained with cell culture models, indicate that co-incubation of insulin and FSH with bovine oocytes promotes up-regulation of LH receptors on granulosa cells of antral follicles. It contributes to arrest of follicular growth, inhibits of aromatase activity, and

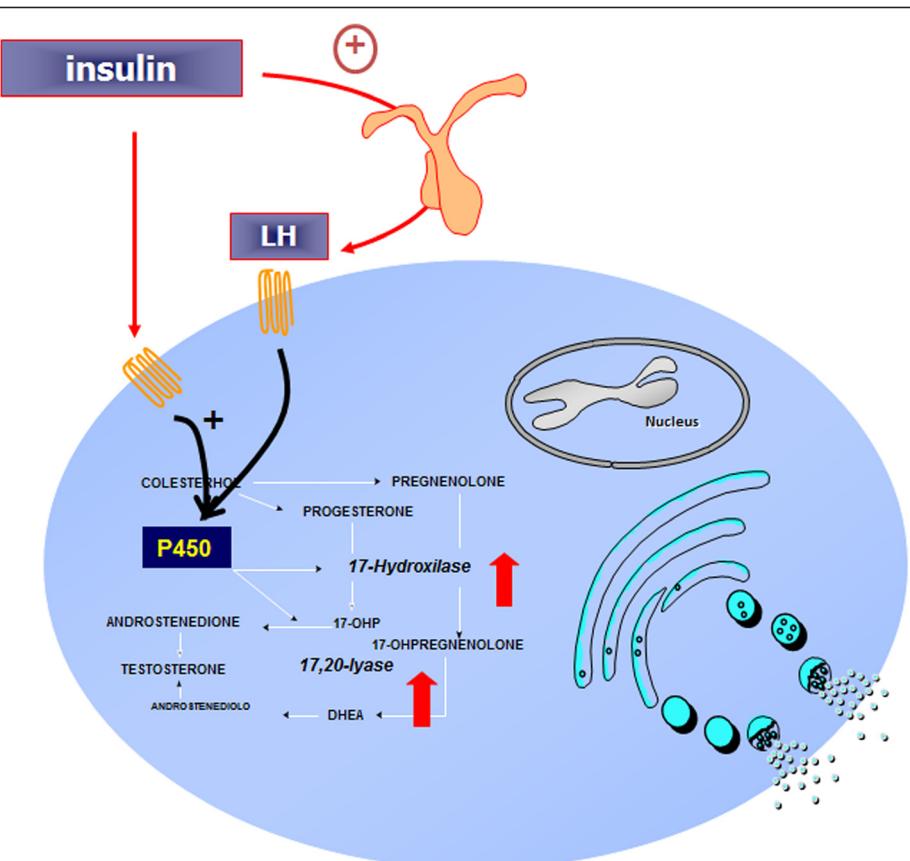


Fig. 5 Hyperinsulinemia stimulates directly cytochrome p450 enzymes in the ovary or indirectly through action of LH or IGF-1, causing hyperandrogenism

potentially triggers to ovarian hyperandrogenism. Looking at the molecular level, insulin binds to its receptor on granulosa and thecal cells and on oocytes where it may alter expression of certain genes involved in the meiotic process of the oocyte [59].

In vitro studies have demonstrated that insulin also has receptors at hypothalamus and pituitary levels, through which it stimulates the release of FSH and LH under basal conditions and after GnRH stimulation [5, 59].

Furthermore, insulin also influences hyperandrogenism by inhibiting liver synthesis of SHBG² and IGFBP-1, which binds IGF-1 [5, 59]. IGF-1 is a growth factor with endocrine action. It is mainly synthetized by the liver, but is also produced by other tissues, including the ovaries, where it has autocrine/paracrine functions. Many studies have shown a significant increase in the IGF-1/IGFBP-1 ratio in women with PCOS. An increased availability of IGF-1 in thecal cells can induce increased production of androgens. Moreover, IGF-1 stimulates oestrogen production by granulosa cells and synergically acts with FSH and LH in modulating expression of aromatase in granulosa cells. IGF-1, like insulin, also exerts an indirect control on ovarian steroidogenesis through the hypothalamus-pituitary axis. It induces, in fact, expression of GnRH and release of gonadotropins by the pituitary [5, 59]. Treatment with insulin-sensitising drugs increases IGFBP-1 levels, reduces the IGF-1/IGFBP-1 ratio and decreases IGF-1 availability in peripheral tissues [77].

Intra and extra-ovarian factors

Epidermal growth factors (EGF)

Epidermal growth factor (EGF) plays an important role in regulation of cell growth, as well as in proliferation and differentiation through interaction with its receptor EGFR (ErbB1, ErbB2-4) [59, 71]. In the human ovary, EGF is present in follicular fluid (FF), where it regulates follicle development and oocyte maturation. In women with PCOS, FF EGF levels are higher than in normal ovulating women. In PCOS condition, EGF may inhibit granulosa cell oestrogen synthesis, which is translated into arrest of follicle growth [59, 71].

Insulin-like growth factors (IGF)

These growth factors are multifunctional polypeptides with insulin-like activity that play important regulatory functions for follicle and oocyte development [59, 71, 78]. Circulating IGFs are produced by the liver: IGF-1 is secreted by thecal cells, whereas IGF-2 is synthesised by granulosa cells and IGFBP (insulin-like growth factor binding protein) has been found in FF and is expressed by granulosa and thecal cells [78]. FF IGF-1 levels in PCOS women are elevated than in normal women,

whereas IGFBP-1 are lower in PCOS patients, causing the arrest follicle growth [78].

Neurotrophin growth factor (NGF)

NGF is not only involved in development of the nervous system but also acts in the ovaries of humans and other mammals. It plays a fundamental role in folliculogenesis and oocyte maturation [59, 71, 78]. This factor promotes nuclear and cytoplasmic maturation of oocytes, and processes essential for the development of good quality oocytes and embryos. Elevated NGF concentrations in FF have been reported in women with PCOS [59, 71, 78].

Transforming growth factor-*b* (TGF-beta)

Members of the TGF-beta family play a role in follicle growth and oocyte development. They include anti-mullerian hormone, activin, follistatin, inhibins, bone morphogenetic protein (BMP)-9 and growth and differentiation factor (GDF)-9 [78, 79]. In different occasions, these growth factors may promote or block follicle growth and/or differentiation [74, 80].

Anti-Mullerian hormone (AMH)

AMH is a homodimeric glycoprotein that inhibits the development of Mullerian ducts in male embryos [59]. It is expressed by granulosa cells in the ovaries of women of reproductive age, where it controls the formation of primary follicles and follicle recruitment by FSH. Therefore playing an important role in folliculogenesis [74, 78, 79]. Women with PCOS have higher serum and FF concentrations of AMH compared to controls. This is closely correlated with greater development of antral follicles and arrest of follicular growth [79, 80]. High serum levels of AMH are directly correlated with an increase in testosterone and/or LH concentrations in women with PCOS, as well as with altered oocyte maturation and low embryo quality [64, 80]. Furthermore, elevated concentrations of AMH in FF of women with PCOS are correlated with a higher percentage of immature oocytes and lower fertilisation rates compared to women with endometriosis or pelvic adhesion syndrome [80].

Activin, follistatin and inhibin

Activin, follistatin (FS) and inhibin are polypeptides, which were originally isolated from ovarian FF. FS is a binding protein produced by ovarian granulosa cells; cellular growth and differentiation is regulated by autocrine/paracrine action. Over-expression of FS has been associated with arrest of follicle growth and reduced oocyte development. Activin is mostly secreted by smaller follicles. It promotes follicle development by increasing granulosa cell response to FSH stimulation; it decreases androgen synthesis and stimulating oocyte maturation. Besides inhibiting FSH production, inhibins

are produced by the dominant follicle and stimulate thecal cells to produce androgens as substrate for estrogen formation [59, 74, 78, 79]. An increased FS/activin ratio and elevated concentrations of inhibin B have been found in PCOS [59, 74, 78, 79].

Vascular endothelial growth factor (VEGF)

VEGF is a homodimeric glycoprotein expressed in granulosa and thecal cells [78] and also present in FF [59]. It plays an important role in angiogenesis, follicular vascularisation and intra-follicular oxygenation. It has therefore an impact of follicle maturation, oocyte quality, fertilisation and embryo development [59, 74, 78, 79]. The alterations in FF concentrations of VEGF in patients with PCOS is indicative of oocyte immaturity [78]. The elevated concentrations are useful as an indicator of oocyte maturity, successful fertilisation and embryo development in women with PCOS [78].

Interleukins (IL)

Interleukins are a group of cytokines produced by leukocytes. In particular, IL-1, IL-2, IL-6, IL-8, IL-11 and IL-12 play different roles in the regulation of folliculogenesis, ovulation and corpus luteum function. Concentrations of IL-12 in FF differ from immature follicles and those in pre-ovulatory phase [78], and reduced FF concentrations of IL-12 and elevated FF concentrations of IL-13 in patients with PCOS are correlated with reduced oocyte maturation, fertilisation and pregnancy [59, 74, 78, 79].

Tumour necrosis factor α (TNF- α)

TNF- α is involved in the regulation of ovarian function, exerting an influence on proliferation, differentiation, follicle maturation, steroidogenesis and apoptosis. TNF- α is expressed by the oocyte, thecal cells, granulosa cells and the corpus luteum in the ovary. Alterations in TNF- α levels in FF are correlated to poor oocyte quality. Increased FF concentrations of TNF- α in women with PCOS are also significantly inverse correlated to FF concentrations of E2, which are indicative of poor oocyte and embryo quality [78].

Fas and Fas ligand (FasL)

Fas and FasL are membrane proteins belonging to a TNF subfamily, and they respectively have anti- and pro-apoptotic functions. Concentrations of Fas in FF are positively correlated with oocyte maturity [78]. In women with PCOS treated with metformin, a reduction in FF concentrations of FasL has been reported, with a consequent increase in implant and pregnancy percentages [59, 74, 78, 79].

Biomolecules related to carbohydrate metabolism

Proteomic studies show modulation of several proteins related to the carbohydrate metabolism. The abundance of many proteins such as aconitate hydratase, fructose bisphosphate aldolase A, malate dehydrogenase, isoenzymes M1/M2 of pyruvate kinase, and transaldolase has been found to be increased in ovarian tissue and in ovarian granulosa cells from PCOS patients. Instead, UDP-glucose 6-dehydrogenase protein was reduced in PCOS women.

Moreover, triosephosphate isomerase was shown to have increased gene expression in ovarian tissue from PCOS patients.

Biomolecules related to lipid metabolism

Women with PCOS frequently present an atherogenic serum lipid profile consisting of increased triglycerides, cholesterol, low-density lipoprotein cholesterol concentrations and reduced apolipoprotein A-I levels. Insulin resistance, androgen excess and obesity may all contribute to the abnormalities of lipid metabolism observed in women with PCOS.

Apolipoprotein A-1 (ApoA-I), the major structural protein component of HDL-cholesterol particles, has several pleiotropic biological functions: promotion of macrophage cholesterol efflux, stimulation of reverse lipid transport, inhibition of LDL oxidation, removal of toxic phospholipids and also many other anti-inflammatory properties. Proteomic techniques found a decreased abundance of ApoA-I in visceral adipose tissue and in whole ovarian tissue from women with PCOS [80–82]. Moreover, reduced ApoA-I abundance in granulosa cells from these women may influence the expression of steroidogenic enzymes and the production of the steroid hormone progesterone [83].

Apolipoprotein C-I (ApoC-I) inhibits lipoprotein metabolism in the liver. Several authors showed, thus, increased serum ApoC-I levels in women with PCOS compared to normal controls, especially in those presenting with insulin resistance [84].

Adipocyte plasma membrane-associated protein (APMAP) may represent a novel member of paraoxonases [85], which are known to be involved in antioxidant processes. Lower level of APMAP has been found in visceral adipose tissue in patients with PCOS [81] might contribute to the impairment in antioxidant defense characteristic of PCOS [86].

Biomolecules related to protein metabolism

Proteomic techniques indicated that ovarian tissue (in patients with PCOS) presents high levels of proteins involved in the metabolism of amino acids, in post-translational protein modification and in protein degradation [82].

Methionine adenosyltransferase II (MAT2B), an enzyme involved in the removal of homocysteine, is decreased in the PCOS ovary [82]. Moreover, cathepsin D, an acid protease involved in intracellular protein breakdown implied in the pathogenesis of several diseases, such as, breast cancer [87, 88]; it is decreased in T lymphocytes from women with PCOS. The biological significance of this decrease is not clear [89].

Other factors

Heat shock proteins (HSPs)

Heat shock proteins (HSPs) are a highly conserved family of molecules involved in protein folding. Many components of survival and apoptotic pathways are regulated by molecular chaperones such as heat shock proteins [90]. The decrease at the protein level of Hsp10, Hsp27 and Hsp60 in ovarian tissue and granulosa cells from patients with PCOS [79, 80] might contribute to apoptosis within the ovarian follicle. In accordance, Hsp60 is down-regulated in adipose tissue in PCOS gene expression studies [91].

Transferrin

Transferrin is the major iron transporter in the circulation and it is increased in PCOS women. High levels of transferrin may not be related to inflammation but represent a compensatory mechanism against the limitation of iron availability for erythropoiesis characteristic of chronic disorders [92]. Similarly, the decrease in $\alpha 2$ macroglobulin observed in patients with PCOS might be related to the increased body iron stores, observed in these women [93, 94].

Homocysteine

Homocysteine (Hcy) is a homologue of the amino acid cysteine and may be converted into methionine or cysteine in the presence of B-complex vitamins. Many studies have shown that elevated Hcy levels in serum and FF are inversely proportional to oocyte and embryo quality [59, 74, 78, 79]. High FF and serum concentrations of Hcy may suppress E2 synthesis and therefore interfere with follicle growth and oocyte maturation in women with PCOS [59, 74, 78, 79].

Leptin

Leptin is a protein hormone that plays a key role in regulating energy supply and demand. High FF and serum concentrations of leptin are closely associated with a decrease in oocyte maturity and embryo quality in patients with PCOS. Certain studies have also demonstrated that high levels of leptin in women with PCOS play a role in PCOS pathogenesis, acting by inhibiting E2 production and interfering with follicle development and oocyte maturation. On the other hand, some

authors have demonstrated that leptin is reduced in FF of women with PCOS and is therefore not a useful marker for evaluating oocyte quality [59, 74, 78, 79]. In-depth research is therefore needed to elucidate the role of leptin in the pathophysiology of PCOS.

Oxidative stress (OS)

Oxygen free radicals or reactive oxygen species (ROS) are involved in many physiological functions where they act as mediators in a variety of signal transduction pathways [59]. An excess of these substances can cause cellular damage. In women with PCOS, elevated levels of ROS in FF and reduced antioxidant capacity are closely associated with reduced oocyte maturation and low embryo quality [59, 74, 78, 79]. These molecules may reduce oocyte quality by altering the equilibrium of FFFs in the follicular microenvironment.

The decrease in mitochondrial O₂ consumption and glutathione (GSH) levels, along with increased ROS production, explains the observed mitochondrial dysfunction in PCOS patients [95]. The mononuclear cells of women with PCOS are increased in this inflammatory state [96], which occurs more often in response to hyperglycemia and C-reactive protein (CRP). Physiological hyperglycemia generates increased levels of ROS from mononuclear cells, which then activate the release of TNF- α and increase inflammatory transcription factor NF-kappa B. As a result, the concentrations of TNF- α , a known mediator of insulin resistance, are further increased. The resulting OS creates an inflammatory environment that promotes insulin resistance and contributes to hyperandrogenism [97].

Clinical manifestations

The typical clinical indications of PCOS are: anovulatory cycles, ultrasonographic evidence of polycystic ovaries and hirsutism. Many women are also overweight or obese and have an increased risk of developing metabolic syndromes in later life. During pregnancy, there is a higher chance of miscarriage, gestational diabetes and hypertension.

Anovulatory cycles

Anovulatory cycles often manifest with oligoamenorrhea, secondary amenorrhea or abnormal uterine bleeding. The term oligomenorrhea refers to cycles of more than 35 days, while secondary amenorrhea is an absence of menstruation for more than three months. Polymenorrhea condition, meaning more frequent cycles, generally with an interval of less than 24 days, may occur in a minority of cases. Since regular cycles do not exclude chronic anovulation, it is necessary to measure serum concentrations of progesterone in luteal phase of the

cycle (days 20–24). If they are below 5 ng/mL, the cycle is probably anovulatory.

Menstrual irregularities often begin after menarche and decrease when the patient approaches menopause [98]. This correlated to a decline in androgen levels with advancing age in women with PCOS [98]. While evaluating the length of the menstrual cycle, it should be recalled that oligo-anovulation is quite common in adolescents, especially in the first year after menarche. Settling into regular cycles may be a slow process, which, in some cases, may take three years after the first period. This is why it is important to be cautious in diagnosing and treating PCOS in adolescents. The incidence of irregular cycles in adolescents with PCOS seems to vary significantly: about 43 % with oligomenorrhea, 21 % with primary or secondary amenorrhea, 21 % with regular menstrual cycles and 7 % with polymenorrhea [99]. 95 % of adult women with PCOS have amenorrhea [5, 99].

Ultrasonographic features of the ovaries

The Rotterdam guidelines of 2003 include ultrasonographic evidence of polycystic ovaries as a criterion for the diagnosis of PCOS. This finding is not exclusive because young healthy women may have ovaries with polycystic features. Polycystic ovaries may also be observed during pubertal development in patients with hypothalamic amenorrhea and hyperprolactinemia [100].

The diagnostic criteria of PCOS are based on the presence of 12 or more follicles of diameter 2–9 mm or an ovarian volume of more than 10 mL in follicular phase. Another feature is an increase in stromal tissue. These morphological changes in the ovary may be encountered in more than 80 % of women with a clinical diagnosis of PCOS [100].

Hirsutism

Hyperandrogenism may manifest with hirsutism, acne and alopecia. Hirsutism is the presence of terminal hair on the face and/or body in a masculine pattern. It is the most common symptom, found in about 60 % of women with PCOS and it widely varies according to the ethnicity. For this reason, the threshold of hirsutism should be set considering the patient ethnicity. The most widely used method to determine the degree of hirsutism is the Ferriman-Gallwey score [101] which gives a score of 0 in the absence of terminal hair in a given area of the body, and a score of 4 for extensive hair growth. Hair is scored in 9 different areas of the body, such as, chin, upper lip, periareolar and intermammary areas, upper and lower back, upper and lower abdomen, upper and lower limbs. The score from each area is summed to obtain a final score used for diagnosis. A score of 7 is indicative of hirsutism. It is defined as “slight” for scores of 7–9, “moderate” for 10–14 and “severe” for scores ≥ 15 [101].

Hirsutism may be simultaneously due to androgen production, increased circulating levels of free testosterone (Ft) in women with PCOS; together with an increased activity of androgens in the pilosebaceous units through action of 5- α reductase, an enzyme that transforms testosterone into the more active dihydrotestosterone.

Acne

Acne occurs in 12–14 % of women with PCOS and varies according to ethnicity: the highest reported incidence regards Indo-Asian women and lowest, Pacific islanders [102]. Acne consists of comedones, due to accumulation of sebum and epithelial cell debris, which is colonised by the bacterium *Propionibacterium acnes*. Inflammation of the comedones leads to the formation of papules, pustules and nodules. Androgens may exacerbate this process, increasing sebum production by pilosebaceous units. About 50 % of women with acne have no clinical or biochemical evidence of hyperandrogenism. Moreover, many hirsute women with PCOS do not have acne. These differences may be due to different peripheral sensitivity of androgen receptors [102].

Alopecia

Alopecia consists in progressive hair loss or thinning. The intensity varies from subject to subject. Androgenic alopecia is often accompanied by seborrhea and dandruff. Sensitivity of the pilosebaceous unit to androgens is highly variable and there is little correlation between clinical features and biochemical profiles of hyperandrogenism [102]. Hair loss in PCOS usually involves thinning at the vertex with maintenance of the frontal hairline.

PCOS in adolescence and at menopause

It has been known for several years that PCOS patients have higher risk for a certain range of diseases compared to the general population. This risk exposes them to high morbidity and it is associated with high social impact, both economic and in healthcare. These pathologies include type II diabetes, metabolic syndrome, cardiovascular disease, endometrial carcinoma and many gestational complications. The clinical indicators of hyperandrogenism are another important aspect for adolescents with PCOS, considering of self-perception in this delicate period of life, when physical appearance is fundamental for self-acceptance and relationships with others. Hirsutism, acne and obesity cause psychological distress that may develop into personality disorders and depression. Early diagnosis and treatment of PCOS in adolescence is therefore fundamental because it can slow down or prevent the appearance of these pathologies in adulthood. Diagnosis of PCOS in adolescence is more

problematical than in adulthood and, according to some authors, should be based on all three Rotterdam criteria [103]. Oligomenorrhea should have a history of at least two years since menarche and diagnosis of polycystic ovary by abdominal ultrasonography should only be based on increased ovarian diameter ($>10 \text{ cm}^3$). If diagnosis cannot be confirmed patients should be carefully monitored until adulthood, and if symptoms persist the diagnosis should be reassessed [103].

The clinical manifestations of PCOS in perimenopause period are not well known. There is histological evidence that women with PCOS have a larger cohort of primary follicles than healthy women of the same age, a greater number of antral follicles detectable by ultrasonography and higher serum concentrations of AMH [104]. These results suggest prolonged reproductive function and greater ovarian reserves. Women with PCOS also seem to achieve better menstrual regularity and probability of ovulation with age (despite lower pregnancy rates). A study of a prospective cohort of women during menopause shows that those with PCOS go into menopause an average of two years later than controls [104].

Long-term sequelae

Insulin resistance in young healthy women raises the problem of other risk factors such as impaired glucose tolerance (IGT), diabetes, hyperlipidemia, hypertension, abdominal obesity and risk of cardiovascular disease [5, 105]. Since PCOS patients tend to have abdominal fat deposition and insulin resistance, it has been suggested that they may also have other metabolic alterations typical of so-called metabolic syndrome. This syndrome is characterised by a series of symptoms, such as insulin resistance, obesity, hypertension and hyperlipidemia. Women with PCOS have elevated blood pressure, serum

triglycerides, LDL, total cholesterol and lower HDL cholesterol than age-matched controls [5, 105]. Furthermore, PCOS patients have a seven times higher risk of myocardial infarction than controls of the same age (Fig. 6).

Insulin resistance is recognised as a major risk factor for type II diabetes [5, 105]. Factors such as obesity and family history of type II diabetes can increase the risk of diabetes in PCOS. About 30 % of obese women with PCOS have IGT. A retrospective study by Dahlgren et al. showed that prevalence of non-insulin-dependent diabetes mellitus (NIDDM) was 15 % in PCOS patients and 2 % in controls. Dunaif et al. [5, 105] suggested that up to 20 % of PCOS patients have IGT or NIDDM in the third decade.

It cannot be argued that PCOS patients with excess of androgens and anovulation are more vulnerable to metabolic dysfunction than other women. Women with PCOS and anovulation, but with normal levels androgens, and those with hyperandrogenism but regular cycles, usually have normal insulin sensitivity and presumably do not have the same risk of IGT or type II diabetes as those with the "classical phenotype" of the syndrome [106].

Besides, women with PCOS are also at higher risk for endometrial hyperplasia and carcinoma. This risk is, in fact, influenced by various factors, such as obesity, hyperandrogenism and infertility. All these factors can be present in women with PCOS. A recent prospective study of 56 PCOS patients showed a high prevalence of endometrial hyperplasia [5, 105]. An interesting recent review and meta-analysis confirms that women of all ages with PCOS have an increased risk of endometrial cancer but the risk of ovarian and breast cancer was not significantly increased [107]. For this reason, preventive

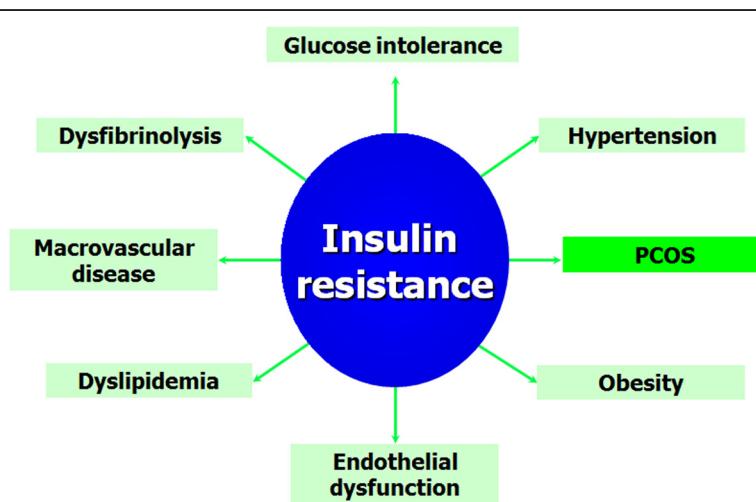


Fig. 6 Insulin resistance is the link between PCOS and metabolic syndrome

measures on PCOS patients for endometrial carcinoma are suggested. These include recognition and treatment of relative hyperestrogenism by periodic administration of progesterone and/or ultrasonography and endometrial biopsy in cases of long periods of amenorrhea. In any case, at least four episodes of suspension bleeding per year (every 3 months) are recommended.

PCOS and pregnancy: gestational complications

Women with PCOS show higher risk of gestational complications, such as miscarriage, gestational diabetes, hypertension and pre-eclampsia. These problems expose them to a higher risk of premature delivery and caesarean section [108]. Recent epigenetic theories suggest that during PCOS pregnancy the embryo is exposed to an excess androgens that disrupts functional reprogramming of foetal tissues [109, 110]. Maternal, placental or foetal hyperandrogenism can distress epigenetic reprogramming of tissues, especially of genes regulating reproduction and metabolism. Which can contribute to diseases such as type II diabetes, hypertension, autism^{31–32} and PCOS. Epigenetic alterations of the androgen receptor gene on chromosome X have, indeed, been observed in women with PCOS. However, a recent study failed to find any significant differences in overall methylation of peripheral leukocyte DNA between women with PCOS and matched controls [109, 110], so aforementioned theory has not yet been confirmed.

Women with PCOS have a 30–50 % of risk of miscarriage, which is three times higher than normal women [111]. The mechanisms probably involved in the pathogenesis of miscarriage in these women are:

1. overexpression of androgen and steroid receptors and simultaneous reduced expression of molecules

of implantation, such as α vs β 3 integrin and glycodelin [111];

2. hyperinsulinemia which inhibits endometrial and stromal differentiation *in vitro* (decidualisation) and locally down-regulates IGFBP-1 [111];
3. hypofibrinolysis mediated by high levels of plasminogen activator inhibitor (PAI) [111];
4. increased resistance of the uterine arteries blood flow leading to reduced sub-endometrial and endometrial vascularisation [111] (Fig. 7).

Moreover, women with PCOS have a higher incidence of gestational diabetes (20–30 %) and pre-eclampsia/pregnancy-induced hypertension (PE/PIH) (10–15 %) [108]. These alterations could be caused by obesity, alterations in glucose metabolism or in uterine vascularisation [112]. Obesity in pregnancy is, in fact, associated with various complications, such as miscarriage, pre-eclampsia, gestational diabetes, foetal macrosomia and caesarean section [112]. Fat tissue produces adipokines, including leptin, adiponectin, TNF- α , IL-6, resistin and visfatin, which could be involved in activation of insulin resistance in pregnancy. Adipokines can also produce an excessive local and systemic inflammatory reaction, which would play a key role in the pathophysiology of PE/PIH and the birth of SGA babies. It is also possible that placental macrophages contribute to inflammation within the placenta by secretion of pro-inflammatory cytokines such as IL-1, TNF- α and IL-6 in cytotrophoblast and syncytiotrophoblast cells [112].

Glucose intolerance and insulin resistance are elevated in women with PCOS even before pregnancy. Since pregnancy causes physiological insulin resistance through the action of placental hormones such as placental lactogen (hPL), placental growth hormone (hPGH) and

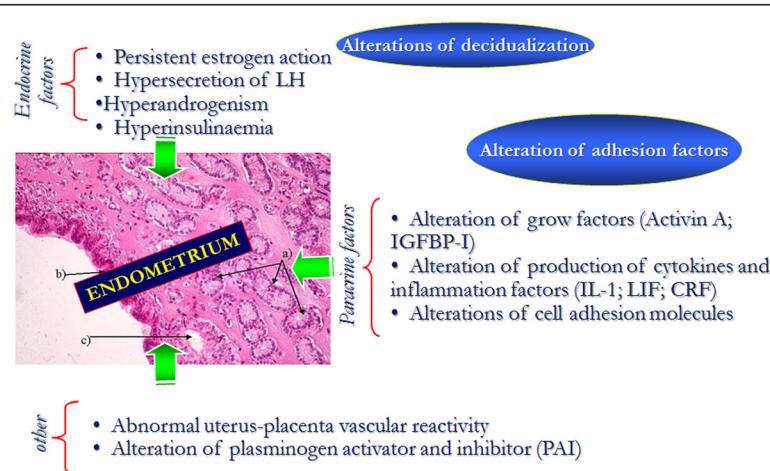


Fig. 7 Factors involved in the etiopathogenesis of miscarriage in women with PCOS

progesterone, women with PCOS have even an higher risk of developing gestational diabetes. However, studies on the prevalence of gestational diabetes in women with PCOS show conflicting results that reflect the heterogeneity of the syndrome and the diversity of methods used to diagnose gestational diabetes [108].

Furthermore, alterations of uterine vascularisation reported in these women can determine reduced trophoblastic invasion leading to increased incidence of hypertension and delivery of SGA babies [112].

Maternal and placental hyperandrogenism may contribute to an increased risk of PE/PIH. In normal condition, the androgens synthesised by the placenta are rapidly converted to oestrogens by placental aromatase. Insulin inhibits placental aromatase and stimulates 3 β HDS activity. Expression of androgen receptors is significantly increased in the placentas of women with PE/PIH and this may induce vasoconstriction and thrombosis [108, 112]. Finally, all these complications expose pregnant women with PCOS to a greater risk of premature delivery and caesarean section [108].

Outcome of newborns of mothers with PCOS

A meta-analysis aimed at evaluating neonatal complications in women with PCOS was recently conducted [108]. The newborns of PCOS patients had a significantly elevated risk of admission to the neonatal intensive care unit and a higher possibility of perinatal mortality [108]. Access to neonatal intensive care is partially linked to premature delivery, which causes hypoglycemia, jaundice and respiratory distress. Many women with PCOS also undergo ovulation induction and in vitro fertilisation and are therefore at chance for multiple pregnancies [113]. Multiple pregnancy is another major cause of increased perinatal morbidity. However, the studies aforementioned did not show any difference in multiple pregnancy between women with PCOS and healthy women [113].

Given the excessive rate of gestational diabetes in women with PCOS, an increased incidence of foetal macrosomia could be expected. However, newborns of women with PCOS show a significantly lower birth weight than controls, although the size of this difference (mean 40 g) is probably of limited clinical significance [108].

The foetus of PCOS mothers is exposed to greater glucose load, but placental distress can reduce the manifestation of macrosomia. The association of PCOS and PE/PIH suggests placental distress, especially in cases of pre-term delivery [108]. The above-mentioned meta-analysis had some limitations regarding heterogeneity of PCOS patients enrolled in the different studies. BMI, medically assisted procreation and smoking during pregnancy were not always considered, all of which are factors that may affect obstetric and neonatal outcome [108].

Conclusions

PCOS is not only a reproductive pathology but also a systemic condition and its etiopathogenesis is still not completely understood. Recently, the approach of clinical practice has been a progressive changed and improved towards prevention together with the standard treatments for diseases. Therapeutic tools are represented by hormonal contraceptives, antiandrogen drugs, metformin and inositol.

In this context, PCOS is an excellent example of pathology in which early diagnosis and treatment can prevent or delay its typical long-term sequelae.

In the past, therapy for PCOS has been centred on treatment of hirsutism and restoration of ovulation. However, it should be taken more into account the observation of hyperinsulinemia and insulin resistance, which are often implicated in the pathogenesis of the syndrome. Due to the fact that these alterations have major repercussions on health in the long period, the researchers should evaluate more appropriate strategies for control of the metabolic alterations of PCOS.

Abbreviations

17-OHP, 17-hydroxy progesterone; A, androstenedione; AES, androgen excess society; AMH, anti-mullerian hormone; APMAP, Adipocyte plasma membrane-associated protein; ApoA-I, apolipoprotein A-I; BMI, body mass index; BMP, bone morphogenetic protein; CRP C, reactive protein; DHEAS, dehydroepiandrosterone sulphate; DM, diabetes mellitus; E2, oestradiol; EGF, epidermal growth factor; FAI, free androgen index; FasL, fas and fas ligand; FBN3, fibrillin-3; FF, follicular fluid; FFFs, follicular fluid factors; FS, follistatin; FSH, follicle stimulating hormone; Ft, free testosterone; GDF, growth and differentiation factor; GSH, glutathione; Hcy, homocysteine; HOMA, Homeostatic model assessment; Hpgf, placental growth hormone; hPL, placental lactogen; HSPs, heat shock proteins; IGF, insulin like growth factor; IGT, impaired glucose tolerance; IL, interleukin; IR, insulin resistance; KP, kisspeptin; LH, luteinising hormone; LHR, LH receptor; MAT2B, Methionine adenosyltransferase II; NGF, neurotrophin growth factor; NIDDM, non-insulin-dependent diabetes mellitus; NIH, National Institutes of Health; OS, oxidative stress; PCOS, polycystic ovary syndrome; PE/PIH, pre-eclampsia/pregnancy-induced hypertension; ROS, reactive oxygen species; SGA, small for gestational age; SHBG, sex hormone-binding globulin; T, testosterone; TGF, transforming grow factor; TGF-beta, Transforming growth factor beta; TNF- α , tumor necrosis factor α ; TT, total testosterone; VEGF, vascular endothelial growth factor

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Authors' contribution

Conception and design of the review: VDL, GM; write the article and collect the references: MCM, VC, MGM; final approval of the version to be submitted: FP. All authors read and approved the final version of the manuscript.

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Review

Hirsutism, Normal Androgens and Diagnosis of PCOS

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Abstract: Hirsutism is defined as the presence of terminal hair with male pattern distribution in women. While in the general population, hirsutism affects around 4–11% of women, it is the main manifestation of hyperandrogenism in women with polycystic ovary syndrome (PCOS), with a prevalence estimated at 65–75%. Hirsutism in PCOS is associated with both androgen excess and individual response of the pilosebaceous unit to androgens. The modified Ferriman–Gallwey (mFG) scoring system has been widely used in clinical practice to visually score excessive terminal hair, thus standardizing hirsutism evaluation and facilitating data comparison. Although a universal mFG score cutoff would be useful for comparisons, ethnic variations, as well as skin type and other factors, should be considered when evaluating hirsutism in distinct populations. In turn, androgen levels, measured by conventional techniques, have been shown to correlate poorly with the severity of hirsutism. Indeed, while most women with PCOS and hirsutism also have higher than reference values for serum androgen levels, some of them may not present with biochemical hyperandrogenism, representing a challenge to the diagnosis of PCOS. In this article, we critically review this not uncommon condition in women with PCOS presenting with hirsutism but normal androgen levels.



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1. Introduction

Hirsutism is defined as an abnormal amount of terminal hair in a male pattern distribution in women and is the main manifestation of hyperandrogenism in women with polycystic ovary syndrome (PCOS). Acne and female pattern hair loss (FPHL) are also clinical manifestations of hyperandrogenism, although mild acne and FPHL are not recommended as diagnostic criteria in adolescents due to the paucity of data in this population, with progressive hirsutism remaining the primary marker of hyperandrogenism [1].

In response to increased androgen levels at puberty, vellus hair follicles in specific areas develop into terminal hair (larger, curlier, and darker, hence more visible), becoming sexual-hair follicles [2]. While pubic and axillary hair are quite sensitive to small amounts of androgens, other areas may need higher androgen concentration for follicle terminalization [3]. Free testosterone is the main active portion of plasma testosterone and is responsible for this action [4].

The broad and heterogeneous clinical expression of PCOS gave rise to the perception that no single criterion should be mandatory for the diagnosis of PCOS, which resulted in

the 2003 Rotterdam diagnostic criteria. According to that consensus, PCOS should be diagnosed when at least two of the following criteria are present: ovulatory dysfunction (oligo- or amenorrhea), hyperandrogenism (either biochemical or clinical), and polycystic ovarian morphology (follicle number per ovary of ≥ 20 and/or an ovarian volume ≥ 10 mL on either ovary, preferably with an endovaginal ultrasound) [1,5,6], excluding other related or mimicking disorders. The Rotterdam criteria for defining PCOS were endorsed by the US National Institutes of Health (NIH) in 2012 (<https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/evidence-based-methodology-workshop-polycystic-ovary-syndrome-pcos> (accessed on 21 June 2022)) and by the International Guideline on PCOS in 2018, based on the best available evidence [1] (Expert Panel from a NIH Evidence-Based Methodology Workshop on PCOS, December 2012). Indeed, while most women with PCOS and hirsutism also have higher than the reference values for serum androgen levels, some of them may not present with biochemical hyperandrogenism, representing a challenge for the diagnosis of PCOS. In this article, we critically review this not uncommon condition in women with PCOS presenting with hirsutism but normal androgen levels.

2. Hirsutism and Hair Follicle Cycling

Hirsutism is defined as the presence of terminal hair of the female body in male pattern. The male sexual pattern is observed in androgen-sensitive anatomic sites that include the face, chest, breast areola, linea alba, lower back, buttocks, inner thighs, and external genitalia [7,8]. While in the general population, hirsutism affects 4–11% of women, in PCOS, its prevalence is estimated at 65–75% [9] and severity varies according to the degree of androgen excess and individual variability in the sensitivity of the pilosebaceous unit to androgens [10,11].

Hair follicles are small organs formed by the interaction between epidermis and dermis and are important skin appendages. They exhibit a periodic growth cycle that occurs continuously throughout the human lifespan and have high regenerative capacity. These characteristics are due to the presence of many stem cell populations in the hair follicle, and the activity of these stem cells and growth of hair follicles are highly regulated by various signaling pathways [12]. Moreover, hair growth is affected by many factors, such as age, environment, and health status, which can influence the development of hair follicle tumors, alopecia areata, and other related diseases, such as hirsutism [13].

In humans, there are three types of hair: lanugo, vellus, and terminal hair. Lanugo is the very fine hair that covers the fetal body and disappears during the first weeks of life. Vellus hair is very short, fine, and usually non-pigmented, whereas terminal hair is longer, thick, and pigmented. In women, terminal hair is found mostly in such areas as the eyebrows, eyelashes, scalp, axilla, and pubis. Less commonly, women may also have terminal hair in areas of the so-called male sexual pattern. Hormonal influence may alter the pattern of hair distribution in women, leading to excessive hair growth [11,13].

The hair follicle cycle is divided into three stages named anagen, catagen, and telogen, which characterize the perpetual cycle of growth, involution, and rest, respectively. The anagen stage is the most active period of hair follicle growth, when the hair grows rapidly and forms a complete hair shaft. Epithelial cell differentiation and hair pigmentation occur during this stage. The duration of the anagen stage determines hair length and is associated with the continuous proliferation and differentiation of stromal cells at the base of hair follicles [11,13,14]. Moreover, there is substantial variation in anagen duration according to body region: up to 6 years in the scalp, 1 to 3 months in the arms, 4 to 6 months in the legs, and 1 to 2 months in the thighs. Approximately 85% to 90% of all scalp hair is in the anagen stage at any given moment. This figure changes according to the body region, age, and possibly gender. In the arms and legs, approximately 46% and 58% of all hair, respectively, is always in the anagen stage [11]. When hair follicles enter the catagen stage, hair usually stops growing and, at the end of this phase, the hair follicles have atrophied. Therefore, the catagen stage starts when the supply of matrix cells declines, leading to a

slowdown in the differentiation of the hair shaft and the inner root sheath (apoptosis-driven regression) [13,14]. During catagen, hair follicle degeneration is highly regulated, and a large number of keratinocytes from the hair follicle begin to undergo programmed death. At this stage, melanin production in hair follicles stops and melanin-containing cells in some hair follicles also begin to undergo apoptosis [13]. After regression, the hair follicle enters the telogen stage, recognized as a resting phase. This stage is characterized by low biological activity of the follicle and a drop in hair shaft. Telogen duration changes according to body region: 2 to 4 months in the scalp, 2 and a half months in the chest, 2 to 4 months in the arms, and 3 to 6 months in the legs [11,13,14]. The follicle remains in the telogen stage until it is reactivated. At this point, the expression and activity of the relevant regulatory factors in the hair follicle controlling its cyclical growth will be significantly enhanced to prepare for the beginning of the next anagen [11,13,14].

3. Actions and Metabolism of Androgens in the Hair Follicle

The importance of androgens for hair growth in humans was first established by Hamilton and colleagues in the 1950s [15], with observations that castration before puberty prevented the development of beard and axillary hair, whereas castration after puberty led to the atrophy of beard and axillary hair. In addition, patients with androgen insensitivity do not have pubic or axillary hair. Since then, androgens have been shown to increase hair follicle size in different body regions, hair diameter, and the proportion of time hair remains in the anagen stage [16]. The conversion of vellus to terminal hairs is mainly stimulated by androgens, through the prolongation of the anagen stage. Successive hair cycles and longer anagen duration promote an increase in follicle size. These larger follicles produce longer, thicker hair in androgen-dependent body areas. For this reason, androgen excess-related conditions, such as PCOS, are often associated with hirsutism [11,17].

It is important to note that the occurrence and severity of hirsutism are also associated with the sensitivity of hair follicles to androgens. In fact, not only do hair follicles respond to androgens, broadly expressing androgen receptors, but they also contain androgen-metabolizing enzymes that play a critical role in regulating the level of androgens in the hair follicle [11,17,18]. Main enzymes include cytochrome P450 aromatase, which converts testosterone and androstenedione to estrogens (17β -estradiol and estrone, respectively), type 2 17β -hydroxysteroid dehydrogenase (17β -HSD), which inactivates testosterone to androstenedione, and 5α -reductase, which converts testosterone to dihydrotestosterone (DHT). Therefore, altered expression of these enzymes may be associated with a greater or lesser androgenic activity in the hair follicle.

Previous studies have shown that the expression of the type 2 17β -HSD gene is lower in scalp hair follicles of women with hirsutism than of women without it but similar to that of men [19], and higher in the subumbilical region and arm skin [20]. These results suggest that type 2 17β -HSD may play a role in the development of hirsutism, as the enzyme is responsible for inactivating more potent sex steroids (such as testosterone) by oxidation reactions [19]. Other gene expression analyses using 5α -reductase confirmed the presence of isotype 1 on the vertex of the scalp in women, but there was no significant difference in the expression patterns of women with or without hirsutism [21]. No correlation was found between 5α -reductase type 1 and 2 gene expression in dermal papillae from the lower abdominal region and severity of hirsutism [22]. In turn, variants in the gene encoding 5α -reductase type 1 were associated with hirsutism in women with PCOS [23]. In previous studies, we found no associations between 17β -HSD or aromatase gene variants and the severity of hirsutism in women with PCOS [24,25] (Figure 1).

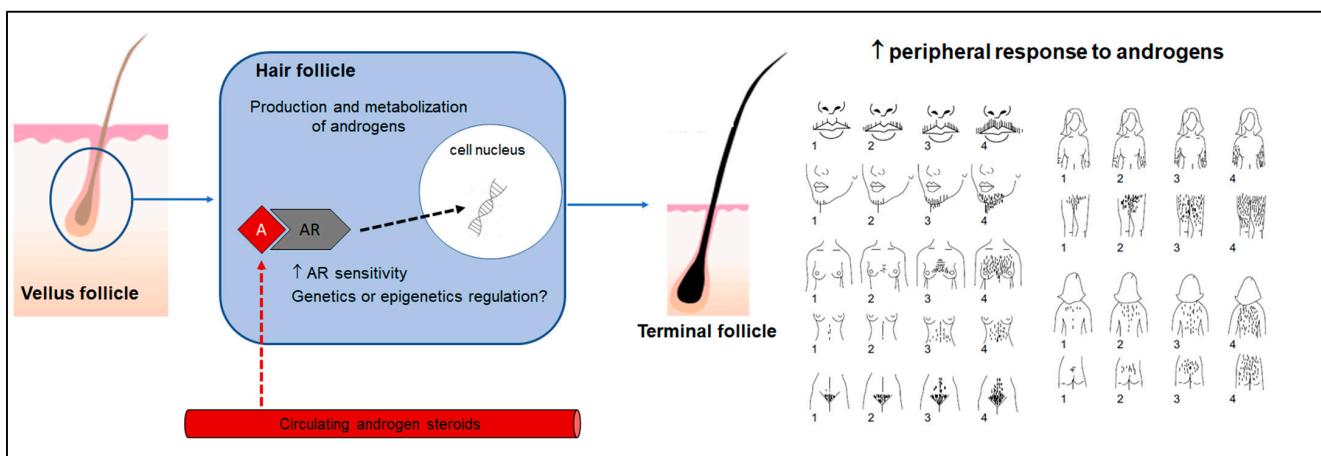


Figure 1. Role of androgens in the hair follicle and its peripheral response. A: androgens; AR: androgen receptor; ↑ peripheral response to androgens is expressed graphically by the modified Ferriman–Gallwey scale.

4. Molecular and Genetic Regulation of Hair Follicle

Different molecular signaling pathways are involved in the control of hair follicle growth and cycling [13]. MicroRNAs and gene variants in the androgen receptor gene appear to be promising for understanding the pathophysiology of hirsutism. MicroRNAs can contribute to the regulation of hair follicle morphogenesis and regeneration [13,14]. Shorter CAG repeat polymorphisms of the androgen receptor gene may be associated with increased activity of the receptor, leading to PCOS and hirsutism [26]. However, while some studies have shown a negative association between CAG repeat lengths and the prevalence of hyperandrogenic states, such as PCOS [27–31], or more severe clinical hyperandrogenism, such as hirsutism in women with PCOS [32], meta-analyses of studies correlating CAG repeat lengths with PCOS [33,34] and data in hirsute women with and without hyperandrogenemia [35,36] do not confirm this association. Therefore, many questions remain unanswered regarding the precise mechanisms underlying androgen/androgen receptor signaling pathways.

5. Scoring Hirsutism in the Context of PCOS

Although hirsutism reflects androgen action in the hair follicle, local factors, sensitivity to androgen, duration of exposure and local conversion of testosterone to a more potent androgen, DHT, by 5 α -reductase may be more important than plasma androgen levels [37,38]. Among local factors, an important contributor to hair follicle development and growth is the activity of L-ornithine decarboxylase, an enzyme that catalyzes the synthesis of polyamines implicated in cell migration, proliferation and differentiation of hair follicles, androgen receptor concentration, and 17 β -HSD and 5 α -reductase activities [3]. Most women with androgen levels more than twice the upper limit of the reference range have some degree of hirsutism, but it has been demonstrated that androgen levels, measured by conventional techniques, correlate poorly with the severity of hirsutism [39]. Likewise, women may present with excessive body hair growth but normal plasma androgen levels. Because of these observations, the most used criteria for the diagnosis of PCOS consider the hyperandrogenism criterion as clinical and/or biochemical [1]. Clinical hyperandrogenism is still very important while defining hyperandrogenism for the PCOS diagnosis, especially in women with normal androgens.

The Ferriman–Gallwey (FG) scoring system has been widely used in clinical practice to visually score excessive terminal hair [40], thus standardizing hirsutism evaluation and facilitating data comparison. The modified FG (mFG) score evaluates hair growth in nine body areas. Hair growth is rated from 0 (no terminal hair) to 4 (male pattern hair) in each area, with scores of 1, 2, and 3 indicating intermediate levels of body hair growth,

for a maximum score of 36 (Figure 1). The original method had a cutoff of 5 to define hirsutism [41], which was increased to 8 in the mFG score, based on the original data published by Ferriman and Gallwey considering the 95th percentile [42]. In shaved areas, self-scoring can be clinically useful especially for follow-up, as it correlates only modestly with scoring by a trained observer [43].

Although a universal mFG score cutoff would be useful for comparisons, ethnic variations, as well as skin type and other factors, should be considered when evaluating hirsutism in distinct populations [44]. Importantly, the data reported by Ferriman and Gallwey were derived from women attending a northern London general medical outpatient clinic, a selected homogeneous population. Besides that, other factors, such as obesity and insulin resistance, are known to play a role in the phenotypic expression of PCOS, and its predisposition also varies in different ethnic backgrounds [45]. Indeed, the international evidence-based guideline for the assessment and management of PCOS, published in 2018, proposes to consider ethnic origin when evaluating mFG scores in different populations [1]. The Endocrine Society also suggests different cutoffs for the mFG score depending on ethnicity, as follows: United States and United Kingdom black or white women, ≥ 8 ; Mediterranean, Hispanic, and Middle Eastern women, ≥ 9 to ≥ 10 ; South American women, ≥ 6 ; and Asian women, a range of ≥ 2 for Han Chinese women to ≥ 7 for Southern Chinese women [46]. Subsequently, data from a systematic review comparing hirsutism in women with PCOS from populations of different ethnicities showed that, compared with white women, East Asian women were less hirsute, whereas Hispanic women, South Asian women and Middle Eastern women were more hirsute [47]. In another systematic review and meta-regression analysis, FG scores were presented according to their distribution in different countries [48]. However, few data are available on hirsutism in women with PCOS from Latin America. In this respect, Figure 2 shows a comprehensive distribution of mFG scores based on studies from different countries [49–87], which include available data from the database of a systematic review on Latin American women with PCOS that we have recently published [88]. Importantly, most studies come from referral populations, which may have influenced the difference in FG scoring between regions, according to ethnicities.

In addition to ethnicity, skin type might be of some relevance to the hirsutism evaluation. The Fitzpatrick scale classifies skin type according to susceptibility to sunburn and melanin production in response to sunlight: type I (always burns, never tans), type II (usually burns, tans minimally), type III (sometimes burns mildly, tans uniformly), type IV (burns minimally, always tans well), type V (very rarely burns, tans very easily), and type VI (never burns, never tans) [89]. A study evaluating hirsutism according to the Fitzpatrick classification in 341 women (276 patients meeting the Rotterdam criteria for PCOS) found a significant difference in total mFG score and prevalence of hirsutism between different Fitzpatrick groups. Patients in group 3 (skin types V and VI) had the highest mFG scores and prevalence of hirsutism, followed by group 2 (skin types III and IV) and group 1 (skin types I and II). For the most part, the variation in hirsutism among skin types was due to differences in truncal mFG scores [90].

Age should also be considered when evaluating hirsutism, since it is well known that both clinical and biochemical characteristics change with age in women with PCOS [91–94]. Androgen secretion from ovaries and adrenal glands may diminish as a function of aging, and hirsutism scores accompany this trend [94]. In fact, hyperandrogenism may partially resolve before menopause in women with PCOS [93]. Serum concentrations of sex hormones increase from the pre- to postmenarchal periods as well [95], and mild hair growth is frequently seen in the late stages of puberty and early adolescence and may persist for several years; therefore, the diagnosis of PCOS is often not made until adulthood, when endocrine and metabolic dysfunctions have been firmly established [1,93]. Hence, ethnic origin, skin type, age and associated comorbidities (e.g., obesity and insulin resistance) must be combined when evaluating hirsutism in women with PCOS. Further studies with

different populations may deeper clarify this issue and find practical ways to clinically evaluate hirsutism in distinct populations.

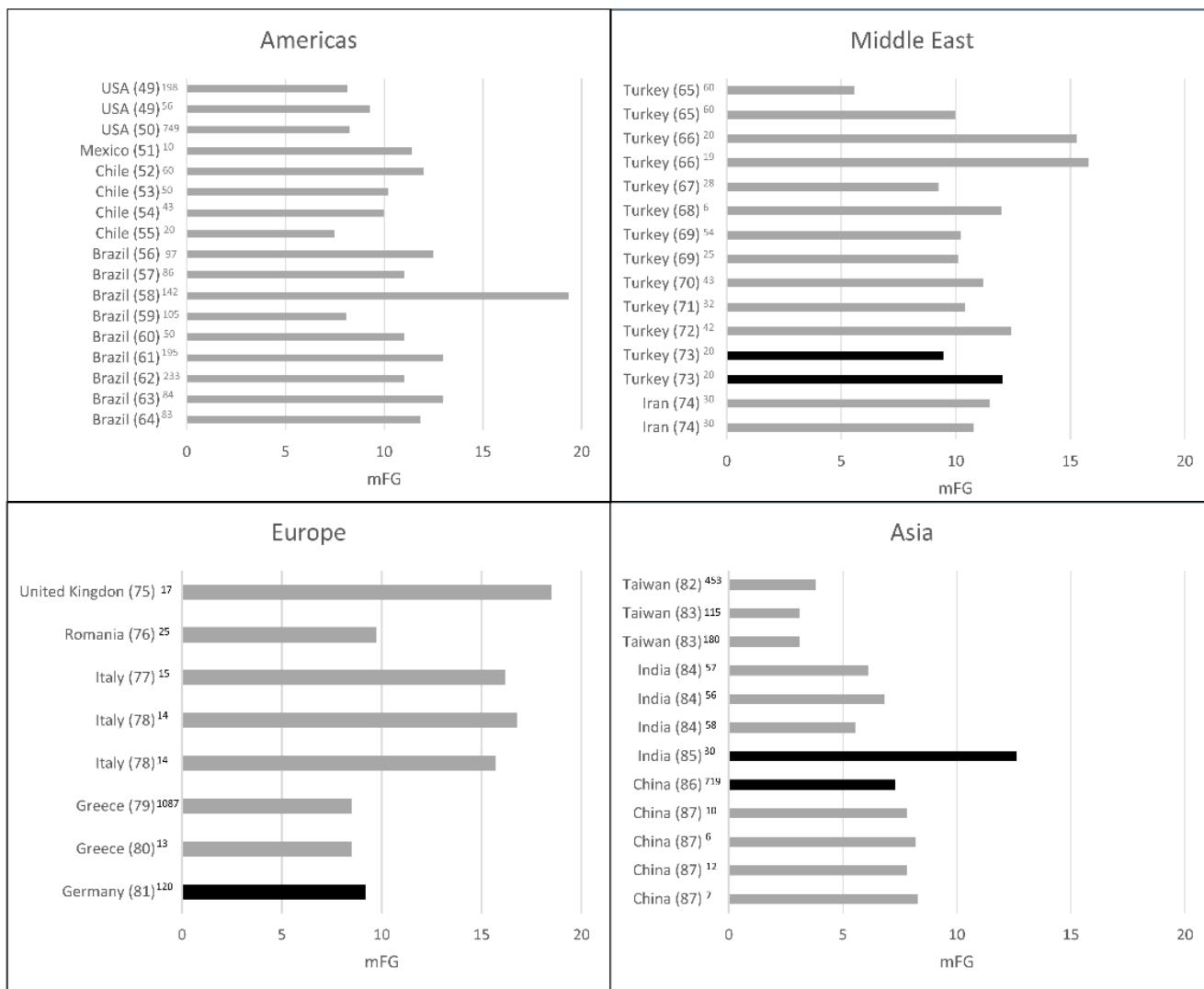


Figure 2. Hirsutism scores in women with polycystic ovary syndrome (PCOS) according to geographic distribution. PCOS was diagnosed by the Rotterdam, US National Institutes of Health (NIH), or Androgen Excess Society (AES) criteria. Black lines indicate unselected studies. Superscript numbers indicate sample size. mFG: modified Ferriman–Gallwey score.

6. Diagnosing PCOS: Clinical versus Biochemical Androgen Excess

Measurements of biochemical parameters of hyperandrogenism are very useful, particularly in patients without obvious signs of clinical hyperandrogenism, such as hirsutism, acne vulgaris, and FPHL [96]. Hirsutism has a multifactorial pathogenesis that is mainly affected by androgen levels, with the sensitivity of hair follicles to androgens also playing a role in this process. In fact, the correlation of biochemical hyperandrogenism with hirsutism severity was found not to be as significant as expected, suggesting that there may be other factors contributing to the mechanism described above. In vitro studies have shown that both insulin and insulin-like growth factor-1 may also have a dose-dependent effect on hair follicle growth [97,98]. In fact, sex hormone-binding globulin, a modulator of testosterone bioavailability, is suppressed by hyperinsulinemia resulting from insulin resistance. Therefore, not only biochemical hyperandrogenism, but also insulin resistance may contribute to the development of hirsutism [99]. Data from a large sample of Korean volunteers showed that the homeostasis model assessment of insulin resistance (HOMA-IR) was positively

associated with the FG score, even after adjustment for biochemical hyperandrogenism parameters [100]. Importantly, although within the reference range, patients with idiopathic hirsutism may have higher serum androgen levels and lower estradiol/testosterone ratio than healthy individuals, leading to relative hyperandrogenemia at the tissue level [101]. In addition, the response of the pilosebaceous unit to androgen varies considerably according to the skin area and between individuals, so not all patients with hirsutism have demonstrable hyperandrogenemia [102–106].

The biochemical assessment of sex steroids has important technical limitations. Androgen measurements in blood capture a moment in time, subject to the known pulsatility of these hormones [96]. Even in the setting of androgen excess, women usually show a slight increase in sex steroids, but the enzyme-linked immunosorbent or chemiluminescent assays used currently have low sensitivity and specificity in women. Indeed, the testosterone measurement may not be accurate at low levels (as expected in women), but liquid chromatography tandem-mass spectrometry, the most accurate method, is expensive and still not widely available [1,5]. Furthermore, serum androgen levels vary according to age, menstrual cycle day, and sampling time, but there is still no standardization based on these parameters [105]. Cross-reactivity between different steroids is another relevant issue related to the variability observed in androgen measurements in women [106]. In the clinical setting, only one-third of samples of patients with PCOS show abnormal testosterone, reaching 70% of samples for elevated serum concentration levels of free testosterone, the single most sensitive test for hyperandrogenemia [107]. Regarding other androgens, only 10% and 9% of patients with PCOS have isolated elevation of dehydroepiandrosterone sulfate (DHEAS) and androstenedione levels, respectively [108,109].

The concept of hyperandrogenism should be based primarily on clinical findings. Androgen measurements are not a substitute for clinical judgement, and it is particularly in patients without obvious signs of hyperandrogenism that biochemical evaluation is indispensable. Nonetheless, an abnormal scale of hirsutism associated with ovulatory dysfunction or ovarian morphological findings is sufficient for the diagnosis of PCOS, after the exclusion of related disorders as previously mentioned (96). The term idiopathic hirsutism should be applied only to hirsute women with normal ovulatory function and detectable normal androgen levels (testosterone, androstenedione, and DHEAS). In these cases, the cause of hair growth may be associated with abnormalities in peripheral androgen activity or increased sensitivity of the hair follicle [110].

7. Conclusions and Future Directions for Research

Several factors can potentially hinder the proper biochemical assessment of hyperandrogenism. Prominent among these are the questions of which androgens should be measured, which assay methods should be used, and how the reference ranges should be defined. Also of timely interest are the significant overlap of values obtained in women with PCOS and controls and the availability of and access to high-quality assays. Regarding clinical assessment, most patients with PCOS present with clinical features of hyperandrogenism, which are relatively inexpensive to assess and require only skilled vigilant clinicians. Both medical and cosmetic treatments of hirsutism have an impact on assessment.

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Impact of a Lifestyle Modification Program on Menstrual Irregularity among Overweight or Obese Women with Polycystic Ovarian Syndrome

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Abstract

Purpose: This study aimed to evaluate the impact of a lifestyle modification program on menstrual irregularity among overweight or obese Women with polycystic ovarian syndrome. **Methods:** A quasi experimental research design was used to conduct this study on 82 women with polycystic ovarian syndrome at the Gynecology and Obesity clinics of Mansoura University Hospital, Egypt. Two groups were included; the study group received a lifestyle modification program for 48 weeks, while the control group was not subjected to this program. Three tools were used for data collection. The first was a structured questionnaire to assess the woman's general characteristics, anthropometric measurements, and menstrual pattern, the second was the Ferriman-Gallwey scale to assess the hirsutism score, while the third was 24-hours dietary recall to monitor food and drink intake. **Results:** After one year of lifestyle modification, the number of menstrual cycles significantly increased from 2.7 ± 1.6 to 6.9 ± 1.5 ($t=12.26$, $p<0.001$) in the study group compared to insignificant minor changes among the control group ($t= 0.69$, $p= 0.488$). Additionally, 58.5% were menstruating regularly compared to none in the control group ($\chi^2=33.93$, $p<0.001$). **Conclusion:** Participating in a lifestyle modification program was effective in reducing menstrual cycle's irregularity among overweight and obese women with PCOS. Thus, nurses need to be aware of and actively promote the benefits of lifestyle modification and supportive follow up for overweight/obese POCS women.

Keywords: Lifestyle modification, polycystic ovarian syndrome, menstrual cycle, overweight, obesity.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders; it affects 5-10% of women at reproductive age worldwide [1]. In Egypt, PCOS shows up to 26% of familial PCOS and 5.4% of women do not have a familial history [2]. Its hallmarks are biochemical and/or clinical hyperandrogenism in addition to chronic anovulation with subsequent menstrual disturbances such as oligo/amenorrhea [3].

Obesity, especially the truncal type, affects 17.2 % of Egyptian PCOS women [2]. It adversely influences the degree of associated insulin resistance, which in turn affects the androgen level; therefore, resulting in menstrual irregularity and hirsutism [4]. A previous study concluded that severe caloric restriction for weight reduction is associated with restoration of menstrual cycles [5]. However, long-term severe caloric restriction resulting in rapid weight loss, can lead to poor patient compliance; accordingly, the body gains its baseline weight within one year [6].

The increasing rates of obesity, among Egyptian population, are largely attributed to their lifestyles; including unhealthy dietary habits, like consuming the widely distributed junk, fast food coupled with increasing sedentary lifestyles, as it was reported that 63% of the Egyptian population at the age of twenty or more have sedentary lifestyles [7].

Recently, large studies investigated the impact of the lifestyle modification in PCOS women and suggested that modest weight loss, even as little as 5% from baseline body weight can positively affect hyperinsulinemia. As a result, it causes a decrease of androgens and normalization of menstrual cycles. Evidence supports the role of the healthcare providers in encouraging women with menstrual irregularities to change their lifestyle [8, 9].

Significance of the problem

PCOS has always been considered as a systemic problem that carries many risks at the time of presentation and later in a woman's life. For example, infrequent menstrual flow carries 3-fold increased risks of endometrial hyperplasia and endometrial carcinoma [10]. This stimulates the current study to evaluate the impact of a lifestyle modification program on menstrual irregularity among overweight or obese Women with polycystic ovarian syndrome, where Egyptian studies which investigated this topic are so limited.

1. Purpose of the study

The purpose of this study was to evaluate the impact of a lifestyle modification program on menstrual irregularity among overweight or obese Women with polycystic ovarian syndrome.

2. Hypothesis of the study

Overweight or obese women with PCOS who participate in a lifestyle modification program will experience less menstrual irregularity than those who do not participate.

METHODS

1. Study design and setting

This was designed as a quasi-experimental study. It was conducted at the obesity outpatient clinic of Rheumatology department in collaboration with the gynecology outpatient clinic of Obstetrics and Gynecology department at Mansoura University Hospitals, Egypt.

2. Sampling

A convenience sample of single women who had attended the study settings from January to August 2012, were eligible to participate in this study if they are: 1) diagnosed with PCOS based on the presence of menstrual cycle disturbances after ≥ 2 years of menarche; either in the form of oligomenorrhea (i.e. fewer than six menstrual cycles during the previous year), or amenorrhea (i.e. no menstruation for ≥ 6 months), and features of androgen excess such as hirsutism and acne (hirsutism based on the Ferriman-Gallwey score ≥ 8 after two weeks of omitting management of excessive hair) [11], 2) overweight or obese women (i.e. with a BMI of 25.0-29.9 or ≥ 30.0 respectively) [12], and 3) free from any serious medical disease requiring medical supervision and not on medical treatment known to cause menstrual disturbances.

Recruitment and group assignment

This study was comprised of a total sample of 82 clients based on visiting the study setting during the assigned study period. Each eligible client was consecutively allocated either to study or control group according to her attendance; giving two equal groups by the end of the study period. Accordingly, the study group comprised a total number of 41 clients and similarly the control group. During the study period,

five women dropped from the study group because they did not comply with the minimum number of follow-up interviews ($n=10$), and three were lost from the control group; two of them did not comply with the minimum number of follow-up interviews, while one was lost due to marriage, and all were replaced with the next potential candidates. The flowchart of the studied sample is presented in Figure 1.

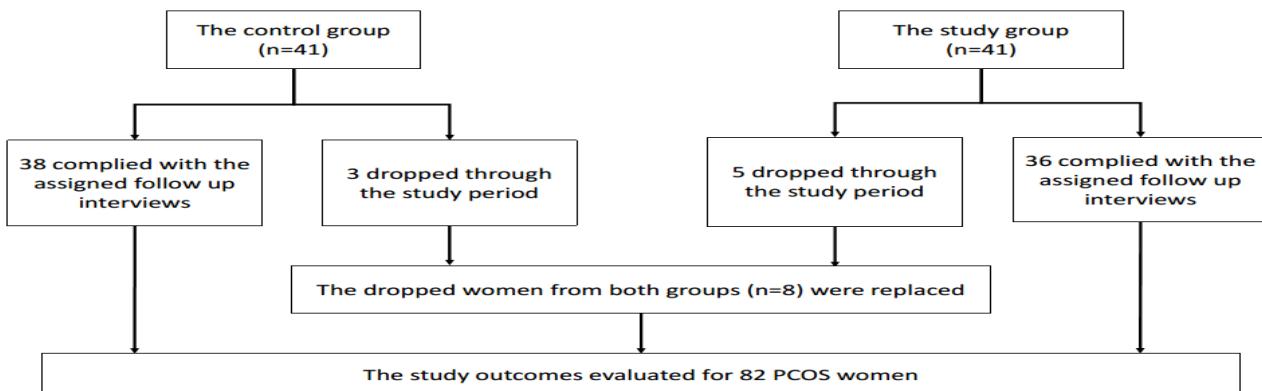


Figure (1): Flowchart of the sample

3. Measurement

Participants' general characteristics and study outcomes

A structured Questionnaire was developed by the researchers to assess the general characteristics of the participants and the study outcomes. It consists of three sections. The first section consisted of eight items on age, residence, education, and lifestyle habits (e.g., number of meals per day, components of meals, duration and form of exercise, duration of watching television per day). The second section included the menstrual history such as age of menarche, cycle length, duration of menstrual blood flow, and number and rhythm of menstrual cycles through the previous year. All the items of this section were self-reported by the clients. Moreover, the third section included anthropometrics measurements; specifically body weight, waist circumference, and BMI, those were measured by the nurse researcher.

Body weight was obtained using the same weighting scale and recorded to the nearest 0.1kg, height was measured with a fixed stadiometer and recorded to the nearest 0.5cm; while participants in bare feet, and waist circumference was measured during expiration according to the National Health and Nutrition Examination Survey anthropometric manual [13] and recorded in centimeters to the nearest 0.1cm.

Hirsutism

The Ferriman-Gallwey scale [11] is a valid universal scoring system that was used to evaluate the degree of hair growth in nine key anatomic areas (i.e. lips, chin, hands and legs, breasts, abdomen, pubic area, lower and upper back). The degree of hirsutism of each area was scored using a 4-grade scale ranged from 0 to 4, where 0 represents no hair growth and 4 means a maximum hair growth. For each respondent the scores of the nine areas were summed up to obtain the Ferriman-Gallwey Hirsutism total score. From a maximum possible score of 36, a score of ≥ 8 indicates androgen excess [11]. To maintain reliability of the collected data, hirsutism score was assessed only by the nurse investigator. This assessment was performed in a separate room and the client's privacy was strictly maintained.

Food and drink intake

A 24-hour dietary recall was used to describe the food and drink intake. It is a standardized design consisting of 3 items on a single sheet (i.e., time, quantity, and type of intake) [14]. It is a valid clinical tool filled in by every participant daily for the week preceding the clinic visit to be checked by the investigators on the interview day. Examples of type of food and drink include: At 7 am, 1/4 slice of brown bread, 5 spoons of light cheese, and a cup of tea with one spoon of sugar were consumed. At 2 pm, a chicken chest, 5 spoons green salad, two spoons of rice, and a glass of orange juice. At 7 pm, one cup of yoghurt and two apples.

4. The lifestyle modification program

The lifestyle modification program was designed as a comprehensive approach based on counseling the subjects about energy-restricted diet, eating behaviors, and physical activity. Energy-restricted diet depends on reducing the total caloric needs/day by 500 calories. The total caloric needs per day were calculated for every participant by means of the Harris-Benedict equation based on her activity level [15]. For the study group subjects, the daily caloric needs ranged from 1200-1800 calories that was divided on small frequent meals with 10-15 % from proteins, 30-35 % from fat and 55% from carbohydrates of low glycemic index [16].

Along with the energy-restricted diet, healthy balanced diet was recommended by asking the participants to consume 4-5 servings of fresh vegetables and fruits, whole grains, food rich with fibers content, daily drink a minimum of 1.5 liter of water and take a daily multivitamin supplement as ordered by the dietitian. Conversely, they were instructed to decrease food rich with saturated fats (e.g., meats, fried food), and fast food and caffeine were discouraged as a part of the healthy diet plan.

Additionally, participants were instructed on modifying their eating behaviors (e.g. avoid eating during the times of watching television or immediately before bedtime, avoid drinking through/immediately after meals; rather drink before meals time). Moreover, at least 150 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity per week were recommended [17, 18]. The lifestyle modification program contents were prepared by the research team and revised by an interdisciplinary team of dietitian, exercise physiologist and a specialist of maternity and gynecology nursing before providing it to the participants.

5. Research process

The process of this research was carried out via three phases; initial assessment, implementation of the program, follows up visits, and outcomes evaluation.

1) Initial assessment

At the baseline and before the group assignment, gynecologic history was obtained to ensure women eligibility for participation; thereafter the aim and approach of this research were explained to the clients in order to get their informed consent. Full general and clinical assessment for anthropometrics was performed by the nurse investigator, the hirsutism score was assessed, menstrual history which describes the menstrual cycle characteristics during the year preceding enrollment was obtained and recorded as baseline data.

2) Implementation of the program

I. Study group

A lifestyle modifications program was provided to the study group through two educational sessions in small groups ($n=3-5$) on two consecutive days at the Obesity Clinic with duration of approximately 45-60 minutes for each session. PCOS

definition, symptoms, and complications, in addition to the importance of weight reduction were discussed during the 1st session, while the 2nd session concerned with the permitted, forbidden food, eating behaviors, and different forms of physical activity. Both sessions were presented in a power point presentation by the nurse researcher. The study group was provided with an instructional brochure to be used as a guide for the permitted and forbidden foods and behaviors. They were asked to accurately record their dietary intake daily for the week preceding the assigned clinic visit; using a 24-hour dietary recall.

II. Control group

On the other hand, the control group was not subjected to the lifestyle modification program.

3) Follow up schedule and Outcomes evaluation

Initially for the 1st two months of enrollment, participants were followed through biweekly face-to-face interview that the nurse investigator went along with a registered dietitian at the Obesity clinic to monitor the participant's compliance with the lifestyle modification program. Then, they moved on monthly face-to-face interviews, giving a total number of fifteen face-to-face individual interviews by end of the study, including the initial interview. A telephone conversation with a pre assigned researcher was made to the client who found a difficulty in attending one or two biweekly/monthly interview. Attending the two educational sessions and a minimum number of ten follows up face-to-face/telephone interviews was considered as sufficient participation to stay in the study.

Each interview took about 10-15 minutes. During this interview the investigators had to monitor the participant's compliance with the program by way of reviewing the 24-hours dietary recalls for the one week preceding the assigned interview. As well as, inquiring the clients verbally about the type and duration of performed exercise and their eating behavior during the same period. All the outcome measures including, anthropometric measures, menstrual history, and the hirsutism score were recorded at the initial assessment and were recorded again after one year of enrollment.

6. Ethical Considerations

This study was approved by the Ethics Committee in Faculty of Nursing and Faculty of Medicine, Mansoura University, Egypt. Informed consent was obtained from each participant after clarifying the study aim and approach. Participants were assured about the confidentiality of their data as well they were informed that they have the right to withdraw at any time. Additionally, at the end of the study, clients who had been allocated to the control group were invited to be involved in the same lifestyle modification program, but separate from the intervention group, so that they were not disadvantaged.

7. Data analysis

All statistical analyses were performed using SPSS for windows version 17.0 (SPSS, Chicago, IL). Continuous data were obtained at baseline and after 12 months follow-up period were expressed as mean \pm SD and compared pre- and post-test scores in each group using paired t test. Categorical data were expressed in numbers and percent and compared using the χ^2 test. The 95 % confidence intervals (CI) for the difference in means were calculated. Statistical significance was set at $p<0.05$.

RESULTS

1. General and Clinical Characteristics of the Groups

Table 1 reveals that the general characteristics of the two groups were similar at the baseline ($p >0.05$). BMI for the study and control groups were almost identical (33.1 \pm 1.6 and 33.4 \pm 1.9 respectively; $t= 0.77$, $p= 0.442$). Most of the study and control groups (90.2% and 92.7% respectively) were obese, while the minorities (9.8% and 7.3% respectively) were overweight. Mean number of menstrual cycles was almost similar for the study and control groups (2.7 \pm 1.6 and 2.5 \pm 1.3 respectively; $\chi^2= 0.62$, $p=0.536$). Around two thirds of the study and control groups (68.3% and 65.9% respectively) were amenorrhea. Differences observed between the two groups for waist circumference and hirsutism score were not statistically significant ($t= 0.27$, $p= 0.785$; and $t= 1.03$, $p= 0.305$ respectively).

2. Effects of Lifestyle Modification on Weight, BMI, Waist Circumference, and Hirsutism score

Table 2 shows that after one year of lifestyle modification, mean weight for the study group significantly decreased by 7.4 kg reflecting a reduction of 8.7% from the baseline value ($t=5.27$ & $p<0.001$), compared to insignificant reduction in the control group by 2.5 kg reflecting a weight loss of 2.9% at end of the study ($t= 1.55$, $p= 0.125$). Similarly, among the study group BMI decreased by 2.89 ($t=7.45$, $p<0.001$), and waist circumference decreased by 8.3 cm at the end of the study ($t= 3.48$, $p=0.001$). On contrary, the changes reported in the control group were insignificant. Moreover, the hirsutism score was similar in the two groups at baseline, after one year of lifestyle modification the hirsutism score was significantly reduced in the study group by 4.2 ($t=3.65$, $p<0.001$) compared to insignificant decrease by 0.6 in the control group ($t= 0.51$, $p= 0.609$).

3. Effects of Lifestyle Modification on Menstrual Patterns

Figure 2 illustrates that the number of the menstrual cycles among the two groups did not differ significantly at baseline. It was significantly increased by 4.2 points from 2.7 ± 1.6 at baseline to 6.9 ± 1.5 after one year of lifestyle modification program in the study group ($t=12.26$, $p<0.001$), compared to insignificant change in the control group ($t=0.69$, $p= 0.488$).

Table 3 shows that no subjects in both groups had regular menses at baseline. After one year of lifestyle modification, 24 women (58.5%) in the study group were menstruating regularly compared to none in the control group. Among the study group, women who were amenorrhea and oligomenorrhea (31.7% and 68.3% respectively) were approximately halved at one year (12.2% and 29.3% respectively) with statistically significant differences ($\chi^2= 4.56$, $p= 0.033$ for amenorrhea; $\chi^2= 12.49$, $p< 0.001$ for oligomenorrhea), in contrast to the control group, which showed insignificant minor changes.

Table1. General and clinical characteristics of the study and control groups at baseline N=82

Variables	Study group	Control group	χ^2 or t test	P
	(n=41)	(n=41)		
Age (year)	24.4 ±3	24.8 ±2.8	0.62	0.534
Education level				
Secondary school	26 (63.4%)	24 (58.5%)	0.20*	0.651
University	15 (36.6%)	17 (41.5%)		
Residence				
Rural	11 (26.8%)	14 (34.1%)	0.52*	0.472
Urban	30 (73.2%)	27 (65.9%)		
Height (cm)	161.0 ±4	161.2 ±6	0.18	0.859
Body weight (kg)	85.8±5.5	86.7 ±7.3	0.63	0.540
BMI (kg/m²)	33.1 ±1.6	33.4 ±1.9	0.77	0.442
Obesity categories				
Overweight (no & %)	4 (9.8%)	3 (7.3%)	0.16	0.693
Range	29.7 – 29.9	28.6 – 29.7		
Mean ±SD	29.8 ±0.1	29.7 ±0.6	1.05	0.296
Obese (no & %)	37 (90.2%)	38 (92.7%)	0.16	0.693
Range	31.4 – 36.1	30.5 – 37.9		
Mean ±SD	33.5 ±1.3	33.8 ±0.6	1.34	0.184
Waist circumference (cm)	104.9 ±10.8	104.2 ±12.3	0.27	0.785
Hirsutism score	19.1 ±5.9	17.8 ±5.5	1.03	0.305
Menstrual rhythm in last year pre enrollment				
Number of menstrual cycles	2.7 ±1.6	2.5 ±1.3	0.62	0.536
Amenorrhea	13 (31.7%)	14 (34.1%)	0.05*	0.842
Oligomenorrhea	28 (68.3%)	27 (65.9%)		

* Chi square test

Table 2. Comparison between the study and control groups in body weight, BMI, waist circumference, and hirsutism score

Variables	Groups	Pre	Post	Difference	t	P
Body weight (kg)	Study (n=41)	85.8 ± 5.5	78.4 ± 7.1	-7.4 ± 0.8	5.27	<0.001
	Control(n=41)	86.7 ± 7.3	84.2 ± 7.3	-2.5 ± 0.3	1.55	0.125
BMI (kg/m^2)	Study (n=41)	33.1 ± 1.6	30.2 ± 1.9	-2.89 ± 0.2	7.45	<0.001
	Control(n=41)	33.4 ± 1.9	32.4 ± 1.6	-0.68 ± 0.2	1.75	0.083
Waist circumference (cm)	Study (n=41)	104.9 ± 10.8	96.6 ± 10.8	-8.3 ± 0.9	3.48	0.001
	Control(n=41)	104.2 ± 12.3	103.3 ± 12.5	-0.09 ± 0.01	0.33	0.743
Hirsutism score	Study (n=41)	19.1 ± 5.9	14.9 ± 4.4	-4.2 ± 1.1	3.65	<0.001
	Control(n=41)	17.8 ± 5.5	17.2 ± 5.1	-0.6 ± 0.2	0.51	0.609

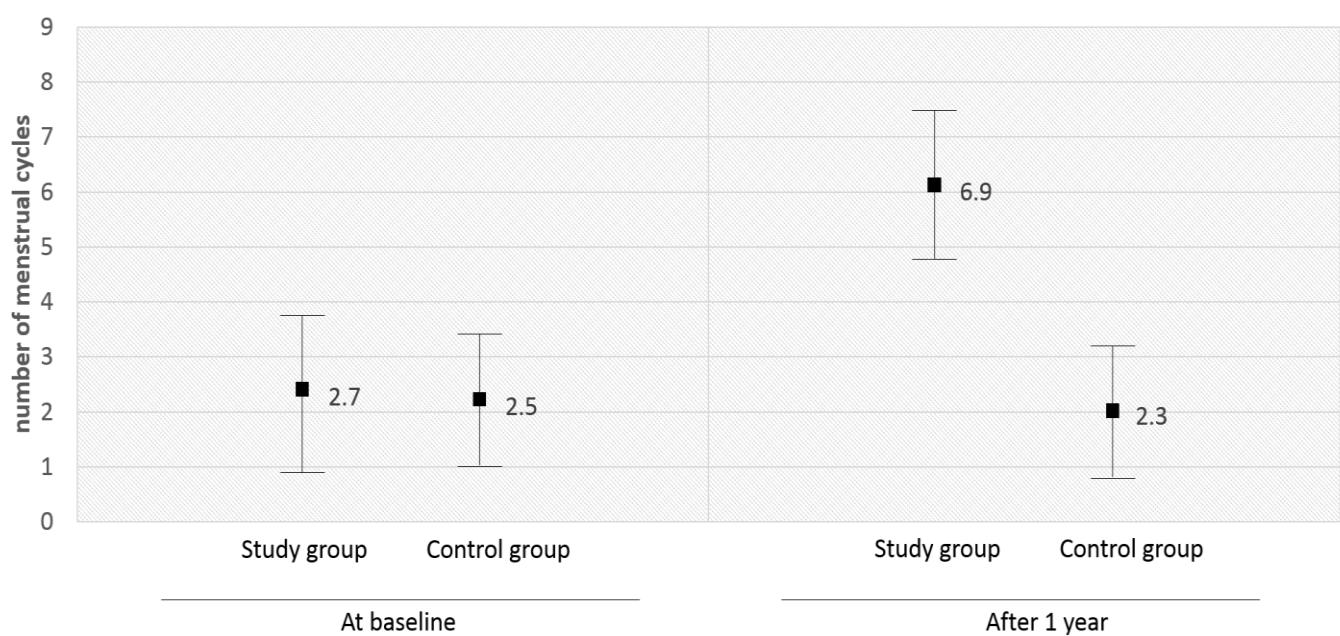


Figure 2. Number of menstrual cycles among the study and control groups at baseline and after one year of enrollment.

Table 3. Comparison between the study and control groups in rhythm of menstrual cycles

Variable	Groups	At baseline	After one year	χ^2	P
Rhythm of menstrual cycles (no & %)					
Amenorrhea	Study(n=41)	13(31.7%)	5 (12.2%)	4.56	0.033
	Control(n=41)	14 (34.1)	17(41.5%)	0.47	0.494
Oligomenorrhea	Study (n=41)	28 (68.3%)	12 (29.3%)	12.49	<0.001
	Control(n=41)	27 (65.9%)	24 (58.5%)	0.47	0.494
Regular	Study (n=41)	0 (0%)	24 (58.5%)	33.93	<0.001
	Control(n=41)	0 (0%)	0 (0%)	-	-

DISCUSSION

The present study aimed to evaluate the impact of a lifestyle modification program on menstrual irregularity among overweight or obese Women with polycystic ovarian syndrome. This aim was achieved through the present study finding which revealed a significant decrease in menstrual cycle irregularities among the study group after one year of lifestyle modification. Accordingly, the study hypothesis was confirmed, "overweight or obese women with PCOS who participate in a lifestyle modification program experience less menstrual irregularity than those who do not participate."

This study finding is consistent with previous studies that investigated the impact of lifestyle modification on managing PCOS symptoms among adult women. Such studies concluded that lifestyle modification results in weight loss with subsequent improvement of menstrual cycle irregularities and androgen excess [19-22].

The present study showed that among the study group with 8.7% weight reduction from the baseline value, frequency of amenorrhea and oligomenorrhea was significantly decreased and led more than half of the participants to have regular menstruation after one year of lifestyle modification compared to none at baseline. Similar to the present study, a previous study had analyzed the impact of a comprehensive lifestyle modification program on menstrual irregularities among 59 obese German girls with PCOS. After one year of lifestyle modification the authors

dichotomized the studied group into successful weight loss group (n=26) and unsuccessful weight loss group (n=33) and reported a significant decrease in the prevalence of amenorrhea and oligomenorrhea from baseline (by 42% and 19%, respectively) among the successful weight loss group compared to insignificant decrease (by 6% and 3% respectively) among the unsuccessful weight loss group [23].

Also, Hoeger et al. [24] conducted a clinical trial in New York; over one year, to study the effect of intensive lifestyle intervention and/or metformin on menstrual events among 38 overweight or obese women with PCOS. They found a significant restoration of ovulation and menstrual events only when the lifestyle modifications were implemented along with the medical treatment.

Such agreement between the present study findings and the findings of the previously described two studies [23, 24] may be explained by the fact that insulin resistance is more likely to be associated with hyperinsulinemia, and it is evidenced that hyperinsulinemia acts as a leading cause of elevated androgen levels among PCOS women [25]. Based on that notion the researchers of the present study attributed the improvement of menstrual irregularities to the decrease in insulin resistance in the study group; that was evidenced by a significant reduction in the waist circumference at end of the study [26], causing a reduction in hyperinsulinemia, accordingly improving menstrual irregularity.

Also, the present study investigated the changes in the number of menstrual cycles over the study period and revealed a significant increase in the study group compared to insignificant changes in the control group. Interestingly the present study results agreed with the findings of Ornstein et al. [27]. They had conducted a pilot study in New York on 24 young adult/adolescent women with PCOS, aiming to investigate the effect of weight loss on menstrual function by assigning the participants randomly into low fat or low caloric diet. The authors had found a significant increase in the average menstrual cycles over the study period from 0.6 ± 0.6 pre-treatment to 1.6 ± 1.3 post-treatment ($p=0.003$), with a weight loss of 6.5% ($p < 0.001$) in both dietary regimens groups. Moreover, by dichotomizing the participants into successful weight

loss or unsuccessful weight loss groups, the authors [27] observed that women who successfully lost their weight were 3.4 times more likely to have improvement in their menstrual function compared to those who did not loss their weight ($P = 0.001$). Our study recommended ‘energy-restricted diet’ for the study group and there were no specific recommendations for the control, which makes direct comparison with Ornstein’s study difficult, but we also found that menstrual patterns improved with weight loss. The reported significant increase in the number of the menstrual cycles may be related to the decrease in the stimulation of ovarian androgen production as a result of the associated reduction in hyperinsulinemia [19].

Using the Ferriman-Gallwey score, hirsutism showed a significant decrease in the study group compared to insignificant changes among the control group. Such finding is congruent with the finding of a prospective intervention study [28] conducted in Ain Shams maternity hospital, Egypt. It investigated the effectiveness of lifestyle modification; specifically, dietary counseling and exercise on PCOS symptoms in 64 women in their reproductive age. The investigators had concluded that women with PCOS who attained weight reduction as a result of lifestyle modification had showed a significant improvement in total hirsutism score. Such agreement between our finding and the Egyptian study finding [28] may be related to the improvement of the androgen excess level as a result of lifestyle modification that results in a decrease in hirsutism score.

Conversely, the present study disagrees with Hoeger et al. [24], mentioned above, which did not find significant changes of hirsutism scores by lifestyle intervention and/or metformin use. Such disagreement may be explained by two rationales; firstly, it may be related to how Hoeger and his colleagues had evaluated the hirsutism score. As in the current study the researchers considered that most women with PCOS are using cosmetic methods to manage their hirsutism, thus the women enrolled in this study were instructed to omit the hair management for the two weeks preceding hirsutism evaluation, while in the Hoeger's study [24] the interval between the excessive hair management and assessing hirsutism score is not clear, whether it was the same, shorter, or longer time interval and whether clients continued to manage the

hirsutism or not. Secondly, it may be due to the younger age group of enrolled clients in the current study. All the participants were young (in mid-twenties, compared to the Hoeger's sample [24] who had a mean age of 29.4 ± 5.7 years), post-pubertal, single, and had variable degrees of hirsutism, reflecting the exposure to the excess androgen in a relative shorter period of life.

Two limitations were raised in this study. First, the investigators relied only on the waist circumference as an indicator of insulin resistance, rather relying on more specific measures such as fasting glucose, HDL cholesterol, triglycerides and blood pressure would have been advantageous to confirm the study findings. Second, the dietary intake was evaluated according to the 24-hours dietary recalls for the last week preceding the assigned interview; indicating lack of data about the other days of the preceding month; however it was not applicable to ask the woman to daily record her intake.

Considering PCOS as heterogeneous in nature with a wide range of symptoms; health care providers working in gynecology clinics need an in-depth understanding of its pathophysiology, diagnostic measures, and symptom management. This study and others stress nurses' and gynecologists' role to ensure patients receive adequate oral and written information on lifestyle modification to be of guidance for them.

CONCLUSION & RECOMMENDATIONS

Based on the study findings the researchers conclude that lifestyle modification results in a significant reduction of menstrual irregularity with 8.7% weight reduction from the baseline value. Such findings stimulate the following recommendations:

1. Nurses need to be aware of and actively promote the benefits of lifestyle modification and supportive follow up for overweight/obese PCOS women.
2. Future research with larger sample size at different institutions is recommended.

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Summary Statement

What is already known about this topic?

Lifestyle modification for PCOS women has been found to be successful in weight loss and normalization of menstrual cycles. However, there is lack of studies that employed a control group to ensure the effect of lifestyle modification where these subjects might have lost weight without any intervention.

What does this paper add?

Using a quasi-experimental design, a multidisciplinary team approach offered support/counseling in a lifestyle modification intervention to overweight/obese PCOS women for 48 weeks and was effective in reducing irregularity of menstrual cycles.

Implications for practice, education and/or policy

It is important for nurses to be aware that young Egyptian women with PCOS may be reluctant to seek help, and to actively promote the benefits of lifestyle modification and supportive follow up for overweight/obese PCOS women.

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Insulin Resistance and the Polycystic Ovary Syndrome: Mechanism and Implications for Pathogenesis¹

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► I. Introduction

A. Background and historical perspective

POLYCYSTIC ovary syndrome (PCOS) is an exceptionally common disorder of premenopausal women characterized by hyperandrogenism and chronic anovulation ([1](#), [2](#)). Its etiology remains unknown. Although there have been no specific population-based studies, a 5–10% prevalence of this disorder in women of reproductive age is probably a reasonable conservative estimate. This is based as an upper limit on studies of the prevalence of polycystic ovaries, which found that ~20% of self-selected normal women had polycystic ovary morphology on ovarian ultrasound ([3](#)). Many of these women had subtle endocrine abnormalities ([3](#)). The lower estimate is based on the reported 3% prevalence rate of secondary amenorrhea for 3 or more months ([4](#)) and the fact that up to ~75% of women with secondary amenorrhea will fulfill diagnostic criteria for PCOS ([5](#)). PCOS women can also have less profound disturbances in menstrual function ([1](#), [3](#), [6](#)).

Since the report by Burghen *et al.* ([7](#)) in 1980 that PCOS was associated with hyperinsulinemia, it has become clear that the syndrome has major metabolic as well as reproductive morbidities. The recognition of this association has also instigated extensive investigation of the relationship between insulin and gonadal function ([1](#), [8](#), [9](#), [10](#), [11](#)). This review will summarize our current understanding of insulin action in PCOS, address areas of controversy, and propose several hypotheses for this association. Abnormalities of steroidogenesis and gonadotropin release will not be discussed in detail; these changes have been reviewed recently by Ehrmann and colleagues ([12](#)) and by Crowley ([13](#)), respectively.

The association between a disorder of carbohydrate metabolism and hyperandrogenism was first described in 1921 by Achard and Thiers ([14](#)) and was called "the diabetes of bearded women (diabète des femmes à barbe)." The skin lesion, acanthosis nigricans, was reported to occur frequently in women with hyperandrogenism and diabetes mellitus by Kierland *et al.* ([15](#)) in 1947. Brown and Winkelmann ([16](#)) noted in 1968 that it was insulin-resistant diabetes mellitus, and a genetic basis was suggested by reports of

affected sisters (17), including a pair of identical twins who also had acromegaloid features (18). Several additional syndromes with distinctive phenotypic features, acanthosis nigricans, hyperandrogenism, and insulin-resistant diabetes mellitus have been identified (Table 1+). These include the lipoatrophic (total and partial) diabetes syndromes, leprechaunism (intrauterine growth retardation, gonadal enlargement, elfin facies, and failure to thrive), and Rabson-Mendenhall syndrome (unusual facies, pineal hypertrophy, dental precocity, thickened nails, and ovarian enlargement) (8, 19, 20).

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Table 1. Syndromes of hyperandrogenism and hyperinsulinemia

Attention was focused on the association of hyperandrogenism, insulin resistance, and acanthosis nigricans in 1976 when Kahn and colleagues (21) described a distinct disorder affecting adolescent girls, which they designated the type A syndrome. These girls were virilized (*i.e.*, increased muscle bulk, clitoromegaly, temporal balding, deepening of the voice) and had extreme insulin resistance with diabetes mellitus as well as striking acanthosis nigricans. This group identified a second distinct extreme insulin resistance syndrome in postmenopausal women with acanthosis nigricans and features of autoimmune disease, which they termed the type B syndrome and determined that it was caused by endogenous antiinsulin receptor antibodies (22, 23). Subsequent studies have identified insulin receptor mutations as the cause of leprechaunism, Rabson-Mendenhall Syndrome, and some cases of type A syndrome (19, 23).

In 1980 Burghen and colleagues (7) reported that women with the common hyperandrogenic disorder, PCOS, had basal and glucose-stimulated hyperinsulinemia compared with weight-matched control women, suggesting the presence of insulin resistance. They noted significant positive linear correlations between insulin and androgen levels and suggested that this might have etiological significance. In the mid-1980s several groups noted that acanthosis nigricans occurred frequently in obese hyperandrogenic women (24, 25, 26, 27) (Fig. 1+). These women had hyperinsulinemia basally and during an oral glucose tolerance test, compared with appropriately age- and weight-matched control women. The presence of hyperinsulinemia in PCOS women, independent of obesity, was confirmed by a number of groups worldwide (28, 29, 30).



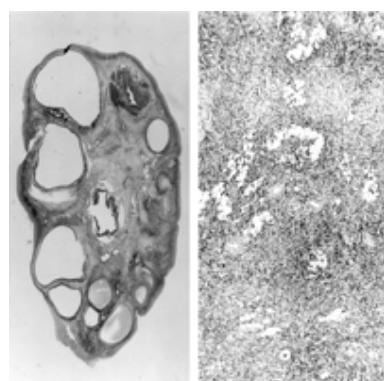
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Figure 1. A woman with PCOS who has acanthosis nigricans, a cutaneous marker of insulin resistance (panel A). She also has severe hirsutism on her face and chest (panels B and C). [Reproduced from A. Dunaif *et al.*: *Obstet Gynecol* 66:545–552, 1985 (25) with permission from The American College of Obstetricians and Gynecologists.]

Our study (25) suggested that these women had typical PCOS, except for increased ovarian stromal hyperthecosis, which is diagnosed by finding islands of luteinized theca cells within the ovarian stroma (25). When this is very extensive, it is called hyperthecosis and is associated with more profound hyperandrogenism (31). Hughesdon (32) reported, however, that upon careful examination of ovaries from PCOS women, small islands of hyperthecosis were usually present. This morphological change was more extensive in insulin-resistant PCOS women, suggesting that hyperinsulinemia had an impact on ovarian morphology as well as on function (25) (Fig. 2•). This hypothesis has been further supported by the finding, in a subsequent study (33), of a positive correlation between hyperinsulinemia and ovarian stromal hyperthecosis.



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Figure 2. Section of a polycystic ovary with multiple subcapsular follicular cysts and stromal hypertrophy (*left panel*). At higher power (x100) islands of luteinized theca cells are visible in the stroma (*right panel*). This morphological change is called stromal hyperthecosis and appears to be directly correlated with circulating insulin levels. [Figure is used with permission from A. Dunaif.]

B. Definition of PCOS

The current recommended diagnostic criteria for PCOS are hyperandrogenism and ovulatory dysfunction with the exclusion of specific disorders, such as nonclassic adrenal 21-hydroxylase deficiency, hyperprolactinemia, or androgen-secreting neoplasms (1) (Table 2). The polycystic ovary morphology is consistent with, but not essential for, the diagnosis of the *syndrome* (1, 3). Polycystic ovaries are defined on ultrasound by the presence of eight or more subcapsular follicular cysts ≤ 10 mm and increased ovarian stroma (2, 3). These changes, however, can be present in women who are entirely endocrinologically normal (2, 3). Thus, the ovarian morphological change must be distinguished from the endocrine *syndrome* of hyperandrogenism and anovulation.

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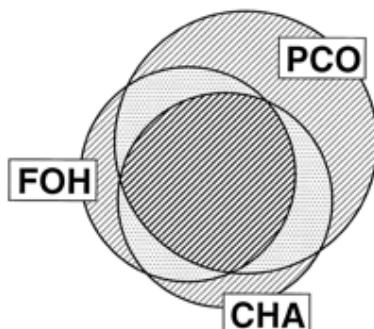
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Table 2. Diagnostic criteria for PCOS—% participants agreeing at 1990 NICHD PCOS Conference (1)

Gonadotropin-secretory changes, with a characteristic increase in LH relative to FSH release, have long been appreciated in PCOS (34, 35). Frequent (e.g., every 10 min), prolonged (12–24 h) serial blood sampling studies have revealed that there is a significant increase in the frequency and the amplitude of LH release with normal FSH release in PCOS (36, 37). The increased LH pulse frequency reflects an increase in GnRH release and suggests the presence of a hypothalamic defect in PCOS (13, 37). Other causes of hyperandrogenism, however, can result in similar gonadotropin-secretory changes, such as androgen-secreting neoplasms (38) or adrenal hyperandrogenism resulting from nonclassic 21-hydroxylase deficiency (39). Ovulatory women with the polycystic ovary morphology can have increased LH/FSH ratios (2). Because of the pulsatile nature of gonadotropin release, a single blood sample can fail to detect an increased LH/FSH ratio (40). This, as well as its lack of specificity, has led to the recommendation that LH/FSH ratios not be included in the diagnostic criteria for PCOS (1).

Other nomenclature has been proposed for the *syndrome*, e.g., chronic hyperandrogenic anovulation (CHA) (1). Many hyperandrogenic anovulatory women have significantly increased ovarian steroidogenic responses to stimulation with GnRH analogs that Rosenfield and colleagues (41) have termed functional ovarian hyperandrogenism (FOH). They have proposed this as an alternative name for PCOS (12). The majority of

women who have hyperandrogenemia and chronic anovulation will have polycystic ovary (PCO) on ultrasound and will have responses to GnRH analogs consistent with FOH (1, 2, 12) (Fig. 3*). Thus, the terms PCOS, FOH, and CHA define similar groups of women (Fig. 3*).



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Figure 3. The majority of women with CHA will also have polycystic ovary morphology (PCO) and responses to GnRH analogs consistent with FOH. [Figure is used with permission from A. Dunaif.]

PCOS often has a menarchal age of onset characterized by a failure to establish a regular pattern of menses (42). Hirsutism may develop peripubertally or during adolescence (42) or it may be absent until the third decade of life (43). Seborrhea, acne, and alopecia are other common clinical signs of hyperandrogenism (44, 45). Some women never develop signs of androgen excess because of genetic differences in target tissue number and/or sensitivity to androgens (46). The clinical consequence of chronic anovulation is some form of menstrual irregularity ranging from oligomenorrhea (menses every 6 weeks to 6 months), amenorrhea, or dysfunctional uterine bleeding (2, 5, 6). Infertility may be the presenting symptom of the anovulation. Depending on the population studied, 16–80% of PCOS women are obese (47, 48, 49). Mild to moderate acanthosis nigricans is commonly present in obese PCOS women (25, 26, 27, 49, 50). A rapid progression of androgenic symptoms and/or true virilization (increased muscle bulk, clitoromegaly, temporal balding, and/or deepening of the voice) are rare in PCOS (2, 6, 42). PCOS women can occasionally have acromegaloïd features (44).

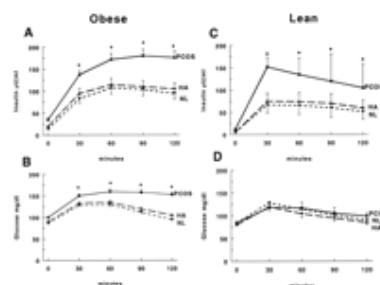
It is important to recognize that there is an inherent bias of ascertainment in studies of PCOS that constrains the assessment of the frequency of associated clinical and biochemical findings. Obviously, all women will have polycystic ovaries when this feature is an essential diagnostic criterion. Studies that use an increased LH/FSH ratio as a selection criterion will be biased toward finding increased pulsatile LH release when gonadotropin secretion is examined. The appropriate study would be a population-based one in which clinical and biochemical features were systematically examined in a defined population of women. Until such a study is performed, the prevalence of PCOS and frequency of associated findings will remain subject to debate.

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► II. Insulin Action in PCOS

A. Glucose tolerance

Insulin resistance is an important defect in the pathogenesis of noninsulin-dependent diabetes mellitus (NIDDM) (51). Despite the fact that hyperinsulinemia, reflecting some degree of peripheral insulin resistance, was well recognized in PCOS by the mid-1980s (Fig. 4•), glucose tolerance was not systematically investigated until our study in 1987 (49). We found that obese PCOS women had significantly increased glucose levels during an oral glucose tolerance test compared with age- and weight-matched ovulatory hyperandrogenic (*i.e.*, elevated plasma androgen levels) and control women (Fig. 4•). Twenty percent of the obese PCOS women had impaired glucose tolerance or frank NIDDM by National Diabetes Data Group Criteria (49, 52) (Fig. 4•). The women studied ranged in age from 18–36 yr with a mean age of 27 yr for the obese PCOS women. There were no significant differences, however, in glucose levels during the oral glucose tolerance test in the nonobese PCOS women compared with age- and weight-matched control women (Fig. 4•).



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Figure 4. Insulin (panels A and C) and glucose (panels B and D) responses basally and after a 40 g/m² oral glucose load in obese and lean PCOS women, ovulatory hyperandrogenic women (HA) women, and age- and weight-matched ovulatory control women. Insulin responses are significantly increased only in PCOS women, suggesting that hyperinsulinemia is a unique feature of PCOS and not hyperandrogenic states in general (panels A and B). Glucose responses are

significantly increased only in obese PCOS women (C), and ~20% of obese PCOS women have impaired glucose tolerance or NIDDM using National Diabetes Data Group Criteria (52). [Derived from Ref. 49.]

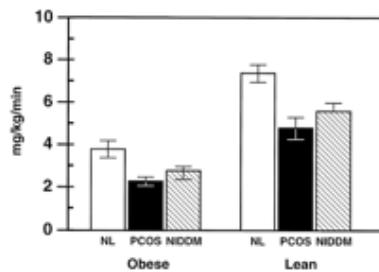
A subsequent study in postmenopausal women with a history of PCOS found a significantly increased prevalence of NIDDM as well as of hypertension (see below) (53). We have continued to find prevalence rates of glucose intolerance as high as ~40% in obese PCOS women when the less stringent World Health Organization (WHO) criteria are used (49, 52, 54, 55, 56, 57). The majority of affected women are in their third and fourth decade of life, but we and others (58) have encountered PCOS adolescents with impaired glucose tolerance or NIDDM. These prevalence rates of 20–40% are substantially above prevalence rates for glucose intolerance reported in population-based studies in women of this age (5.3% by National Diabetes Data Group criteria and 10.3% by WHO criteria in women aged 20–44 yr) (59). We have found that the prevalence of glucose intolerance is significantly higher in obese PCOS women (~30%) than in concurrently studied age-, ethnicity-, and weight-matched ovulatory control women (~10%) (48). In contrast, we have found that nonobese PCOS women have impaired glucose tolerance only occasionally, consistent with the synergistic negative effect of obesity and PCOS on glucose tolerance (54, 55). Finally, based on the prevalence of glucose intolerance in women (59), the prevalence of glucose intolerance in PCOS (49), and on a conservative estimate of the prevalence of PCOS (~5%), it can be extrapolated that PCOS-related insulin resistance contributes to approximately 10% of cases of glucose intolerance in premenopausal women. The study in postmenopausal women with a history of PCOS found a 15% prevalence of NIDDM (53), consistent with our extrapolated prevalence estimates. It is thus clear that PCOS is a major risk factor for NIDDM in women, regardless of age.

B. Insulin action *in vivo* in PCOS

Although insulin has a number of actions, in addition to those regulating glucose metabolism, such as inhibition of lipolysis and stimulation of amino acid transport (51), the effects of insulin on glucose metabolism are usually examined in studies of insulin resistance (60). This can be studied quantitatively in humans with the euglycemic glucose clamp technique: a desired dose of insulin is administered and euglycemia is maintained by a simultaneous variable glucose infusion whose rate is adjusted based on frequent arterialized blood glucose determinations and a negative feedback principle (60, 61, 62). At steady state, the amount of glucose that is infused equals the amount of glucose taken up by the peripheral tissues and can be used as a measure of peripheral sensitivity to insulin, known as insulin-mediated glucose disposal (IMGD) or M (61, 62). The suppression of hepatic glucose production by insulin can be assessed by the use of a simultaneous infusion of isotopically labeled glucose. Insulin-mediated glucose disposal occurs only in muscle (skeletal and cardiac) and in fat; muscle accounts for about 85% of this (60).

Euglycemic glucose clamp studies have demonstrated significant and substantial decreases in insulin-mediated glucose disposal in PCOS (54, 55) (Fig. 5•). This decrease (~35–40%) is of a similar magnitude to that seen in NIDDM (Fig. 5•). Obesity (fat mass *per se*), body fat location (upper vs. lower body, *e.g.*, waist to hip girth ratio), and muscle mass all have important independent effects on insulin sensitivity (63, 64, 65, 66). Alterations in any of these parameters could potentially contribute to insulin

resistance in PCOS. PCOS women have an increased prevalence of obesity ([6](#), [47](#)), and women with upper, as opposed to lower body, obesity have an increased frequency of hyperandrogenism ([66](#)). Since muscle is the major site of insulin-mediated glucose use ([60](#)) and androgens can increase muscle mass ([67](#)), potential androgen-mediated changes in lean body (primarily muscle) mass must also be controlled for in PCOS ([54](#), [55](#)). Studies in which body composition, assessed by the most precise available method (hydrostatic weighing), has been matched to normal control women, and in which lean PCOS women, who had body composition and waist to hip girth ratios similar to controls, were studied, have confirmed that PCOS women are insulin resistant, independent of those potentially confounding parameters ([1](#), [55](#), [68](#)). The impact of hyperandrogenism on insulin sensitivity is discussed below, but studies in cultured cells have confirmed the impression from these *in vivo* studies that an intrinsic defect in insulin action is present in PCOS ([69](#)).



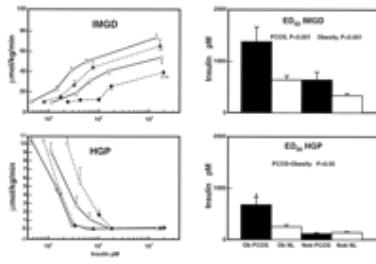
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Figure 5. Insulin-mediated glucose disposal at steady-state insulin levels of ~600 pmol/liter (~100 μ U/ml) is decreased by 35–40% in PCOS women compared with age- and weight-matched control women. This decrease is similar in magnitude to that seen in NIDDM. [Figure is used with permission from A. **Dunaif**.]

Basal hepatic glucose production and the ED₅₀ value of insulin for suppression of hepatic glucose production are significantly increased only in obese PCOS women ([54](#), [55](#)) (Fig. 6•). This synergistic negative effect of obesity and PCOS on hepatic glucose production is an important factor in the pathogenesis of glucose intolerance ([49](#), [54](#), [55](#), [70](#)). This is analogous to NIDDM in general where defects in insulin action, presumably genetic, synergize with environmentally induced insulin resistance, primarily obesity-related, to produce glucose intolerance ([51](#), [60](#)). Sequential multiple-insulin-dose euglycemic clamp studies have indicated that the ED₅₀ insulin for glucose uptake is significantly increased, and that maximal rates of glucose disposal are significantly decreased in lean and in obese PCOS women ([55](#)) (Fig. 6•). It appears, however, that body fat has a more pronounced negative effect on insulin sensitivity in women with PCOS ([68](#), [71](#)).



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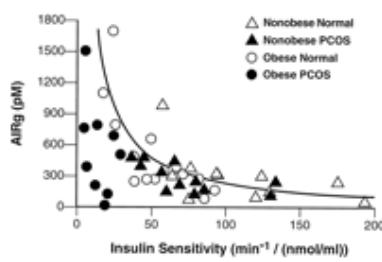
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Figure 6. Parameters of *in vivo* insulin action during sequential multiple-dose euglycemic glucose clamp studies in nonobese PCOS women (\blacktriangle , Nob PCOS); nonobese normal women (\triangle , Nob NL); obese PCOS women (\bullet , Ob PCOS); and obese normal women (\circ , Ob NL). The maximal response in the dose-response curves (*top left*) for insulin-mediated glucose disposal (IMGD) is significantly decreased in obesity ($*P < 0.001$) and in PCOS ($**P < 0.01$). The ED₅₀ insulin IMDG is significantly increased in PCOS women ($P < 0.001$) and in obese women ($P < 0.001$) (*top right*). Basal rates of hepatic glucose production (HGP) are not significantly different in the four groups (*bottom left*). The statistical interaction is significant between PCOS and obesity on the ED₅₀ insulin for suppression of HGP (*bottom right*), which is increased significantly in obese PCOS women ($*P < 0.001$) indicating a synergistic deleterious effect of obesity and PCOS on hepatic insulin sensitivity. [Reproduced with permission by A. Dunaif *et al. Diabetes* 41:1257–1266, 1992 (55).]

C. Insulin secretion in PCOS

In the presence of peripheral insulin resistance, pancreatic β -cell insulin secretion increases in a compensatory fashion. NIDDM develops when the compensatory increase in insulin levels is no longer sufficient to maintain euglycemia (72, 73). It is essential, therefore, to examine β -cell function in the context of peripheral insulin sensitivity. Under normal circumstances, this relationship is constant (72, 74) (Fig. 7*). β -Cell dysfunction is felt to be present for values falling below this hyperbolic curve (73, 74). This relationship can be quantitated as the product of insulin sensitivity and first-phase insulin release known as the disposition index (72).



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Figure 7. The relationship between insulin sensitivity (SI) determined by frequently sampled intravenous glucose tolerance test and first-phase insulin secretion to an intravenous glucose load (AIRg). The majority of PCOS women fall below the normal curve determined in concurrently studied age- and weight-matched control women as well as normative data in the literature. [Derived from Ref. 57.]

Fasting hyperinsulinemia is present in obese PCOS women and this is, in part, secondary to increased basal insulin secretion rates (Fig. 4+ and Ref. 75). Insulin responses to an oral glucose load are increased in lean and obese PCOS women (Fig. 4+), but acute insulin responses to an intravenous glucose load (AIRg), first-phase insulin secretion, are similar to weight-matched control women (49, 57). When the relationship between insulin secretion and sensitivity is examined, lean and obese PCOS women fall below the relationship in weight-matched control women, and the disposition index is significantly decreased by PCOS as well as by obesity (57) (Fig. 7+). Further evidence for β -cell dysfunction in PCOS is provided by the elegant studies of Erhmann *et al.* (76), who have demonstrated defects in β -cell entrainment to an oscillatory glucose infusion and decreased meal-related insulin secretory responses (75). These defects are much more pronounced in PCOS women who have a first-degree relative with NIDDM, suggesting that such women may be at particularly high risk to develop glucose intolerance (76). There are reports of increased insulin secretion in PCOS, but these studies have not examined insulin secretion in the context of insulin sensitivity and/or have included women in whom the diagnosis was made on the basis of ovarian morphological changes rather than endocrine criteria (71, 77). In summary, the most compelling evidence suggests that β -cell dysfunction, in addition to insulin resistance, is a feature of PCOS. The ability to diagnose PCOS at the time of puberty will make possible prospective longitudinal studies of the ontogeny of these defects.

D. Insulin clearance in PCOS

Hyperinsulinemia can result from decreases in insulin clearance as well as from increased insulin secretion. Indeed, decreased insulin clearance is usually present in insulin-resistant states since insulin clearance is receptor-mediated, and acquired decreases in receptor number and/or function are often present in insulin resistance secondary to hyperinsulinemia and/or hyperglycemia (78, 79). Thus, PCOS would be expected to be associated with decreases in insulin clearance; however, relatively few studies have examined this question. Direct measurement of posthepatic insulin clearance during euglycemic clamp studies has not been abnormal in PCOS (54, 56). Circulating insulin to C-peptide molar ratios are increased in PCOS, suggesting decreased hepatic extraction of insulin, but such ratios also reflect insulin secretion (28, 80). Direct measurement of hepatic insulin clearance in non-PCOS hyperandrogenic women has found it to be decreased (81). The one study of this question in PCOS found decreased hepatic insulin extraction by model analysis of C-peptide levels (75). Therefore, in PCOS, hyperinsulinemia is probably the result of a combination of increased basal insulin secretion and decreased hepatic insulin clearance.

E. Cellular and molecular mechanisms of insulin resistance

1. *Molecular mechanisms of insulin action (Figs. 8+ and 9+).* Insulin acts on cells by binding to its cell surface receptor (51, 82, 83). The insulin receptor is a heterotetramer

made up of two α , β - dimers linked by disulfide bonds (84) (Fig. 8•). Each α , β -dimer is the product of one gene (85, 86). The α -subunit is extracellular and contains the ligand-binding domain whereas the β -subunit spans the membrane, and the cytoplasmic portion contains intrinsic protein tyrosine kinase activity, which is activated further by ligand-mediated autophosphorylation on specific tyrosine residues (87) (Fig. 8•). The insulin receptor belongs to a family of protein tyrosine kinase receptors that includes the insulin-like growth factor-I (IGF-I) receptor, with which it shares substantial sequence and structural homology, as well as the epidermal growth factor (EGF), fibroblast growth factor, platelet-derived growth factor, and colony-stimulating factor-1 receptors (88). A number of oncogene products are also protein tyrosine kinases (85, 89).

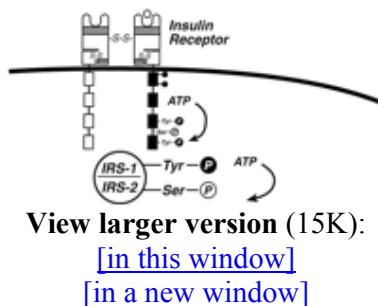


Figure 8. The insulin receptor is a heterotetramer consisting of two α , β -dimers linked by disulfide bonds. The α -subunit contains the ligand-binding site, and the β -subunit contains a ligand-activated tyrosine kinase. Tyrosine autophosphorylation increases the receptor's tyrosine kinase activity whereas serine phosphorylation inhibits it. [Adapted with permission from C. R. Kahn: *Diabetes* 43:1066–1084, 1994 (51).]

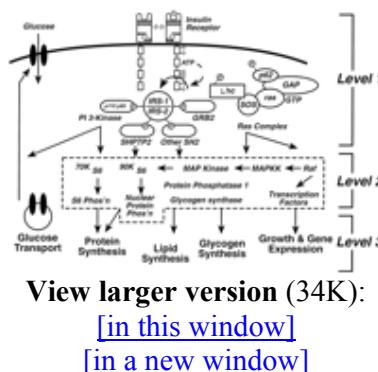


Figure 9. The tyrosine-phosphorylated insulin receptor phosphorylates intracellular substrates, such as insulin receptor substrate (IRS)-1 and IRS-2, initiating signal transduction and the pleiotropic actions of insulin. The activation of PI3-K (PI3-kinase) by tyrosine-phosphorylated IRS-1 appears to be the pathway for insulin-mediated glucose transport. The Ras-MAP kinase pathway appears to regulate cell

growth and glycogen synthesis. [Adapted with permission from C. R. Kahn: *Diabetes* 43:1066–1084, 1994 (51).]

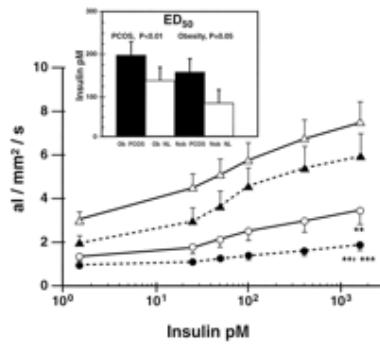
Ligand binding induces, probably via conformational changes, autophosphorylation of the insulin receptor on specific tyrosine residues and further activation of its intrinsic kinase activity (Fig. 8+) (90, 91, 92). The activated insulin receptor then tyrosine phosphorylates intracellular substrates to initiate signal transduction (Fig. 9+) (82). Over the last few years a number of these substrates have been characterized. The first was insulin receptor substrate-1 (IRS-1), which serves as a docking molecule for signaling and adaptor molecules (93, 94). The tyrosine-phosphorylated insulin receptor tyrosine phosphorylates IRS-1 on specific motifs, and these phosphorylated sites then bind signaling molecules, such as the SH2 domain of phosphatidylinositol 3-kinase (PI3-K), or the adaptor molecule, Nck (51, 82, 94). This leads to activation of downstream signaling pathways, such as that leading to insulin-mediated glucose transport, which appears to be modulated through the PI3-K signal cascade (82). More recently, insulin receptor substrate-2 (IRS-2), another substrate for the insulin receptor, has been identified (95, 96). Shc (an adaptor molecule) can also bind directly to the insulin receptor initiating signal transduction (82, 97).

Insulin has numerous target tissue actions, such as stimulation of glucose uptake, gene regulation, DNA synthesis, and amino acid uptake (51, 82). The mechanisms of insulin receptor signal specificity are currently a subject of intense investigation. It now appears that the Ras-Raf-MEK pathway is involved in the regulation of cell growth and metabolism whereas the PI3-K pathway is involved in glucose uptake (98, 99, 100, 101). The mechanisms by which the insulin signal is terminated remain incompletely understood. Receptor-mediated endocytosis and recycling are well known to occur and may be important to signal termination (83, 102). Serine phosphorylation has been shown to terminate signaling by the EGF receptor (103, 104), another tyrosine kinase growth factor receptor, and it can be shown under a variety of experimental conditions that insulin receptor serine phosphorylation decreases its tyrosine kinase activity (105, 106, 107, 108). It has been postulated that protein kinase C (PKC)-mediated serine phosphorylation of the insulin receptor is important in the pathogenesis of hyperglycemia-induced insulin resistance (102, 109). Recent evidence suggests that tumor necrosis factor- α (TNF- α)-mediated serine phosphorylation of IRS-1 inhibits insulin receptor signaling and is the mechanism of TNF- α -induced insulin resistance (110). Studies addressing this important question have been constrained by a lack of sensitive anti-phosphoserine antibodies. Identification of phosphoserine residues usually requires painstaking phosphoamino acid analysis of 32 P-labeled receptors (111). The use of fluorophore labeling of phosphoserine promises to provide a sensitive methodology for examining *in vivo* serine phosphorylation events (112).

In summary, insulin action is mediated through a ligand-activated tyrosine kinase receptor, similar to a number of other growth factors. A variety of phosphorylation-dephosphorylation signaling cascades are then activated, leading to the pleiotropic actions of insulin. The mechanisms of signal specificity and termination require further investigation.

2. Molecular insulin action defects in PCOS. Studies in adipocytes, a classic insulin target tissue, have failed to confirm earlier reports in blood cells of decreases in insulin receptor number and/or receptor affinity in PCOS (25, 26, 27, 113) when appropriately

weight-matched controls have been included. The one adipocyte study reporting a decrease in insulin receptor number used a control group consisting primarily of lean individuals (114). Studies of insulin action in isolated PCOS adipocytes have revealed marked decreases in insulin sensitivity together with less striking, but significant, decreases in maximal rates of insulin-stimulated glucose transport (55, 115) (Fig. 10+). There is evidence for decreases in adipocyte levels of adenosine in PCOS (116), but whether this is a primary defect or secondary to hyperinsulinemia is unclear. The decrease in maximal rates of adipocyte glucose uptake is secondary to a significant decrease in the abundance of GLUT4 glucose transporters (117). Similar defects are present in NIDDM and in obesity but are ameliorated by control of hyperglycemia and hyperinsulinemia as well as by weight reduction, suggesting acquired rather than intrinsic defects (65, 118, 119, 120). In contrast, in PCOS such defects can occur in the absence of obesity, glucose intolerance, or changes in waist to hip girth ratios (55, 117). Moreover, these abnormalities are not significantly correlated with sex hormone levels, suggesting that abnormalities of insulin action in PCOS may be intrinsic (55, 117).



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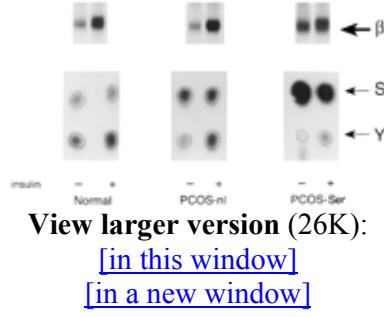
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Figure 10. Insulin-stimulated adipocyte U-[¹⁴C]glucose transport in nonobese PCOS women (\blacktriangle , Nob PCOS); nonobese normal women (\triangle , Nob NL); obese PCOS women (\bullet , Ob PCOS); and obese normal women (\circ , Ob NL). Basal rates of glucose transport are decreased significantly (*) in PCOS vs. normal women ($P < 0.01$) and in nonobese vs. obese women ($P < 0.001$). Maximal insulin-stimulated increments above basal are significantly decreased in PCOS vs. normal women (***, $P < 0.01$) and in obese vs. nonobese women (**, $P < 0.001$). The ED₅₀ insulin is increased significantly in PCOS vs. normal and in obese vs. nonobese women (inset). [Reproduced with permission from A. Dunaif *et al.*: *Diabetes* 41:1257–1266, 1992 (55).]

To further evaluate the postbinding defect in insulin action in PCOS, we examined insulin receptor function in receptors isolated from cultured skin fibroblasts. Because fibroblasts are removed from the *in vivo* environment for several generations, they provide a constant source of insulin receptors that are not influenced by the hormonal imbalance of PCOS. Consistent with our earlier results from the adipocyte studies, fibroblasts from PCOS women showed no change in insulin binding or receptor affinity

(69). However, in approximately 50% of PCOS fibroblasts (PCOS-ser), we observed decreased insulin receptor autophosphorylation (69). This was secondary to markedly increased basal autophosphorylation with minimal further insulin-stimulated autophosphorylation (Fig. 11+). Phosphoamino acid analysis revealed decreased insulin-dependent receptor tyrosine phosphorylation and increased insulin-independent receptor serine phosphorylation (69) (Fig. 11+). The ability of the PCOS-ser insulin receptors to phosphorylate an artificial substrate was also significantly reduced (Fig. 12+).

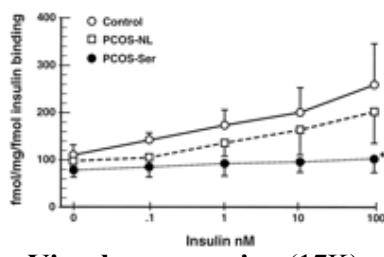


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Figure 11. Representative autoradiograms of autophosphorylated skin fibroblast insulin receptor β-subunits (*top*) and phosphoamino acid analysis (*bottom*) ± 1 μM insulin from a normal (control), a PCOS woman with normal insulin-stimulated tyrosine phosphorylation (PCOS-nl) and a PCOS woman with high basal autophosphorylation on serine residues (PCOS-ser); S-serine, Y-tyrosine. Basal autophosphorylation is increased and there is minimal further insulin-stimulated phosphorylation in the PCOS-ser β-subunits. The high basal phosphorylation represents phosphoserine, and phosphotyrosine content does not increase in response to insulin in the PCOS-ser β-subunits. [Reproduced from A. Dunaif *et al.*: *J Clin Invest* 96:801–810, 1995 (69) by copyright permission of The American Society for Clinical Investigation.]



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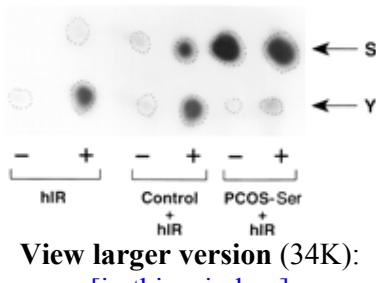
Figure 12. Phosphorylation of poly GLU4:TYR1 by partially purified skin fibroblast insulin receptors. Skin fibroblast insulin receptors were directly extracted from confluent cell cultures, partially purified, and incubated in the presence of 0–100 nM, and assays of the phosphorylation of poly GLU4:TYR1 were performed.

One-way ANOVA, $P < 0.005$; PCOS-ser < control and PCOS-nl, $P < 0.05$ Tukey's test. The values are the mean \pm SEM from five PCOS-ser (●), four PCOS-nl (■), and four control (○) subjects. [Reproduced from A. Dunaif *et al.*: *J Clin Invest* 96:801–810, 1995 (69) by copyright permission of The American Society for Clinical Investigation.]

Serine phosphorylation of the insulin receptor has been shown in cell-free systems and *in vivo* to inhibit the receptor's tyrosine kinase activity, analogous to our findings in the PCOS-ser insulin receptors (69, 105, 106, 107, 108). Thus, this defect in the early steps of the insulin-signaling pathway may cause the insulin resistance in PCOS-ser women. Increased insulin-independent serine phosphorylation in PCOS-ser insulin receptors appears to be a unique disorder of insulin action since other insulin-resistant states, such as obesity, NIDDM, type A syndrome, and leprechaunism, do not exhibit this abnormality (1, 51, 65, 69) (Table 1+). The PCOS-ser phosphorylation abnormality appears to be physiologically relevant because it is present in insulin receptors partially purified from skeletal muscle, a classic insulin target tissue, and because the same pattern of abnormal phosphorylation occurs in insulin receptors phosphorylated in intact cells (69).

Fibroblasts from approximately 50% of PCOS women (PCOS-nl) have no detectable abnormality in insulin receptor phosphorylation (69) (Figs. 11+ and 12+). Although these women demonstrate the same PCOS phenotype and the same degree of insulin resistance as the PCOS-ser women with abnormal phosphorylation, insulin receptor phosphorylation in fibroblasts and skeletal muscle from these women is similar to that of control women (69). This observation suggests that a defect downstream of insulin receptor signaling, such as phosphorylation of IRS-1 or activation of PI3-K, is responsible for insulin resistance in PCOS-nl women (51, 69, 102). Indeed, our recent human studies demonstrate a significant decrease in muscle PI3-K activation during insulin infusion in PCOS women (121), consistent with a physiologically relevant defect in the early steps of insulin receptor signaling.

We found no insulin receptor mutations in two PCOS-ser women by direct sequencing of genomic DNA (120), and sequence analysis of the tyrosine kinase domain in the β -subunit of an additional eight PCOS-ser women also revealed no mutations (69). This finding has recently been confirmed by other investigators (122). Immunoprecipitation and mixing experiments suggest that a factor extrinsic to the insulin receptor is responsible for the excessive serine phosphorylation (69). PCOS-ser insulin receptors autophosphorylate normally, if they are first immunoprecipitated from wheat-germ agglutinin (WGA) lectin eluates. Furthermore, mixing control human insulin receptors and WGA eluates from PCOS-ser fibroblasts results in increased insulin-independent serine phosphorylation and decreased insulin-stimulated tyrosine phosphorylation of the normal receptors (69) (Fig. 13+). Both experiments suggest that a factor present in WGA eluates is responsible for the abnormal phosphorylation.



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Figure 13. Phosphoamino acid analysis of immunopurified human insulin receptors (hIR) β -subunits basally and mixed with WGA-Sepharose eluates from control or PCOS-ser fibroblasts. hIRs were immunopurified from WGA-Sepharose eluates, mixed in a ratio of 10 fmol hIR:1 fmol PCOS-ser or control lectin eluate insulin-binding activity, and autophosphorylation \pm 1 μ M insulin was examined.

Phosphoamino acid analysis revealed a striking increase in phosphoserine content and a marked decrease in insulin-stimulated phosphotyrosine content after mixing hIR with PCOS-ser lectin eluates as compared with mixing hIR with control lectin eluates or in the absence of mixing. [Reproduced from A. Dunaif *et al.*: *J Clin Invest* 96: 801–810, 1995 (69) by copyright permission of The American Society for Clinical Investigation.]

The serine/threonine kinase, PKC, is a candidate for the putative serine phosphorylation factor (108). However, evidence against this possibility includes the observation that no phosphothreonine is detected in the PCOS-ser insulin receptors, and PKC has been shown to phosphorylate threonine 1336 of the insulin receptor (123). Furthermore, the IGF-I receptor, which is a known substrate of PKC under certain conditions, phosphorylates normally in PCOS-ser women (69, 124). Finally, preliminary Western blot analyses showed no significant differences in the abundance of PKC isoforms in PCOS-ser fibroblasts compared with controls (A. Dunaif, unpublished observations).

Other serine/threonine kinases that might cause the increased serine phosphorylation of PCOS-ser insulin receptors include a casein kinase I-like enzyme and cAMP-dependent protein kinase (125, 126). However, the casein kinase I-like enzyme has been shown to phosphorylate insulin-stimulated insulin receptors twice as well as unstimulated insulin receptors (125). This phosphorylation pattern differs from what we observe with PCOS-ser insulin receptors, namely excessive serine phosphorylation in the absence of insulin. cAMP-dependent protein kinase is a candidate because increases in cAMP cause serine phosphorylation of insulin receptors in cultured lymphocytes (127). However, insulin receptor phosphorylation by cAMP-dependent protein kinase is probably indirect because the human insulin receptor β -subunit does not contain the amino acid sequences classically recognized by this kinase (128).

Alternatively, a novel serine/threonine kinase or an inhibitor of a serine/threonine phosphatase may be responsible for the abnormal phosphorylation of PCOS-ser insulin receptors (69, 129). Because it is present in WGA eluates, the PCOS-ser factor is either a membrane glycoprotein or a protein associated with a glycoprotein. In some respects, our putative serine phosphorylation factor is similar to a recently identified inhibitor of insulin receptor tyrosine kinase, the membrane glycoprotein PC-1 (130) (Fig. 14•). Both

factors are extrinsic to the insulin receptor, both are present in WGA eluates from human skin fibroblasts, and both appear to inhibit insulin receptor tyrosine kinase activity. This represents an important new mechanism for human insulin resistance related to factors that modulate the tyrosine kinase activity of the insulin receptor (51) (Fig. 14+). The major difference between the two factors is that PC-1 is not associated with increased insulin-independent serine phosphorylation characteristic of the PCOS-ser insulin receptors (69, 130, 131). Recent studies suggest that TNF- α produces insulin resistance by a related mechanism: serine phosphorylation of IRS-1, which then inhibits insulin receptor tyrosine kinase activity (Fig. 7+). Isolation and characterization of the factor in PCOS-ser fibroblasts are now in progress, as is the mapping of phosphorylated serine residues in PCOS-ser insulin receptors.

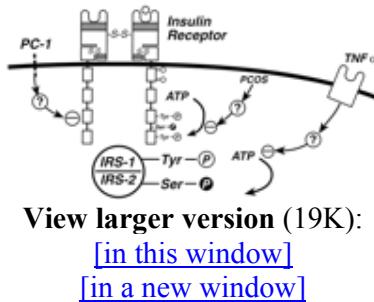


Figure 14. Insulin resistance in ~50% of PCOS women appears to be secondary to a cell membrane-associated factor, presumably a serine/threonine kinase, that serine-phosphorylates the insulin receptor-inhibiting signaling. Serine phosphorylation of IRS-1 appears to be the mechanism for TNF α -mediated insulin resistance. The membrane glycoprotein PC-1 also inhibits insulin receptor kinase activity, but it does not cause serine phosphorylation of the receptor. These are examples of a recently appreciated mechanism for insulin resistance secondary to factors regulating the receptor's tyrosine kinase activity. [Figure used with permission from A. Dunaif.]

Although fibroblasts are not classic insulin target cells, defects identified in insulin receptor number and/or kinase activity in them have reflected insulin receptor mutations (19). Thus, the presence of the putative serine phosphorylation factor in cultured cells of PCOS-ser women suggests that the abnormal insulin receptor phosphorylation is genetically programmed. In addition, we have found that some first degree relatives of PCOS women are insulin resistant, including brothers, consistent with a genetic defect (132). Recent twin (133) and family studies (134) have also suggested that insulin resistance is a genetic defect in PCOS. Our putative serine phosphorylation factor is a candidate gene for a mutation producing the insulin resistance associated with PCOS (see below).

F. Constraints of insulin action studies in PCOS

There is general consensus in the literature that obese PCOS women are insulin resistant. Controversy remains as to the pathogenesis of the insulin resistance, and there are studies that suggest that obesity *per se* or increased central adiposity are responsible

for the associated defects in insulin action (135, 136). Many of the conflicting studies can be explained by differing diagnostic criteria for PCOS and by the inclusion of both lean and obese women in the experimental sample. Our studies (49) and those in the United Kingdom (137, 138) strongly suggest that anovulation is associated with insulin resistance. We found insulin resistance only in women with hyperandrogenism and anovulation (Fig. 4•). Studies using ovarian morphology to ascertain women have found that only anovulatory women with PCO morphology are insulin resistant (137, 138). Women with regular ovulatory menses and hyperandrogenism [elevated plasma androgen levels (49)] (Fig. 4•) or with PCO detected by ovarian ultrasound (137, 138) are not insulin resistant. Therefore, studies that have defined PCOS by PCO morphology without further assessment of ovulation could have included women who were not insulin resistant. Similarly, studies that have included ovulatory hyperandrogenic women will bias the sample with insulin-sensitive subjects.

One reason for the general acceptance of the diagnostic criteria for PCOS of hyperandrogenism and anovulation (1) (Table 2•, see above) is that they define the insulin-resistant subset. Even with subjects so identified, not all are insulin resistant, despite using the relatively lenient criterion of 1 SD below the control mean value for insulin action. Moreover, the occasional PCOS woman can have insulin sensitivity more than 2 SDs (95% confidence interval) above the control mean (117). There is clearly heterogeneity in this feature of the syndrome. Obesity is another important factor, and it appears that it has a more pronounced effect on insulin action in PCOS than in control women (71). Ideally, lean and obese PCOS women should be studied separately (30, 49, 54, 55, 68). If groups are pooled, PCOS women should be matched to controls so that the spectrum of body weights are equally represented. This is often not the case so that, although mean body mass may be similar, the PCOS group often contains more obese individuals, thereby skewing the results (114). Moreover, there are very few studies in the literature in which lean PCOS woman have been separately studied (30, 54, 55, 68, 135). There are also major ethnic variations in insulin sensitivity, and this is another less well appreciated potential confounding factor (56). Recent studies from Denmark suggest that adiposity accounts for insulin resistance in their PCOS population in contrast to our US population (135, 136).

We have consistently found significant decreases in insulin-mediated glucose disposal in both lean and obese PCOS women (54, 55, 56). Similarly, our group (57) as well as Yen's group (68) have found significant decreases in insulin sensitivity (SI) determined by modified frequently sampled intravenous glucose tolerance test with minimal model analysis in such PCOS women (57). Insulin resistance has been found in PCOS women of many racial and ethnic groups including Japanese, Caribbean and Mexican Hispanics, non-Hispanic Whites, and African Americans (55, 56, 139, 140).

G. PCOS as a unique NIDDM subphenotype (Table 3•)

Our studies in premenopausal women, extrapolated data based on prevalence estimates of PCOS and glucose intolerance, and studies in postmenopausal women with a history of PCOS all suggest that PCOS-related insulin resistance confers a significantly increased risk for NIDDM (see above). Familial clustering of affected individuals as well as studies in monozygotic twins indicate that NIDDM has an important genetic component (51, 102, 141, 142, 143, 144). Insulin resistance is a major inherited abnormality, but studies in which insulin secretion has been examined in the context of insulin sensitivity demonstrate that β -cell dysfunction may also be an important contributing factor to the ultimate development of the NIDDM phenotype (51, 145,

[146](#)). There is clearly genetic heterogeneity with insulin resistance being absent in some affected individuals ([146](#), [147](#)).

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Table 3. Adult NIDDM syndromes

The underlying genetic defects have been identified in fewer than 5% of NIDDM individuals and consist of mutations in genes such as the insulin receptor gene, mitochondrial DNA, or the glucokinase gene (Table 3+) ([19](#), [51](#), [102](#), [144](#), [148](#), [149](#)). Defects in a number of candidate genes, such as GLUT4, GLUT2, and hexokinase, have been excluded ([102](#), [150](#)). The major cause of insulin resistance in typical NIDDM is reduced insulin-stimulated muscle glycogen synthesis. Defects found in NIDDM in insulin receptor number and/or phosphorylation or glucose transport, however, are reversible with the control of hyperglycemia ([51](#), [65](#), [102](#), [151](#)), elevated free fatty acid levels ([152](#)), and/or hyperinsulinemia ([119](#)). Only one study has shown an intrinsic abnormality in NIDDM-cultured cells ([153](#)): decreased insulin-stimulated glycogen synthesis. Studies in NIDDM first-degree relatives, who are normoglycemic but insulin resistant, suggest that there is an inherited decrease in both insulin-stimulated muscle glucose transport/phosphorylation and glycogen synthase activity that results in the reduced glycogen synthesis ([154](#), [155](#), [156](#)). In contrast, in PCOS, intrinsic abnormalities in the early steps of insulin receptor signaling are present, making this the first common NIDDM subphenotype in which such defects have been identified ([69](#), [102](#), [151](#)). Moreover, the defective pattern of insulin receptor phosphorylation is unique, suggesting it should be possible to distinguish PCOS-related insulin resistance from that related to other NIDDM genotypes. This should make it possible to assign affected status accurately for linkage studies of the genetics of PCOS-related insulin resistance ([157](#)).

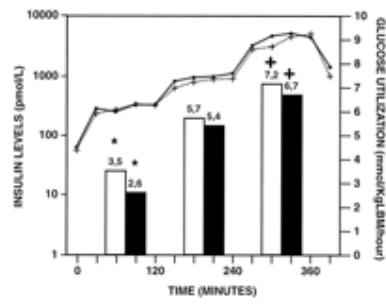
► [Top](#)
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► **III. Hypotheses Explaining the Association of
Insulin Resistance and PCOS**

A. Causal association

1. *Do androgens cause insulin resistance?* If glucose utilization is expressed as a function of muscle mass rather than total body mass, women do appear to be more insulin sensitive than men (158, 159). Moreover, when isolated fat cells are compared, female adipocytes are more sensitive than male adipocytes to insulin-mediated glucose uptake (160). These are subtle differences, however, and do not approach the degree of impairment in insulin sensitivity observed in PCOS (54, 55). Finally, in the rare syndromes of extreme insulin resistance and hyperandrogenism, specific molecular defects in insulin action have been clearly identified as the cause of insulin resistance (19, 161).

It is possible, however, that androgens may produce mild insulin resistance. Women receiving oral contraceptives containing "androgenic" progestins can experience decompensations in glucose tolerance, as can individuals receiving synthetic anabolic steroids (162, 163). Prolonged testosterone administration to female-to-male transsexuals, which produced circulating testosterone levels in the normal male range, resulted in significant decreases in insulin-mediated glucose uptake in euglycemic clamp studies (164). These decreases were largest at lower doses of insulin (~25% at ~300 pM steady-state levels), not significant at moderate insulin doses (~1,000 pM steady-state levels), and minimal at higher doses (~7% at ~5,000 pM steady-state levels) (164) (Fig. 15•). Studies in testosterone-treated castrated female rats have suggested that androgen-mediated insulin resistance may be the result of an increase in the number of less insulin-sensitive type II b skeletal muscle fibers (165) and an inhibition of muscle glycogen synthase activity (166).



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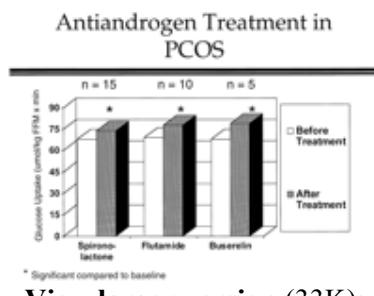
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Figure 15. Hyperinsulinemic euglycemic clamp studies basally and during treatment with virilizing doses of testosterone in 13 female-to-male transsexuals. Insulin-mediated glucose disposal decreased significantly at low and at high doses of insulin. [Reproduced with permission from K. H. Polderman *et al.*: *J Clin Endocrinol Metab* 79:265–271, 1994 (164). © The Endocrine Society.]

It has been more difficult to demonstrate that decreasing androgen levels improve insulin sensitivity in PCOS. We found no significant changes in peripheral or hepatic

insulin action in profoundly insulin-resistant obese PCOS women by single-insulin dose (steady-state insulin levels \sim 600 pM) glucose clamp studies after prolonged androgen suppression produced by the administration of an agonist analog of GnRH (167). Diamanti-Kandarakis and colleagues (168) reported that antiandrogen therapy did not alter insulin sensitivity in PCOS. Other investigators have found modest improvements in insulin sensitivity in PCOS during androgen suppression or antiandrogen therapy (169, 170) (Fig. 16•). Such changes were apparent in less insulin-resistant, less obese, or nonobese PCOS women (169, 170). Moreover, insulin resistance was improved but not abolished (170) (Fig. 16•). It is of considerable interest that the effects of sex steroids on insulin sensitivity appear to be sexually dimorphic. Testosterone administration to obese males improves insulin sensitivity (171), and synthetic estrogen administration to male-to-female transsexuals produces insulin resistance (164).



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Figure 16. Basal and insulin-mediated glucose disposal in 43 hyperandrogenic women and 12 control women. The hyperandrogenic women were studied before and after 3–4 months of antiandrogen therapy with spironolactone, flutamide, or Buserelin. Insulin-mediated glucose disposal increased significantly during treatment ($P < 0.01$). [Adapted with permission from P. Moghetti *et al.*: *J Clin Endocrinol Metab* 81:952–960, 1996 (170). © The Endocrine Society.]

Givens and colleagues (172) have proposed that androgens have differential effects on insulin action, with testosterone worsening insulin sensitivity and the adrenal androgen, dehydroepiandrosterone (DHEA), improving it. This hypothesis is based on differing correlations of these steroids with insulin-binding studies in blood cells and on their observation that women with elevated dehydroepiandrosterone sulfate (DHEAS) levels have normal insulin sensitivity (172). The one direct *in vitro* study supporting this hypothesis was constrained by a small sample size ($n = 3$), and the examination of testosterone and DHEA effects on insulin binding using blood cells rather than a more relevant insulin target tissue (172). Studies in which DHEA or DHEAS have been administered to humans have failed to support this hypothesis. Administration of supraphysiological amounts of DHEA (which also result in testosterone elevations since DHEA is a testosterone prehormone) has produced mild hyperinsulinemia in women, but had no effects on insulin sensitivity in men, as would be expected given the sexually dimorphic effects of androgens on insulin action (173, 174). Moreover, PCOS women with elevated DHEAS levels similar to those in ovulatory hyperandrogenic women are

significantly more insulin resistant, arguing against an insulin-sensitizing action of DHEA ([49](#), [175](#)).

In summary, the modest hyperandrogenism characteristic of PCOS may contribute to the associated insulin resistance. Additional factors are necessary to explain the insulin resistance, since suppressing androgen levels does not completely restore normal insulin sensitivity ([167](#), [170](#)). Further, androgen administration does not produce insulin resistance of the same magnitude as that seen in PCOS ([54](#), [55](#), [164](#)). Finally, there are clearly defects in insulin action that persist in cultured PCOS skin fibroblasts removed from the hormonal milieu for generations (see above) ([69](#)).

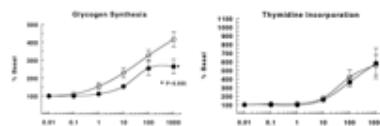
2. Does hyperinsulinemia cause hyperandrogenism? The syndromes of extreme insulin resistance are commonly associated with hyperandrogenism when they occur in premenopausal women ([19](#), [20](#)) (Table 1+). The cellular mechanisms of insulin resistance in these conditions range from antibodies that block insulin binding to its receptor (type B syndrome) to genetic defects in the receptor resulting in decreased numbers and/or depressed function of the receptor (type A syndrome, leprechaunism); the common biochemical feature is profound hyperinsulinemia ([19](#), [20](#)) (Table 1+). Accordingly, it has been proposed that hyperinsulinemia causes hyperandrogenism. Insulin can be shown experimentally to have a variety of direct actions on steroidogenesis in humans ([1](#), [9](#), [20](#)). Insulin can stimulate ovarian estrogen, androgen, and progesterone secretion *in vitro* ([1](#), [20](#), [176](#)). Although some of these actions have been observed at physiological insulin concentrations, most actions have been observed at higher concentrations ([1](#), [20](#)).

The presence of insulin receptors in crude ovarian membranes does not necessarily indicate a physiological role for insulin in the regulation of steroidogenesis since such receptors are widely distributed through the body ([51](#), [83](#)). Insulin is present in human follicular fluid but in concentrations most likely representing an ultrafiltrate of plasma rather than local production ([177](#)). In contrast, IGF-I is produced by human ovarian tissue, and IGF-I receptors are present in the ovary ([178](#), [179](#)). IGF-I and its receptor share considerable sequence, structural, and functional homology with insulin and its receptor, respectively ([180](#)). The IGF-I receptor is a heterotetramer with two $\alpha\beta$ -dimers assembled analogous to the insulin receptor ([85](#), [88](#), [181](#), [182](#), [183](#)) (see above). Insulin can bind to the ligand-binding domain of the IGF-I receptor and activate the tyrosine kinase activity of the β -subunit and the intracellular events normally mediated by IGF-I ([85](#), [88](#), [180](#), [181](#)). IGF-I can bind to and activate the insulin receptor, resulting in rapid effects on glucose metabolism ([85](#), [88](#), [181](#)). In general, the affinity of the IGF-I receptor for insulin is considerably less than it is for IGF-I and *vice versa* ([181](#)). However, this varies by tissue; thus data on receptor affinity cannot be extrapolated from one tissue to another. There are also so-called "atypical" IGF-I receptors that bind IGF-I and insulin with similar affinity ([184](#), [185](#)). $\alpha\beta$ -Dimers of the insulin and IGF-I receptor can assemble together to form hybrid heterotetramers ([11](#), [182](#), [186](#), [187](#)).

Insulin-like growth factor-binding proteins (IGFBPs) are major regulators of IGF action. IGFBPs can specifically bind IGF-I and modulate its cellular actions by altering its bioavailability ([182](#), [188](#)). Insulin decreases hepatic production of IGFBP-1 and may, thus, make IGF-I more biologically available ([182](#)). Growth factor regulation of ovarian steroidogenesis appears to be primarily a paracrine system with locally produced IGF-I and IGFBPs acting on neighboring cells in concert with gonadotropins ([1](#), [178](#), [179](#), [189](#)). A number of other growth factors, including IGF-II, EGF, and transforming growth factor- α and - β , appear to have a role in the regulation (both stimulatory and

inhibitory) of ovarian steroidogenesis (1, 188, 190). Insulin cannot interact directly with the receptors for these hormones (84, 88, 181, 182). However, the receptors for some of these growth factors, such as the EGF receptor (which binds both EGF and transforming growth factor- α), are also protein kinases (1, 84, 88). Thus the potential exists for communication between the insulin-IGF-I system and the other protein kinase growth factor systems through receptor "cross-talk" and/or by shared kinases or phosphatases that may regulate all of these receptors (51, 191). For example, serine phosphorylation of the EGF receptor also decreases its tyrosine kinase activity (103, 104). In rodents, hyperinsulinemia can result in up-regulation of ovarian IGF-I-binding sites, and this may provide yet another mechanism by which insulin can modulate growth factor action (192).

Insulin in high concentrations can mimic IGF-I actions by occupancy of the IGF-I receptor (1, 181, 182), and this has been a proposed mechanism for insulin-mediated hyperandrogenism (8, 9, 10). However, it has recently been shown that insulin has specific actions on steroidogenesis acting through its own receptor (193). Moreover, these actions appear to be preserved in insulin-resistant states (193, 194), presumably because of differences in receptor sensitivity to this insulin action or because of differential regulation of the receptor in this tissue. Our studies in cultured skin fibroblasts suggest that a mechanism for this may be selective defects in insulin action. Both insulin- and IGF-I-stimulated glycogen synthesis are significantly decreased in PCOS fibroblasts whereas thymidine incorporation is similar to control fibroblasts (Fig. 17+) (195). Thus only the signaling pathways regulating carbohydrate metabolism may be impaired in PCOS, while those involved in steroidogenesis are preserved. This would explain the paradox of persistent insulin-stimulated androgen production in insulin-resistant PCOS women. Insulin decreases hepatic IGFBP-1 production, the major circulating IGF-I-binding protein (183). Thus, bioavailable IGF-I levels are increased in insulin-resistant PCOS women, and this may contribute to the ovarian steroidogenic abnormalities via activation of the IGF-I receptor (68). In lean PCOS women, increases in GH release may also affect ovarian steroidogenesis (68).



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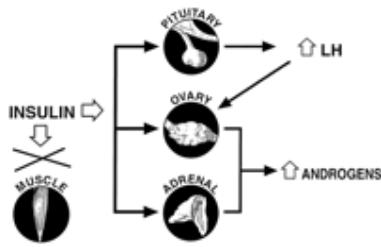
Figure 17. Dose-response curves for insulin-stimulated glycogen synthesis (*left panel*) and thymidine incorporation (*right panel*) in confluent skin fibroblasts from PCOS (•) and control (○, NL) women. Maximal responses for insulin-stimulated glycogen synthesis were significantly decreased ($P < 0.001$). There were no significant differences in thymidine incorporation in the PCOS fibroblasts (*right panel*). The dose-response curves for IGF-I were similar to those for insulin (data not shown). [Reproduced with permission from A. Dunaif (195).]

It has been more difficult to demonstrate insulin actions on steroidogenesis in humans *in vivo* because it is not feasible to administer insulin to nondiabetics for prolonged periods (1, 196, 197, 198). Relatively physiological levels of insulin (100 μU/ml or 600 pM), when infused over approximately 2 h, can slightly increase plasma androstenedione levels in normal women (1). However, these increases are minor and are not in the range seen in women with hyperandrogenism. Moreover, it is arguable whether insulin contributes to androgen production in normal women since insulin levels in the 100 μU/ml (~600 pM) range are generally seen only after meals (1, 196). Furthermore, such transient meal-related increases in insulin do not result in increased androgen levels, whereas the more sustained increases produced by continuous insulin infusion can slightly increase androgen levels (196).

Studies in which insulin levels have been lowered for prolonged periods have been much more informative. This has been accomplished for 7 days to 3 months with agents that either decrease insulin secretion, diazoxide (199) or somatostatin (200), or that improve insulin sensitivity, metformin (201) or troglitazone (202). Circulating androgen levels have decreased significantly in women with PCOS in these studies. Sex hormone binding globulin (SHBG) levels have increased (199, 202), compatible with a major role for insulin in regulating hepatic production of this protein (203, 204). Abnormalities in apparent 17,20-lyase activity have improved in parallel with reduced circulating insulin levels consistent with insulin-mediated stimulation of this enzyme (205). However, estrogen levels also decreased significantly, suggesting that insulin has diffuse effects on steroidogenesis (202). Changes in estrogen levels were seen only when insulin levels were lowered with troglitazone and thus, alternatively, these changes might be the result of troglitazone-mediated increases in sex steroid metabolism, a recently reported action of this agent (Rezulin Package Insert, Parke-Davis, Morris Plains, NJ). It is also possible that troglitazone has direct effects on steroidogenesis. Indeed, the thiazolidinediones have been shown to have such effects on granulosa cell steroidogenesis (206).

Most of the reported actions of insulin on steroidogenesis are observed only in women with PCOS (197, 198) and are greatly enhanced by the addition of gonadotropins when measured in *in vitro* experiments (1, 20, 176, 190, 207). In the one study in normal women in which insulin levels were lowered by diazoxide administration, no significant changes in androgen levels were noted (208). These observations suggest that, if insulin is to produce ovarian hyperandrogenism in women, polycystic ovarian changes (*e.g.*, theca cell hyperplasia) must be present that predispose the ovaries to secrete excess androgens. In normal women insulin does not appear to have any acute effects on ovarian function under physiological circumstances (196, 197, 208).

Although insulin has been shown to stimulate gonadotropin release in isolated rat pituitary cells (209), human studies of insulin action on gonadotropin release have yielded conflicting results. Acute insulin infusion has not changed pulsatile LH or FSH release or gonadotrope sensitivity to GnRH in normal or in PCOS women, despite direct effects on gonadal steroidogenesis in PCOS women (197). Long-term suppression of insulin levels with diazoxide, which resulted in decreases in circulating testosterone levels, did not alter circulating LH levels (199). In contrast, decreases in LH levels were observed after 7 days of somatostatin-mediated insulin lowering (201), after metformin for 8 weeks (205), or after troglitazone for 3 months (202). It is possible that insulin-mediated changes in gonadotropin release contribute to the changes of steroidogenesis produced by insulin in humans (Fig. 18*).



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Figure 18. Studies in which insulin levels have been lowered with the insulin-sensitizing agent, troglitazone, suggest that insulin is a general augmentor of steroidogenesis and LH release. [Figure is used with permission from A. **Dunaif**.]

Acute insulin infusions decrease DHEAS levels in men and women, suggesting that insulin is a negative modulator of adrenal androgen metabolism (176). When insulin levels are chronically lowered, however, circulating DHEA and DHEAS levels rise in men but not in women, suggesting that this regulation of adrenal androgen metabolism is sexually dimorphic (210). Lowering insulin levels with insulin-sensitizing agents, such as troglitazone, has resulted in decreases in DHEAS levels in PCOS women (202) (Fig. 18•). The mechanism of this appears to be a direct action of insulin to increase adrenal sensitivity to ACTH in hyperandrogenic women (211). Insulin can directly decrease hepatic SHBG production (203), explaining the frequently observed inverse correlation between peripheral insulin and SHBG levels (204). Indeed, insulin rather than sex steroids appears to be the major regulator of SHBG production (204).

In summary, studies in which insulin levels have been lowered by a variety of modalities indicate that hyperinsulinemia augments androgen production in PCOS (Fig. 18•). Moreover, this action appears to be directly mediated by insulin acting through its cognate receptor rather than by spillover occupancy of the IGF-I receptor. Intrinsic abnormalities in steroidogenesis appear to be necessary for this insulin action to be manifested since lowering insulin levels does not affect circulating androgen levels in normal women. Further, in many PCOS women, lowering insulin levels ameliorates but does not abolish hyperandrogenism.

B. Possible genetic association of PCOS and insulin resistance

1. Family studies of PCOS. Familial aggregation of PCOS suggesting a genetic etiology has been clearly established (1, 212, 213, 214). Cooper *et al.* (212) reported that a history of oligomenorrhea was more common in the mothers and sisters of PCOS women than in controls. Probands reported that male relatives had increased "pilosity" (212). The proposed mechanism of inheritance was autosomal dominant with decreased penetrance. Givens and colleagues have reported multiple kindreds showing affected women in several generations and have examined some males in considerable detail (1, 215). Diagnostic criteria for PCOS were hirsutism and enlarged ovaries. There was a high frequency of metabolic disorders, such as NIDDM and hyperlipidemia, in both male and female pedigree members. In one kindred there were several males with

oligospermia and one with Klinefelter's syndrome (47, XXY). Elevated LH/FSH ratios were present in some males and 89% of their daughters had PCOS. This would suggest inheritance in either an autosomal or X-linked dominant manner.

Ferriman and Purdie (216) studied 700 women; affected status was assigned on the basis of hirsutism and enlarged ovaries (assessed by gynecography). The frequency of various abnormalities in relatives was determined by history provided by the proband; no relatives were examined. Oligomenorrhea and infertility were most common in women who had both hirsutism and enlarged ovaries. Forty-six percent of female relatives were reported to be similarly affected. There was an increased incidence of baldness reported in male relatives. Similar results were found in a study of 132 Norwegian PCOS probands identified by ovarian wedge resection (217). Information on pedigree members was obtained by questionnaire. Female first-degree relatives had a significantly increased frequency of PCOS symptoms (*i.e.*, hirsutism, oligomenorrhea, infertility), and male first-degree relatives had a significantly increased frequency of early baldness or "excessive hairiness" compared with controls. Human leukocyte antigen typing in PCOS has had conflicting results; an initial report showed no human leukocyte antigen association, whereas a follow-up study reported an association with DQA1^L0501 (218, 219). There have been case reports of polyploidies and X-chromosome aneuploidies in PCOS (220, 221). Larger studies, however, have found normal karyotypes (222).

Studies from the United Kingdom have phenotyped women on the basis of polycystic ovarian morphology detected by ultrasound (223). Familial polycystic ovary morphology was observed in 51 of 62 pedigrees (92%). The proportion of females affected in all sibships was 80.5% (107 of 133), which would exceed the expected ratios for either an autosomal dominant or an X-linked dominant mode of inheritance. However, not all women in each kindred were examined and, thus, an accurate ratio of affected to unaffected women could not be established for segregation analysis. Further, the male phenotype was not sought.

A more recent study prospectively examined the families of probands consecutively identified on the basis of polycystic ovarian morphology on ultrasound (224). The first-degree relatives in 10 families were evaluated by history, measurement of physical indices, and hirsutism as well as serum levels of androgens, 17-hydroxyprogesterone, gonadotropins, and PRL. Transabdominal ultrasound was performed in female first-degree relatives. Only 54% of women with polycystic ovaries had an elevated total testosterone or LH level consistent with the endocrine *syndrome*. Glucose and insulin levels were assessed in obese but not lean probands. Twenty-two males were screened; eight had premature (before age 30 yr) fronto-parietal hair loss, 10 did not, and four were too young to assess. Female affected status was assigned on the basis of ultrasound evidence of polycystic ovaries. If male affected status was considered to be premature balding, and a history of menstrual irregularity was used to assign postmenopausal affected status, the segregation ratio for affected families, excluding the proband, was 51.4%, consistent with an autosomal dominant mode of inheritance with complete penetrance (224). Studies in monozygotic twins, however, have not found complete concordance of polycystic ovary morphology, arguing against this mode of inheritance (133). The study contained only 19 pairs of monozygotic twins as well as a sample of 15 dizygotic twins. The prevalence of polycystic ovary morphology was ~50% in these twins, who were recruited from a twin registry, which was twice the prevalence reported in other randomly selected groups of women (3). This raises concern about the accuracy of the detection of polycystic ovaries.

Family studies have been constrained by small sample sizes and/or failure to examine all available family members. In several studies, PCOS affected status has been assigned on the basis of ovarian morphology rather than hormonal abnormalities. Only one study has proposed a male phenotype on the basis of examination of male relatives, and this study was constrained by a small sample size (224). Nevertheless, these studies strongly suggest that PCOS has a genetic component, most likely with an autosomal dominant mode of transmission (220, 224). If this is true, are there other phenotypes in affected kindreds? The studies cited above have suggested that premature male balding may be a male phenotype (216, 224). This finding could be an artifact, since it is also possible that bald men choose to marry hirsute women. Recent studies in these families, however, suggesting linkage of this phenotype with a candidate gene in the steroidogenic enzyme pathway (Ref. 225; see below), if verified, would confirm genetically that this is a male phenotype.

Our studies have suggested that insulin resistance may be an additional male phenotype as well as a prepubertal and postmenopausal female phenotype (132, 220) (Table 4+). This has been also reported recently in a series of Australian PCOS kindreds. In the small number of families that we have studied (132, 220), when women of reproductive age are insulin resistant, they usually have possessed the other endocrine features of PCOS. The one insulin-resistant prepubertal girl was also hyperandrogenic and developed chronic anovulation after menarche consistent with the diagnosis of PCOS (132). That insulin resistance and hyperandrogenism may be a prepubertal phenotype is supported by recent studies suggesting that PCOS develops in insulin-resistant girls with premature adrenarche (58, 226, 227) (Table 4+). Our studies suggest that hyperandrogenism without insulin resistance is another phenotype in female PCOS kindred members of reproductive age (228) (Table 4+). Finally, we have found postmenopausal hyperandrogenic female family members with normal insulin sensitivity, which may represent an additional postmenopausal phenotype (132) (Table 4+). This possibility is supported by the study of Dahlgren and colleagues (53), which found that postmenopausal women with a history of PCOS had higher androgen levels than age-matched control women. We have found that hyperandrogenism and insulin resistance can segregate independently in PCOS kindreds (132). It is not yet possible to determine whether this reflects separate genetic traits or variable penetrance of a single defect. These studies also indicate that there is considerable phenotypic variation, even within kindreds.

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Table 4. Additional familial phenotypes

2. Candidate genes for PCOS. The biochemical reproductive phenotype in PCOS is characterized by increased LH secretion and acyclic FSH release (2, 12). The ovaries (in response to LH) and, often, the adrenals secrete excessive androgens, and there is decreased ovarian aromatization of androgens to estrogens (12). The circulating androgens feed back on the hypothalamic-pituitary axis (directly or via their

exagonadal aromatization to estrogen) to increase LH relative to FSH release, producing a self-sustaining syndrome ([34](#), [35](#), [36](#), [37](#), [42](#)). The defect that initiates these reproductive disturbances in PCOS is unknown, but it can be shown experimentally that factors that increase either androgen secretion or LH release can reproduce these disturbances ([1](#), [2](#), [12](#), [38](#), [39](#)). Thus any factor regulating gonadotropin secretion or action, adrenal or ovarian steroidogenesis, and/or exagonadal aromatization could be a plausible candidate gene for the reproductive phenotype of PCOS. Indeed, polycystic o



REVIEW ARTICLE

Is the Risk of Polycystic Ovary Syndrome among Working Women Higher and Vice Versa?

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Abstract:

Introduction:

Polycystic ovary syndrome (PCOS), an endocrine glands disorder, caused by hormonal imbalance, is featured by diverse potential effects for women; while individuals perpend to those that are affecting appearance and menstruation disorder. Our aim was to assess PCOS risk factors in working women.

Materials and Methods:

The study was carried out as a literature review work through searching databases including Scopus, PubMed, and ScienceDirect for papers published before December 2019. The databases were searched for the terms such as PCO, job stress, and risk factors of PCO. Risk factors for polycystic ovarian syndrome and occupational risk factors for working women were investigated.

Results and Discussion:

There are several reasons known for PCOS like obesity and insulin resistance along with the stressors that increase its risk. Working women tend to be exposed to several stressors and being in charge of home affairs creates a higher workload and intensified stresses. The risk of PCOS is higher in women with higher stressors at work.

Conclusions:

Working women experience many stressors and taking into account that stress is a precursor or intensifier of PCOS risk factors, working women are at a higher risk of PCOS compared with housewives.

Keywords: Polycystic ovary syndrome, Working women, Stress, Glucose, Risk, Polycystic.

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1. INTRODUCTION

Polycystic ovary syndrome (PCOS), a disorder of endocrine glands, is caused by hormonal imbalance in women [1]. This syndrome is a silent and non-contagious disease [2] and appears as a sort of insulin resistance in women along with probable changes in cortisol and melatonin secretion; which are the key indicators of the hypothalamus, hypophyses, and adrenal function [2, 3]. According to the National Institute of Health (NIH) and Rotterdam Criteria, the prevalence of PCOS is about 6-10% and 15%, respectively [4]. The syndrome

causes a variety of diverse and notable complications such as infertility, hypoestrogenism, hirsutism, insulin resistance, glucose intolerance, diabetes type II, and cardiovascular disorder; in addition to causing anxiety, depression, and low quality of life [1]. Despite all these problems, there is no public awareness of PCOS [5]. Previous studies showed that women with PCOS suffer from higher social stress and other life stresses as well. One of them is occupational stress, which is the second occupational health related to work [6]. By definition, occupational stress refers to any non-useful psychological or physical response caused by a lack of fitness between the responsibility assigned at work and one's capabilities, which might lead to aggressive behaviors, work

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accidents, psychological and mental disorders, or even death. It affects one's health and quality of life and increases the risk of work accidents. Moreover, stress might cause destructive effects on physical and psychological health including hypertension, heart attack, depression, and anxiety [7].

Chronic depression might cause changes in nutritional habits so that many find overeating a way to fight stress, which leads to obesity and abdominal fat – both as key risk factors for diabetes type II [8, 9]. In addition, unhealthy nutrition results in insulin resistance so there is a significant relationship between insulin resistance and clinical problems like non-alcoholic fatty liver and PCOS. On the other hand, some of the occupational risk factors like the inconsistency of circadian rhythm, overnight sleep disruption, the polluted environment at work (particles, solvents), exposure to heavy metals (arsenic, mercury) or stable organic pollutants increase the risk of insulin resistance [10]. Many jobs are featured with these risk factors. As shown by other studies, anxiety, depression, and lack of physical activity are very common in women with PCOS.^{3,9} In general, working women are under heavy stress in addition to their work since they are in charge of home affairs. Therefore, the hypothesis of the present study is that working women are at a higher risk of developing PCOS. Our aim was to assess PCOS risk factors in working women.

2. METHODS

The study was carried out as a literature review work through searching databases including Scopus, PubMed, and ScienceDirect for papers published before December 2019.

The databases were searched for the terms such as "Polycystic ovary syndrome", "PCOS", "stress", "job stress", "working women", and "risk factors of PCOS".

The other references were also reviewed to find the papers that might have been overlooked when searching the databases. Moreover, the studies published in English were selected for analysis. Studies, which investigated irrelevant outcomes and lacked sufficient information for analysis, were excluded. Finally, the search results were reviewed by two authors independently after removing duplicates. The information of the studies, which entered the final phase, was extracted and investigated. All procedures carried out in accordance with the ethical committee of Shoushtar Faculty of Medical Sciences (No. IR.SHOUSHTAR.REC.1399.04).

3. RESULTS

3.1. Risk Factors of PCOS

A variety of risk factors such as obesity, insulin resistance, and hormonal disorders play a role in the development of PCOS [7, 9]. According to the results of studies, stress can be influential as an intermediate factor in the development or intensification of these risk factors. These relationships are further discussed in the following sections:

3.2. Stress and Obesity

Chronic stress increases the risk of changes in nutritional habits and consequential obesity is a risk factor for diseases like diabetes, cardiovascular disease, and PCOS. Overeating is a strategy to fight stress, which results in obesity and abdominal fat – *i.e.* two main risk factors of diabetes type II

[9]. Social stresses like aggression, domination, and work pressure all may lead to diseases like diabetes type II. The prevalence of PCOS in underweight, normal, overweight, and obese women were 8.2, 9.8, 9.9, 9.0% respectively. Therefore, the risk of PCOS increases with obesity [4 - 6]. Studies have also shown that anxiety, depression, and lack of physical activity are common in women with PCOS.

3.3. Stress and Insulin Resistance

PCOS is a type of insulin resistance that is only developed by women. Some of the occupational risk factors like the inconsistency of circadian rhythm and overnight sleep disorders caused by overnight work shifts, exposure to pollution (particles, solvents), heavy metals (arsenic, mercury) or, organic pollutants increase the risk of developing insulin resistance. In turn, insulin resistance leads to cardiovascular diseases and diabetes. There is a significant relationship between insulin resistance and clinical problems like non-alcoholic fatty liver and PCOS [9]. Studies have shown that occupational stress creates unhealthy habits like unhealthy nutrition that results in insulin resistance. Tianwei Xu *et al.* showed that social stresses like aggression, domination, and work pressure may lead to diabetes type II [8], which is an outcome of insulin resistance.

3.4. Stress and Hormonal Disorders

In terms of pathology, PCOS includes hyperandrogenic and probable changes in cortisol and melatonin secretion that reflect the function of the hypophyses and adrenal hypothalamus. Each of the elements of stress paths can halt reproduction function. Severe stress and ovulation failure disrupt steroidogenesis and angiogenesis. Chronic stress intensifies general catabolic conditions; therefore, constant hyperactivity (HPA) might gradually lead to a reduction of lean body mass (muscle and bone) and an increase in visceral fat and insulin resistance, which in turn affects the HPO axis. In the case of PCOS, chronic stress is one of the hemostatic disorders that leads to an endocrine disorder. Functional hypothalamic amenorrhea (FHA) is a chronic annulation that is not diagnosable due to organic reasons. It is mostly associated with stress, weight loss, hyperactivity, or a combination of them. A decrease in GnRH outcome at LH and FSH levels is not enough to preserve folliculogenesis and ovary function [7]. Moreover, psychological stress intensifies hypothalamus amenorrhea through decreasing the HPS activity [7].

3.5. Work and PCOS

There is a relationship between the expansion of stress symptoms and demanding work, low decision-making skills, and low social support [11]. Studies have shown that female managers feel more stress than male ones and the source of this stress is the social roles and expectations of women. This explains the fact that female managers are still a minority [12].

Studies in the USA have shown that women in stressful jobs are twice at the risk of short menstruation in comparison to the ones in non-stressful jobs. The risk of breast cancer is higher in women with shorter menstruation cycles [13]; in addition, the rate of ovary and womb cancers is higher in these women [14].

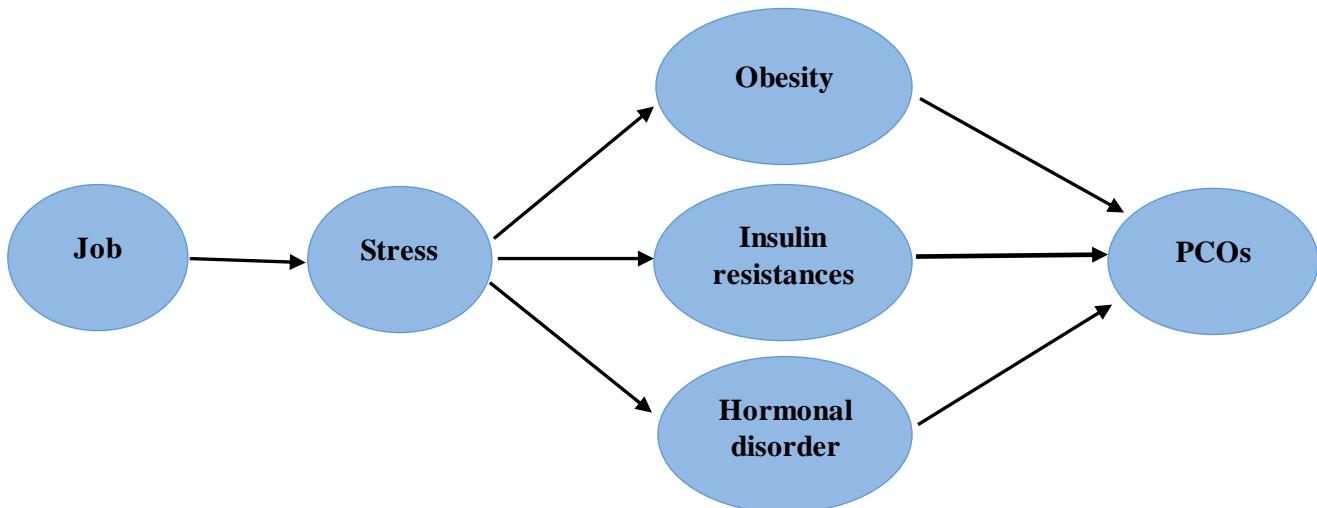


Fig (1). Relationship between job stress and PCO.

Occupational stress or other occupational risk factors have an indirect impact on PCOS in working women by creating insulin resistance, obesity, and hormonal distress (Fig. 1).

CONCLUSION

Working women experience many stressors depending on their job and being in charge of home affairs at the same time increases their stress and workload. Taking into account that stress is a precursor or intensifier of PCOS risk factors (*e.g.* obesity, insulin resistance, and hormonal disorder), working women are at a higher risk of PCOS compared with housewives.

LIST OF ABBREVIATION

PCOS = Polycystic Ovary Syndrome

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Life Modifications and PCOS: Old Story But New Tales

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Polycystic ovary syndrome (PCOS) is defined as a kind of endocrine and metabolic disorder that affects female individuals of reproductive age. Lifestyle modifications, including diet modifications, exercise, and behavioral modification, appear to alleviate the metabolic dysfunction and improve the reproductive disorders of PCOS patients (particularly in obese women). Therefore, lifestyle modifications have been gradually acknowledged as the first-line management for PCOS, especially in obese patients with PCOS. However, the mechanism of lifestyle modifications in PCOS, the appropriate composition of diet modifications, and the applicable type of exercise modifications for specific female populations are rarely reported. We conducted a systematic review and enrolled 10 randomized controlled trials for inclusion in a certain selection. In this review, we summarized the existing research on lifestyle modifications in PCOS. We aimed to illustrate the relationship between lifestyle modifications and PCOS (referring to hyperandrogenism, insulin resistance as well as obesity) and also considered the priorities for future research. These results might be an invaluable tool to serve as a guide in lifestyle modifications as the intervention for PCOS and other related endocrine disorders.

Keywords: polycystic ovarian syndrome (PCOS), lifestyle modifications, insulin resistance, hyperandrogenism, obesity

BACKGROUND

Polycystic ovary syndrome (PCOS) is a kind of common endocrine and metabolic disorder which disturbs reproductive-age female individuals (1). The symptoms of PCOS involved serious reproductive dysfunctions (including infertility and pregnancy complications) (2, 3), unbalanced metabolic functions (including insulin resistance, type 2 diabetes, and so on) as well as psychological disorders (mainly including depression and anxiety) and other implications (4), which disturb female patients whose ages range from adolescence to menopause. Recently, lifestyle modification is widely considered to be the cornerstone of many endocrine and metabolic disorders (5, 6). An increasing number of studies investigated the effectiveness and the frequency of lifestyle modification management in PCOS treatment (5). It is acknowledged that lifestyle plays a vital role in the development of PCOS, and lifestyle interventions are necessary. It seems that the lifestyle

modification for PCOS is an old story without any new tales; however, the kind of lifestyle modification that would be effective for PCOS, the difference between various modifications for different populations, and the underlying mechanism of the modifications are still uncertain. Herein we provide a comprehensive review of the influence of lifestyle modifications on the course of PCOS.

METHODS

Search Strategy and Design

We selected PubMed database for the systematic literature search. The search strategy included (i) “polycystic ovary syndrome” and its synonyms; (ii) “lifestyle”, “exercise therapy”, “behavior therapy”, “diet therapy”, and their synonyms; and (iii) “weight loss” and its synonyms. The outcome of the literature review was weight loss with different interventions (diverse lifestyle modifications).

Selection Criteria

We observed the inclusion criteria including (i) randomized controlled trials (RCTs), (ii) participants with polycystic ovary syndrome according to the Rotterdam criteria, (iii) intervention: lifestyle modification (with a clear description of methods) without pharmacological components, (iv) weight loss as outcome, and (v) follow-up of more than 24 weeks.

RESULTS

From the results in **Table 1**, a healthy eating diet and educational programs would lead to more weight loss. The outcomes after a diet modification, an exercise modification, and a combination of diet and exercise are significantly different. A high-protein diet also leads to weight loss when compared with a standard protein diet. However, there was no significant difference between a vegan diet and a caloric diet. No significant difference was also found between a low-glycemic-index (GI) diet and a hypocaloric healthy eating diet.

PCOS

PCOS is well acknowledged as a kind of disorder with both endocrine dysfunction and metabolic dysfunction (17), which impacts almost 20% of female patients of reproductive age. The symptoms of PCOS include androgen excess (hirsutism and/or hyperandrogenemia) and ovarian dysfunction (oligo-ovulation and/or polycystic ovarian morphology) (18). As studies focus on PCOS in-depth, insulin resistance and, subsequently, compensatory hyperinsulinism are regarded as two main mediators of hyperandrogenism in PCOS, both in animal models and in human bodies. It is widely acknowledged that hyperandrogenism and insulin resistance are common in PCOS. As an increasing number of studies focus on the phenotype and underlying mechanisms of PCOS, it is well demonstrated that insulin resistance and hyperinsulinism are responsible for the excessive androgen secretion in PCOS (19) since insulin could

react on the ovary as a cordonadotropin and trigger androgen secretion from the adrenal glands. Therefore, it is suggested that insulin resistance and hyperinsulinism are the pathophysiological factors in the development of PCOS. Many studies hypothesized that PCOS might be triggered by hyperandrogenism together with some pathophysiological factors and subsequently promote insulin resistance and hyperinsulinism (20). Insulin resistance and hyperinsulinism could induce androgen secretion by the ovaries and adrenal glands in PCOS patients in return (21). Thus, a large proportion of women with androgen excess and/or ovulatory dysfunction are also disturbed by insulin resistance, suggesting that hyperandrogenism and insulin resistance are in a vicious circle in PCOS. One of the characterizations of PCOS is heterogeneity. In view of pathophysiological characteristics, the factors accounting for PCOS heterogeneity mainly include obesity, insulin resistance, abdominal adiposity, and so on. Studies have reported that peripheral insulin resistance (insulin resistance exists in muscle tissues and adipose tissues) is actually a characteristic of PCOS patients with obesity (18). Moreover, insulin resistance might be present even in PCOS women who are not obese (22). However, many studies have reported that hyperandrogenism might be one of the common characteristics (23). Hyperandrogenism alone would induce PCOS without any other factors as shown in some case reports (24). In some cases, PCOS would also be noticed to fully manifest with both hyperandrogenism and the above-mentioned pathophysiological characteristics (obesity, insulin resistance, and abdominal adiposity) (25). Thus, excess androgen might be necessary for developing PCOS. Considering that the frequent familial aggregation of PCOS might also be relative to the primary steroidogenic abnormality and the pathophysiological characteristics, it is not complicated to understand the genetic predisposition of PCOS. Recently, it is well acknowledged that familial aggregation is one of the characteristics in PCOS, which indicates that PCOS might be a kind of disorder with a certain genetic basis (26). However, enormous genome-wide relevant studies reported that the associations of only a few genetic variants and mutations have been replicated in different populations in PCOS patients (27). Familial aggregation might be linked to certain environmental influences which only exist in the families affected, including lifestyle during fetal and childhood development, certain environmental exposure and certain drugs, aging process as well as dietary habits, most of which might contribute to the development of PCOS (28). Based on the characteristic of familial aggregation of PCOS, it is reasonable to speculate that lifestyle modification might benefit the PCOS patients.

Lifestyle Modifications

In recent years, lifestyle modifications are regarded as the cornerstone of all interventions against PCOS. Lifestyle modifications are regarded as the first-line management for patients disturbed by overweight or obesity (17). The most effective interventions include applicable diet modifications, increased physical activity and exercise modifications, and strategies to maintain adherence (29). Lifestyle modifications

TABLE 1 | Results of the 10 enrolled randomized controlled trial studies.

Year	Author	Grouping factors	Results Grouping 1	Grouping 2	Grouping 3	Control group	Significance
2018	Oberg E (7)	Behavioral intervention vs. minimal intervention	Mean weight loss -2.1%			Mean weight loss -1.0%	P = 0.002
2015	Wong J (8)	Low-glycemic-load diet vs. low-fat diet	Mean weight loss ± 0.8 kg (-1.2%)	-1.2	Mean weight loss -4.8 ± 1.6 kg (-5.5%)		P = 0.02
2015	Marzouk T (9)	Hypocaloric and healthy eating diet + educational program vs. healthy eating, no caloric restriction	Mean weight loss 90.8–83.7 kg (-3.9%)		Mean weight loss 90.5–90.1 kg (-0.4%)		P = 0.041
2014	Turner G (10)	Vegan diet vs. low-calorie diet	Mean weight loss 1.1%		Mean weight loss -0%		Not significant
2012	Sorensen L (11)	High-protein diet vs. standard protein diet	Mean weight loss 81.8–74.1 kg (7.7 kg) -9.4%			Mean weight loss 78.7–75.4 kg (3.3 kg) -4.2%	P = 0.002
2011	Egan N (12)	Low-glycemic-index diet vs. hypocaloric healthy eating diet	Median weight change -5.8 kg	Median weight change -4.5 kg			Not significant
2011	Nybacka A (13)	Diet vs. exercise vs. diet + exercise	Mean weight loss -6%	Mean weight loss -3%	Mean weight loss -5%		P < 0.001
2010	Marsh (14)	Low-glycemic-index diet vs. conventional healthy diet	Mean weight loss -5.2%, ITT: -3.2%	Mean weight loss -4.2%, ITT: -2.1%			Not significant
2008	Brown A (15)	Exercise vs. no exercise	Median weight change -1.29%			Median weight change +0.45%	P < 0.001
2008	Thomson R (16)	Diet vs. diet + aerobic exercise vs. diet + aerobic resistance exercise	Mean weight loss ± 1.6%	-8.9	Mean weight loss -10.6 ± 1.7%	Mean weight loss -8.7 ± 1.7%	Not significant

also appear to draw the ovulation function (30) as well as the menstrual cycle (31) into a regular level, which subsequently increases the successful pregnancy rates in PCOS patients. The studies reported that almost half of the PCOS patients would gain improvement both in regular menstrual cycle and ovulation function depending on the lifestyle modifications. In addition, lifestyle modifications could provide improvements such as alleviation of anxiety and improved quality of life, particularly in obese female patients with PCOS.

From the results shown in **Table 1**, a healthy eating diet and involvement in educational programs would lead to more weight loss—for example, Oberg E found that in terms of behavioral intervention, minimal intervention would help people attain weight loss (**Table 1**). The outcomes after diet modification, exercise modification, and the combination of diet with exercise are significantly different. A high-protein diet also leads to weight loss when compared with the standard protein diet. However, there was no significant difference between a vegan diet and a caloric diet. No significant difference was found between a low-GI diet and a hypocaloric healthy eating diet.

Mechanism of Lifestyle Modifications in PCOS

Lifestyle modifications (including diet, exercise, sleep, and so on) are regarded to play roles in the development of PCOS by regulating insulin sensitivity and keeping the weight balanced as well as governing normal androgen production. It was reported that lifestyle changes also appear to influence the restoration of ovulation and regular menstrual cycles and increased the pregnancy rates in overweight or obese anovulatory patients with PCOS. It is widely acknowledged that obesity is a vital

mediator in the development of PCOS. The level of sex-hormone-binding globulin is decreased in obese females (31), resulting in elevated androgen in the circulation and then in the target tissue, which disrupts normal ovulatory function (32). Additionally, obesity is associated with an elevated risk of metabolic syndrome, diabetes mellitus (type 2 diabetes), and insulin resistance in female bodies. Some studies compared the effects of lifestyle modifications with the effects of the combination of metformin and lifestyle modifications against PCOS and found that lifestyle modifications could reduce insulin resistance and increase the serum levels of sex-hormone-binding globulins when compared with metformin (33). Many studies also analyzed the effects of improved manifestations of PCOS by comparing the management of lifestyle modifications to the management of a combination of lifestyle modifications and other interventions (34). Negar reported their analysis based on 12 RCTs including 608 participants in which they witnessed a significant decrease in subcutaneous fat in subjects with “lifestyle (including daily physical activity, limited food intake, and so on) combined with metformin” compared with “lifestyle combined with placebo”. It was reported that both lifestyle modifications alone or a combination of lifestyle modifications and hormonal contraceptives have the potential to improve sexual function (35).

Exercise Modifications

As increasing studies focus on the roles of physical activities in human health, the evidence showed that in the management of PCOS, exercise activities would help female patients gain benefits, and this view is becoming accepted among doctors and patients (36, 37). When considering the appropriate exercise activities to alleviate the symptom of PCOS, it is always puzzling how to set the

appropriate exercise intensity and frequency. Recently, a meta-analysis reported that improvements in health outcomes are more likely to be linked to the exercise intensity rather than the exercise itself. An RCT study indicated exercise modifications with vigorous intensity (eight consecutive weeks and three sessions of supervised exercise training each week for the final four consecutive weeks). Each session lasts approximately 60 min and will involve 40 min of an individualized exercise protocol performed either on a cycle ergometer or a motorized treadmill preceded by a 10-min warm-up and followed by a 10-min cool-down) might have a better impact on the outcomes of PCOS (insulin resistance decreased significantly) (38). On the contrary, PCOS patients are found to be more likely to stay sedentary rather than perform vigorous exercises. Moderate aerobic exercise could also improve the insulin sensitivity of PCOS in the short term. Some other studies reported that women with PCOS could gain improvement, in terms of insulin sensitivity and abnormal androgen level, *via* vigorous aerobic exercise and resistance training (39). The minimum aerobic activity is recommended as more than 150 min per week, including intensive exercise for more than 90 min (2).

Diet Modifications

While it is recommended to reduce the calorie intake and induce weight loss among PCOS women with obesity, most of the current proposed recommendations regarding dietary modifications in PCOS are based on studies in obese women without PCOS. It was reported that there is limited evidence that any specific diet type is better than others (40). Some studies reported that once the intake of carbohydrates is less than 45% of the total daily calories, the low-carbohydrate diet might be helpful to decrease the body mass index as well as the serum levels of total cholesterol in PCOS subjects (41). Furthermore, studies indicate that maintaining the low-carbohydrate diet for more than 1 month could significantly increase the levels of follicle-stimulating hormone and sex-hormone-binding globulin (36). Even though some evidence indicates the effect of the low-carbohydrate diet on PCOS, the definitive mechanisms to explain the relationship are still unclear. It is well acknowledged that metformin has similar effects in decreasing body weight. Some studies compared the effects of diet modifications with the effects of the combination of metformin and lifestyle modifications against PCOS. It was reported that diet modifications could reduce insulin resistance and increase the serum levels of sex-hormone-binding globulins when compared with metformin (34).

What is more, weight loss could improve the features of PCOS patients regardless of dietary composition (42). Unfortunately, lifestyle modifications, including diet modifications, are seldom effective in the long run, which are in line with the results from the management of anti-obesity drugs. The unsatisfactory long-term results might be associated with the fact that the female subjects regain weight and fail to keep a normal body mass index (BMI).

Weight Modifications

While the complex clinical heterogeneity of PCOS brings up the lack of a clear understanding of obesity in PCOS, it is widely

accepted that obesity would increase insulin resistance and hyperandrogenism. It was reported that just a minor weight loss of 5–10% could play a role in significantly alleviating reproductive disorders (43), metabolic dysfunction, and even the psychological symptoms of PCOS patients (44). Thus, weight modification is recommended as a first step in the management of PCOS patients who are overweight or obese (45).

If the PCOS patient is disturbed by infertility, it is recommended that women with PCOS and obesity should delay therapy against infertility and achieve the weight modifications first because obesity is linked to a higher risk of increased rates of miscarriage and preeclampsia in perinatal PCOS women. It is believed that PCOS patients who are overweight/obese are more likely to face mood disorders, including anxiety, depression, and so on. However, the degree of the increased risk of excess weight and the impact on the prevalence and severity of the features of PCOS remains unclear. Anti-obesity drugs, including orlistat, could also be considered in PCOS patients who cannot achieve weight modification with diet modification and exercise modification (45, 46). Women with PCOS and normal weight and BMI also have an increased risk for metabolic disorders and chronic fatigue. A similar exercise program combined with diet modification is also recommended because these modifications could enhance insulin sensitivity (47, 48). Moreover, more studies are needed on the effects of weight modifications on normal-weight patients with PCOS. Thus, it is recommended that females with PCOS pursue weight modifications and prevent excessive weight gain by weight monitoring and maintaining appropriate BMI and waist circumference.

Mood Modifications

An increasing volume of evidence shows that both adolescent and adult females with PCOS are disturbed by mood disturbances, including depression and anxiety (49). It was reported that females with PCOS underwent a higher risk of depression, anxiety, and perceived stress when compared with women without PCOS (50). Since PCOS is linked to an increased risk of depression, anxiety, and some other mood disorders, screening and effective mood modifications for these disorders might be warranted.

There are several shared links and connections between depression- and PCOS-associated abnormalities, such as excessive androgen secretion, insulin resistance as well as obesity. These shared connections between depression and PCOS might help in finding potential therapies for depression in PCOS (51). A kind of appropriate and applicable mood modification for the two treatments is regarded as the potential modification which could help females with PCOS to lead a better life.

Sleep Modifications

It is important that psychological issues are considered as both a potential risk and a maintaining factor of illness, particularly in adolescent and young female subjects (52). As per the in-depth investigation and data analysis, a large proportion of psychological disorders with PCOS are sleep disorders. Since sleep disorders impact the development of PCOS, management relative to sleep modifications is considered an integral part of lifestyle modifications on females with PCOS. There is ample

evidence that sleep deprivation is associated with an increased risk of insulin resistance and obesity as well as type 2 diabetes (53). The mechanisms of the associations have been proven to be linked to relative autonomic pathways, endocrine disorders, and inflammatory status, which are responsible for the development of PCOS (54). Therefore, it is plausible that sleep modifications are of great significance among PCOS patients. Some studies reported that women are more likely to be disturbed by type 2 diabetes if the length of sleep is not more than 5 h per night when compared with women whose length of sleep ranges from 7 to 8 h per night. A study compared the quality of sleep by recording the percentage of rapid eye movement sleep via polysomnography and found that the percent sleep efficiency of obese females with PCOS is lower than that of not only normal-weight females but also obese adolescent females without PCOS (55). Ensuring adequate sleep with high quality would lead to a decreased risk of disturbance not only in obesity and insulin resistance but also in cardiovascular risk, suggesting that sleep modification could modify PCOS as an original modification.

SUMMARY AND PERSPECTIVES

PCOS is a kind of common endocrine and metabolic disorder which disturbs female subjects at reproductive ages. Since increasing evidence indicates that PCOS is frequently linked to abdominal adiposity, insulin resistance, obesity, metabolic disorders, and cardiovascular risk factors and becomes a complex disorder with environmental effects, such as diet and other lifestyle factors, lifestyle modification is therefore regarded as the first line of management for PCOS patients.

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PCOS women who are overweight or obese not only are exposed to metabolic and cardiovascular risk but also suffer from potential mental problems and risk adverse obstetric and perinatal outcomes, such as gestational diabetes and preterm birth. Obesity leads to high healthcare costs, which means that it would increase the investment in lifestyle modification. In **Table 1**, our data suggested that a healthy diet and increased physical activity should be encouraged for weight loss, which was in line with many published suggestions or guidelines. The conclusion would undoubtedly propose new insights and promising strategies to support clinical practices.

We review the lifestyle modifications in PCOS, including diet modifications, exercise modifications, sleep modifications, mood modifications, and weight modifications. While physical modification, appropriate dietary modification, and maintaining healthy sleep modification and mood modification are recommended for the management of various PCOS conditions, more perspective studies are needed on the effects of lifestyle modifications on PCOS to figure out and develop accurate and individualized guidelines. Lifestyle modifications in PCOS are not old stories but also new tales.

AUTHOR CONTRIBUTIONS

YG contributed to writing—original draft. GZ contributed to writing—original draft and editing. FZ contributed to writing—review and editing. QW, CM, and JD contributed to review and editing. KH contributed to writing—review and editing and supervision. All authors contributed to the article and approved the submitted version.

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REVIEW

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Lifestyle management in polycystic ovary syndrome – beyond diet and physical activity

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Abstract

Polycystic ovary syndrome (PCOS) is a common condition affecting reproductive-aged women with reproductive, metabolic and psychological consequences. Weight and lifestyle (diet, physical activity and behavioural) management are first-line therapy in international evidence-based guidelines for PCOS. While these recommend following population-level diet and physical activity guidelines, there is ongoing interest and research in the potential benefit of including psychological and sleep interventions, as well as a range of traditional, complimentary and integrative medicine (TCIM) approaches, for optimal management of PCOS. There is limited evidence to recommend a specific diet composition for PCOS with approaches including modifying protein, carbohydrate or fat quality or quantity generally having similar effects on the presentations of PCOS. With regards to physical activity, promising evidence supports the provision of vigorous aerobic exercise, which has been shown to improve body composition, cardiorespiratory fitness and insulin resistance. Psychological and sleep interventions are also important considerations, with women displaying poor emotional wellbeing and higher rates of clinical and subclinical sleep disturbance, potentially limiting their ability to make positive lifestyle change. While optimising sleep and emotional wellbeing may aid symptom management in PCOS, research exploring the efficacy of clinical interventions is lacking. Uptake of TCIM approaches, in particular supplement and herbal medicine use, by women with PCOS is growing. However, there is currently insufficient evidence to support integration into routine clinical practice. Research investigating inositol supplementation have produced the most promising findings, showing improved metabolic profiles and reduced hyperandrogenism. Findings for other supplements, herbal medicines, acupuncture and yoga is so far inconsistent, and to reduce heterogeneity more research in specific PCOS populations, (e.g. defined age and BMI ranges) and consistent approaches to intervention delivery, duration and comparators are needed. While there are a range of lifestyle components in addition to population-recommendations for diet and physical activity of potential benefit in PCOS, robust clinical trials are warranted to expand the relatively limited evidence-base regarding holistic lifestyle management. With consumer interest in holistic healthcare rising, healthcare providers will be required to broaden their knowledge pertaining to how these therapies can be safely and appropriately utilised as adjuncts to conventional medical management.

Keywords Polycystic ovary syndrome, diet, guideline, physical activity, sleep, cognitive behavioural therapy, quality of life, complementary medicine

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Introduction

Polycystic ovary syndrome (PCOS) is a common condition affecting up to 13% of reproductive-aged women [1]. It is diagnosed through the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESRHE/ASRM) criteria, requiring two of the following features: polycystic ovaries on ultrasound, oligoovulatory or anovulatory cycles and biochemical or clinical hyperandrogenism [2]. Women with PCOS experience a combination of reproductive (infertility, pregnancy complications) [3], metabolic (risk factors for and conditions of type 2 diabetes (T2DM) and cardiovascular disease (CVD)) [4, 5] and psychological (conditions including anxiety, depression, poor quality of life (QoL), disordered eating) comorbidities [6, 7].

Insulin resistance (IR) is defined as a key pathophysiological feature in PCOS, contributing to hyperandrogenism and worsening the clinical presentation of PCOS. While lean women present with IR in a form that is mechanistically different from IR caused by excess weight, overweight and obesity further exacerbate IR and consequent hyperinsulinaemia [8]. Women with PCOS also display a higher rate of weight gain over time [9] and a greater prevalence of overweight and obesity [10], which can further contribute to this worsening of IR and hence worsening of the presentation of PCOS [11]. The reason for this is unclear, but may be related to differences in intrinsic psychological and biological mechanisms [12–15], or extrinsic lifestyle factors such as diet and physical activity [16, 17]. Improving IR and excess adiposity are therefore key targets in PCOS management.

The International Evidence-Based Guideline for the Assessment and Management of PCOS [18], highlights lifestyle intervention as the primary early management strategy. Lifestyle interventions are traditionally defined as those designed to improve dietary intake or physical activity through appropriate behavioural support. In the 2018 PCOS guideline, lifestyle management is recommended for general health benefits [18]. Given that excess weight is associated with increased IR in PCOS [8], the guideline additionally promotes weight management, defined as: 1) weight gain prevention in all women with PCOS, and 2) achieving and maintaining modest weight loss in women with excess weight [18].

Lifestyle interventions in PCOS management can also be viewed as a broader construct beyond physical health. Since the emergence of the biopsychosocial model of healthcare in 1977, health disciplines have seen a gradual shift away from the classical biomedical model (where health is defined as the ‘absence of disease’) towards whole person or holistic care [19]. This is an approach that reflects many facets of the patient context, via integrating care that addresses biological, psychological, social, spiritual and ecological

aspects [20]. It therefore requires a range of different treatment strategies to improve health. Provision of whole person or holistic care has been identified as a core objective of healthcare reforms internationally [21–23]. In line with these reforms the PCOS guideline recognises the importance of emotional wellbeing to overall health and QoL in women living with PCOS [18]. It also highlights evidence which suggests that the psychological impact associated with PCOS is under-appreciated in clinical care [4, 5], and that few women are satisfied with the mental health support they receive [6, 7]. Recommendations for appropriate screening, assessment and treatment strategies for anxiety, depression, psychosexual dysfunction, eating disorders and poor body image are provided [18]. These specific areas of emotional wellbeing are of particular concern, with research showing a higher prevalence and severity of depression and anxiety [24, 25], lower scores for satisfaction with sex life and feeling sexually attractive [26] and a higher prevalence of disordered eating and eating disorders [7] in women with PCOS. Features of PCOS, in particular hirsutism and increased weight, have also been shown to negatively affect body image [27, 28], with poor body image being strongly related to depression in women with PCOS [29, 30].

While the current PCOS guideline is comprehensive, considering all available evidence at the time of development and providing best-practice recommendations for necessary screening, risk assessment and management, it could not possibly cover all aspects of PCOS care. An International Delphi process was used to prioritise clinical questions, with consensus reached through extensive consultation with both consumers and multidisciplinary clinicians with expertise in PCOS care. Therapies, such as traditional, complementary and integrative medicine (TCIM), supplement use, sleep and meditation interventions are either briefly considered or not at all included in the 2018 PCOS guideline. Many of these therapies are novel and there is a paucity of evidence to support intervention efficacy on PCOS outcomes. However, as patient interest in these types of non-pharmacological interventions are growing [31–35], it is prudent to provide more guidance to healthcare providers in this area on their potential efficacy in PCOS. Whole person or holistic care recognises that the doctor-patient relationship should be one of open dialogue, where healthcare providers involve the patient in negotiating their care and recognises patient’s autonomy to guide treatment (Figure 1) [36].

This review provides an extensive overview of evidence to date on lifestyle strategies used to optimise management of PCOS. Using a holistic definition of patient care, this review considers the traditional components of lifestyle change (diet, physical activity and behavioural change), psychological and sleep interventions, as well as TCIM approaches (supplements, herbal medicine,

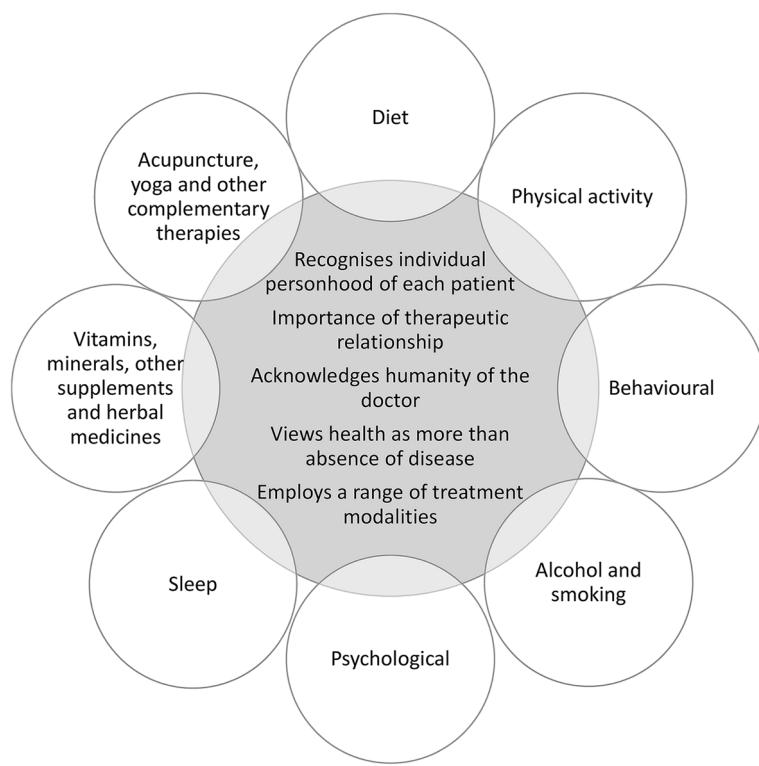


Fig. 1 Viewing lifestyle modifications through a whole person or holistic care lens. The key features of whole person or holistic care listed in the centre of the figure have been adapted from Thomas et al. [20]. ‘Recognises individual personhood’ relates to focusing on the unique needs of the person rather than the disease. ‘Importance of therapeutic relationship’ emphasises patient autonomy and responsibility. ‘Acknowledges humanity of the doctor’ considers the doctors’ ability to self-reflect on how they engage in the care of the patient. ‘Health as more than absence of disease’ incorporates the mental, emotional, physical, environmental and social needs of the patient. ‘Employs a range of treatment modalities’ promotes continuity of care across health disciplines, and while it may include traditional, complementary and integrative medicine (TCIM), TCIM is not holistic if used in isolation and without adequate integration into conventional healthcare

acupuncture and yoga). To improve translation of findings, evidence summaries are accompanied by an overview of relevant recommendations from the existing PCOS guideline. This highlights where emerging evidence supports current recommendations or provides new insights for research. As this is a narrative review, while evidence summaries include peer-reviewed journal articles identified from databases including Medline OVID, this is supplemented by expert opinion of the authors.

Traditional lifestyle and weight management

The PCOS guideline recommends the promotion of healthy lifestyle behaviours in all women with PCOS, to achieve and/or maintain a healthy weight and to optimise general health [18]. In women with excess weight, a weight loss of 5–10% is advised, aiming for an energy deficit of 30% or 500–750 kcal/day (1200–1500 kcal/day). While weight management is seen as a core component of lifestyle interventions, the guideline recognises that a healthy lifestyle provides benefits that occur independent of weight change.

A recent Cochrane review of 15 randomised controlled trials (RCT) and 498 participants, reported that lifestyle interventions compared with minimal intervention or usual care, significantly reduces weight (kg) and body mass index (BMI) and improves secondary reproductive outcomes such as free androgen index (FAI), testosterone (T), sex hormone-binding globulin (SHBG) and hirsutism (Ferriman-Gallwey score) [37]. In terms of metabolic outcomes, lifestyle intervention resulted in significant reductions in total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and fasting insulin (FINS). These findings are largely similar to that of other systematic reviews [38–41]. While no studies in the Cochrane review assessed clinical reproductive outcomes [37], individual trials that were not included in the review have reported that lifestyle interventions resulting in modest weight loss (2–5% total body weight) improve ovulation and menstrual regularity [42–45]. Losing >5% of weight is additionally associated with being able to conceive, having live births, reduction of ovarian volume and reduction in the number of follicles [46–52].

Table 1 Reviews and experimental studies investigating the effects of diet on polycystic ovary syndrome outcomes

Dietary intervention	N study design	N studies; N participants	Main findings ^a	References
Low CHO	2 SR/MA (27 RCT total - 18 RCT using low CHO diet) [56, 85] 1 SR (5 RCT total - 1 RCT using low CHO diet) [16]	14; 901	Low CHO compared with control diets [56]: ↓ BMI, HOMA-IR, TC, LDL-C ↑ SHBG ↔ LH, T, HDL-C Dietary intervention ↓ HOMA-IR, FINS, FGL, BMI, BW, WC compared with minimal intervention, and subgroup analysis showed no additional benefits for low CHO diets [85] Weight loss improved the presentation of PCOS regardless of dietary composition, with no subtle differences observed for low CHO diets [16]	Shang et al. 2020 [85] Zhang et al. 2019 [56] Moran et al. 2013 [16]
Low GI	1 SR/MA (10 RCT total - 8 RCT using low GI diet) [55] 1 SR (5 RCT total - 1 RCT using low GI diet) [16] 4 Pre-post prospective [61, 76, 77, 118] 1 RCT [78]	16 ^b ; 582	High GI compared with low GI diets [55]: ↓ HOMA-IR, FINS, TC, LDL-C, TAG, WC, T ↔ FGL, HDL-C, BW, FAI Low GI diets had greater improvements in IR, TC, HDL-C, fibrinogen, menstrual regularity and QoL [16] Low GI diets followed for ≥ 12 weeks: ↓ BW [76, 77], BMI [76, 77], BFM [77], WC [77], WHR [77], FINS [76, 77], FGL [77], TC [77], LDL-C [77], TAG [77], T [77], LH [77], androstenedione [77], prolactin [77] ↑ insulin sensitivity (HOMA2-IS) [61], synthesis of predominantly anti-inflammatory eicosanoid mediators (e.g. 16(R)/16(S)-HETE, 13(S)-HODE, 9(S)-HODE, 15(S)-HETE, 12(S)-HETE, 5(S)-oxoETE, 5(S)-HETE) [118], fasting glucagon (higher glucagon levels associated with lower levels of self-reported hunger) [78]	Kazemi et al. 2020 [55] Moran et al. 2013 [16] Shishrehgar et al. 2019 [76] Barr et al. 2016 [61] Szczuko et al. 2018 [77] Szczuko et al. 2017 [118] Hoover et al. 2021 [78]
High protein	1 SR (5 RCT total - 3 RCT using high protein diet) [16] 2 Pre-post prospective [73, 74] 6 RCT [92, 94–97]	11; 308	High protein diets improve depression and self-esteem [16] ↓ BFM [74, 97], BW [73, 74, 97], BMI [73, 74], WC [73, 74, 97], WHR [73], FINS [74, 98], FGL [97], HOMA-IR [73, 98], TAG [73], VLDL-C [73], T [73, 98], Ferriman-Gallwey scores [73] High protein and standard/low protein diet ↓ BW [92, 94, 95], BMI [92, 94, 95], BFM [95], WC [92, 94], WHR [94], FINS [95, 96], HOMA-IR [95], TAG [96], LDL-C [98] CRP [96], MPA [96], leptin [95], T [98], DHEAS [98], FAI [98] and there was ↔ between high and standard/low protein diets	Moran et al. 2013 [16] Moran et al. 2010 [96] Moran et al. 2004 [95] Sorensen et al. 2012 [97] Toscani et al. 2011 [92] Nadjarzadeh et al. 2021 [94] Phy et al. 2015 [73] Pohlmeier et al. 2014 [74] Mehrabani et al. 2012 [98]
Low fat	1 SR/MA (19 RCT total - 1 RCT using low fat diet) [85] 1 SR (5 RCT total - 1 RCT using low fat diet) [16] 1 RCT [107]	3; 137	Dietary intervention ↓ HOMA-IR, FINS, FGL, BMI, BW, WC compared with minimal intervention, and subgroup analysis showed no additional benefits for low fat diets [85] Weight loss improved the presentation of PCOS regardless of dietary composition, with no subtle differences observed for low fat diets [16] Low fat (25% E fat) ↓ BW, BFM, BMI though there was ↔ between low fat and standard fat (35% E fat) diets [107]	Shang et al. 2020 [85] Moran et al. 2013 [16] Wong et al. 2016 [107]

Table 1 (continued)

Dietary intervention	N study design	N studies; N participants	Main findings ^a	References
Fatty acids	1 SR (5 RCT total - 1 RCT using MUFA enriched diet) [16] 3 RCT [86, 102, 105] 1 controlled trial (not randomised) [103] ^c	5; 146	MUFA enriched diets may produce greater weight loss when compared to other dietary patterns [16] MUFA enriched compared with PUFA enriched diets ↓ FGL [103], glucose response to OGTT [103], HgBA1 [102] Diets with a higher alpha-linolenic acid, lower omega-6/omega-3 ratio and saturated fat content ↓ TAG, TC/HDL-C, LDL-C-/HDL-C, TAG/HDL-C, and HOMA-IR [105] High total and saturated fat meals compared with high fibre low fat meals produce prolonged ↓ in T [86]	Moran et al. 2013 [16] Yahay et al. 2021 [105] Kalgaonkar et al. 2011 [102] Kasim-Karakas et al. 2004 [103] Katcher et al. 2009 [86]
DASH	1 SR/MA (19 RCT total - 4 RCT using DASH diet) [85]	4; 228	Dietary intervention ↓ HOMA-IR, FINS, FGL, BMI, BW, WC compared with minimal intervention, and subgroup analysis showed DASH diet was more effective at improving insulin sensitivity [85]	Shang et al. 2020 [85]
Plant-based	3 RCT	3; 108	Plant-based (35% animal protein, 35% textured soy protein, 30% vegetable protein) compared to control (70% animal protein, 30% vegetable protein) ↓ BMI, FGL, FINS, TAG, HOMA-IR, T, MDA and ↑ QUICKI [67] Plant-based and control diets (calorie restriction [68] and general dietary recommendations [72]) ↓ BW [68], HOMA-IR [72], T [72], LH/FSH [72] and there was ↔ between plant-based and control diets	Turner-McGrievy et al. 2014 [68] Kazemi et al. 2020 [72] Karamali et al. 2018 [67]
Meal pattern	1 RCT	1; 40	6 meals/day compared with 3 meals/day: ↓ FINS ↑ post-OGTT insulin sensitivity	Papakonstantinou et al. 2016 [111]
Meal timing	1 RCT	1; 60	Consuming a high kilojoule breakfast compared with a high kilojoule dinner: ↓ FGL, FINS, HOMA-IR, T ↑ SHBG	Jakubowicz et al. 2013 [66]

Abbreviations: ↑ significant increase ($P \leq 0.05$), ↓ significant decrease ($P \leq 0.05$), ↔ no significant change, *BFM* Body fat mass, *BMI* Body mass index, *BW* Body weight, *CHO* Carbohydrate, *CRP* C-reactive protein, *DHEAS* Dehydroepiandrosterone-sulfate, *E* Energy, *FAI* Free androgen index, *FBM* Fat body mass, *FGL* Fasting glucose level, *FINS* Fasting insulin level, *FSH* Follicle stimulating hormone, *G* Glycaemic index, *HDL-C* High density lipoprotein cholesterol, *HOMA-B* Homeostatic Model Assessment for Beta Cells, *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance, *IR* Insulin resistance, *LDL-C* Low density lipoprotein cholesterol, *LH* Luteinizing hormone, *MDA* Malondialdehyde, *MUFA* Monounsaturated fatty acid, *OGTT* Oral glucose tolerance test, *PCOS* Polycystic ovary syndrome, *PUFA* Polyunsaturated fatty acid, *QoL* Quality of life, *QUICKI* Quantitative insulin sensitivity check index, *SHBG* Sex hormone-binding globulin, *T* Testosterone, *TAG* Triglycerides, *TC* Total cholesterol, *VLDL-C* Very low density lipoprotein cholesterol, *WC* Waist circumference, *WHR* Waist hip ratio

^a Summarises commonly used measures in PCOS research and does not report on all measured outcomes. For prospective pre-post studies significant changes from baseline are reported. For RCTs significant changes between intervention(s) and control are reported. Only experimental studies not already summarised in included systematic reviews/meta-analysis are presented

^b Shishregar et al. 2019 total study population included 62 women though only findings for the women with PCOS ($n=28$) are included

^c While habitual diet (control) was not enriched with MUFA, nutritional analysis showed that it was rich in oleic acid

Although weight loss has shown clear benefits to PCOS outcomes, including not only on reproductive function, but also glucoregulatory status, androgen status and lipid profiles [42–52], there are varying degrees of responsiveness to weight loss in terms of improvement of PCOS symptoms. One study by Pasquali et al. [53] found that when women achieved similar levels of weight loss (>5% weight) only one-third displayed a full recovery from PCOS, with the remainder showing

only partial or no recovery. Higher waist circumference (WC), waist-hip-ratio (WHR) and androstenedione at baseline were associated with a poorer chance of successful outcomes [53], suggesting that central adiposity and more severe hyperandrogenism may predict responsiveness to weight loss interventions in PCOS. Huber-Buchholz et al. [45] also reported women who achieve greater reductions in central fat and insulin sensitivity show greater symptom improvement with

weight loss. This suggests that lifestyle interventions which simultaneously reduce IR and improve body composition (namely fat distribution), may help to optimise outcomes in PCOS management independent of changes in weight status.

Diet

The 2018 PCOS guideline recognises there is insufficient evidence to suggest that any specific dietary approaches provide greater benefits on health outcomes [18]. Dietary recommendations may take on a variety of balanced dietary strategies according to the individual's lifestyle needs and preferences, as per general population recommendations [18]. This advice is based on a systematic review comparing different dietary compositions (e.g. low carbohydrate, low glycaemic index (GI) and glycaemic load (GL), high protein, monounsaturated fatty acid (MUFA) enriched and fat counting diets) to best manage PCOS, identifying minimal differences between diets on anthropometric outcomes, concluding weight loss improves the presentation of PCOS regardless of dietary composition [16, 54]. There is now an emerging body of evidence that suggests a range of dietary strategies may produce favourable effects on PCOS features that occur independent of weight loss. It is important that the emerging findings from these studies are thoroughly considered to support consumer and health professional interests. To summarise current evidence this review has grouped diets in terms of those that modify carbohydrates, protein and fat, as well as specific dietary patterns.

Carbohydrates

The use of altered carbohydrate composition remains the most researched dietary approach for PCOS management. Two systematic reviews published after guideline inception support altered carbohydrate intake to improve intermediate markers of PCOS [55, 56], finding that altering carbohydrate type, as opposed to content, is preferable to better manage PCOS [55]. RCTs [57–72] and pre-post intervention studies [73–80] demonstrate that following a low GI/GL diet for at least eight weeks significantly reduces WC [55, 73, 74] and BMI when compared to high GI/GL [56] or a regular diet [73–76], although levels of weight loss are generally comparable to other dietary compositions [59, 60, 72, 74]. These reductions are proposed to be a result of decreased hunger, which may reduce energy intake and make it easier to follow dietary recommendations in the long-term [78, 81–84]. Low GI/GL diets also improve insulin sensitivity and reproductive hormones (T, SHBG, FAI) compared to high carbohydrate [16, 55, 57, 79, 85] or control diets [56, 59, 73–76], contributing to improvements in reproductive function, specifically menstrual regularly [60, 79]. Lastly, low GI/GL diets can improve risk factors for T2DM and CVD, including glucose

[86, 87], TC [55, 56, 59, 75, 77], LDL-C [55, 59, 75, 85], TAG [55, 59, 73] and HDL-C [75], when compared to a regular or high GI/GL diet. It must be noted that beneficial effects of low GI/GL diets may also be attributed to proportional increases in protein and/or fat loads.

Protein

In women with PCOS higher protein intakes may be superior at suppressing androgen levels when compared to high carbohydrate diets. Postprandial research has shown that high protein meals can reduce insulin and dehydroepiandrosterone stimulation compared to meals rich in glucose [88]. Research in the general population has also shown that reduced appetite and energy intakes from low GI/GL diets are related to increased protein intakes [89, 90]. RCTs and pre-post intervention studies found that high protein diets (defined here as protein constituting $\geq 25\%$ energy [91]) consumed for at least four weeks reduce weight [12, 73, 74, 92–96], BMI [73, 74, 92, 95], WC [73, 74, 92, 97], WHR [73] and fat mass [74, 92, 97]. These reductions in anthropometric measures are accompanied by improved FINS [12, 74, 95, 98] and HOMA-IR [12, 73, 95, 98], blood lipids [12, 96], T [73, 92, 94] and hirsutism (Ferriman-Gallwey score) [73]. However, only three of these studies were able to show significant improvements in anthropometric measures [97], insulin sensitivity [98] and blood lipids [12] when compared to low/standard protein [12, 97] or control diets [98]. Only one study investigated effects on mental health outcomes and found that a high protein diet reduced depression and improved self-esteem [99].

Fats

Fatty acid composition is also an important consideration as metabolic disorders associated with PCOS can benefit from increased MUFA and polyunsaturated fatty acid (PUFA) intakes [63–65]. Postprandial research in PCOS reported prolonged reductions in T for high fat compared to low fat meals, which likely results from delayed nutrient absorption [86]. Two acute meal studies in lean and obese women with and without PCOS reported that proatherogenic inflammatory markers [100] and oxidative stress [101] were elevated, independent of but augmented by obesity, following saturated fat ingestion with this associated with worsened IR and androgens. Two experimental studies in PCOS investigated the effects of habitual walnut (PUFA rich diet) [102, 103] and almond (MUFA rich diet) [102] intake for at least six weeks and reported no differences in glucoregulatory status, lipids or androgens with the exception of HbA1c significantly decreasing in the walnut relative to the almond group. Kasim-Karakas et al. [103] reported increased fasting and postprandial glucose

(oral glucose tolerance test (OGTT)) for increased walnut intake compared to habitual (control), which they postulated may be related to the control diet being rich in oleic acid. Together these findings suggest minimal benefit for improving dietary PUFA compared to MUFA content. Two RCTs in women with PCOS investigated the effects of diets rich in olive [104, 105], canola [105] and sunflower [105] oil. Yahay et al. [105] reported 25g/day canola oil caused reductions in TAG, TC/HDL-C, LDL-C/HDL-C, TAG/HDL-C and HOMA, but not androgens, compared to 25 g/day olive and sunflower oils [105]. This may be related to the more favourable fatty acid composition of canola oil, with comparable MUFA content to olive oil, higher alpha-linolenic acid, lower omega-6/omega-3 ratio and saturated fat than both olive and sunflower oils. Douglas et al. [104] reported weight and the acute insulin response (OGTT) were lower following a eucaloric low carbohydrate compared to a eucaloric MUFA-enriched olive oil diet, suggesting that reduced carbohydrate intake may have greater glucoregulatory benefits than increased MUFA intake [104]. Lastly, two RCTs compared hypocaloric low-fat diets to a low carbohydrate [106] or low GI [107] diets, with reductions in weight [106], WC [106], body fat [106, 107], FINS [106] and FAI [106] in both groups but no difference between groups.

Dietary and eating patterns

In addition to diets that focus on specific macronutrient manipulations, there are a range of dietary patterns which have been explored in PCOS management. A systematic review (including 19 studies and 1,193 participants) published after guideline development (2020) found that the Dietary Approaches to Stop Hypertension (DASH) diet (rich in fruit, vegetables, wholegrains, nuts, legumes and low-fat dairy and with a predominantly low-GI carbohydrate profile) was the optimal choice for reducing IR [85]. RCTs in PCOS also report beneficial effects on weight [63, 64], BMI [62, 63], IR [62] and hormonal profile, including SHBG [64], androstenedione [64] and FAI [62] for a DASH compared to a control diet after 8–12 weeks. A vegetarian diet also reduced inflammatory markers (CRP, resistin and adiponectin) compared to a meat inclusive diet [80]. A vegan diet improved weight loss at three, but not six months [68], and a pulse-based diet led to similar reductions in weight, insulin sensitivity and reproductive hormones compared to a healthy control diet [72]. All of these dietary patterns are high in fibre and plant proteins, producing favourable effects on microbial diversity and encouraging production of short-chain fatty acids that possess potential anti-inflammatory actions [108, 109]. With mechanistic animal studies suggesting a possible pathophysiological role of gut microbiota in IR and

ovarian dysfunction, it is possible that metabolic and hormonal benefits associated with plant-based dietary patterns in PCOS are related to increased intakes of dietary prebiotics [110]. However, further mechanistic studies exploring the role of gut microbiota in PCOS and RCTs investigating effects of dietary prebiotics on PCOS outcomes are required.

Lastly, particular eating patterns, such as eating smaller more frequent meals across the day [111] and eating a larger breakfast and smaller dinner [66], have also been found to be beneficial for insulin sensitivity [66, 111] and androgen reductions [66]. This is an important finding, as women with PCOS are more likely to either skip breakfast or consume their breakfast and lunch later in the day [112].

Studies examining specific food items in relation to PCOS outcomes, including raw onions [65], concentrated pomegranate juice [69, 113–115] and flaxseed powder [70, 116] have yielded largely inconsistent results. A core limitation of these single food studies is that foods are never consumed alone within the diet, omitting the influence of the dietary matrix and the interactions that occur amongst dietary constituents within meals. These studies provide limited applicability in the context of formulating practical dietary recommendations [117]. Please see Table 1 for a summary of available evidence from reviews and experimental studies investigating the effects of different types of diets on PCOS outcomes.

Physical activity

The 2018 PCOS guideline recommends ≥150 minutes per week of moderate or ≥75 minutes per week of vigorous intensity exercise for weight gain prevention, and ≥250 minutes per week of moderate or ≥150 minutes per week of vigorous intensity exercise for weight loss and weight regain prevention [18]. Minimising sedentary time and the inclusion of strength training exercise for two days per week is also recommended [18].

To date the most comprehensive review in PCOS (including 27 papers from 18 trials up until June 2017) reported that exercise improved FINS, HOMA-IR, TC, LDL-C, TAG, body composition (body fat percentage and WC) and aerobic fitness ($\text{VO}_{2\text{max}}$) [119] compared with usual care or control groups. In regards to exercise type, subgroup analysis reported aerobic exercise improved BMI, WC, body fat percentage, FINS, HOMA-IR, TC, TAG and $\text{VO}_{2\text{max}}$. In contrast, while resistance training produced unfavourable effects on HDL-C (decrease) and BMI (increase), it improved other measures of anthropometry, including WC. Combined interventions (using both aerobic and resistance training) had no effect on any of the measured markers. Subgroup analysis also found that more outcomes improved when

Table 2 Meta-analyses investigating the effects of different types of exercise on polycystic ovary syndrome outcomes

Physical activity intervention	N reviews; N studies; N participants	Main findings ^a	References
Aerobic exercise	4; 48; 1518	↓ WC [119, 121, 124], BMI [119, 122, 124], BF% [119], HOMA-IR [119, 121, 122, 124], TC [119, 124], FINS [119, 124], TAG [119], LDL-C [119], RHR [119] ↑ VO _{2peak/max} [119, 121, 124] ↔ BMI [121], BW [119, 124], HDL-C [124], LDL-C [124], TAG [124], FGL [119, 124], BP [119], HOMA-IR [122], FAI [119, 121, 122], T [119, 122], SHBG [119], E2 [119], LH [119, 122], FSH [119, 122]	Patten et al. 2020 [121] dos Santos et al. 2020 [122] Richards et al. 2021 [124] Kite et al. 2019 [119]
Resistance training	2; 14; 505	↓ WC [119], HOMA-IR [121], FINS [119], HDL-C [119], FAI [121] ↑ BMI [119] ↔ BW [119], BF% [119], FGL [119], HOMA-IR [119], TAG [119], TC [119], LDL-C [119], VO _{2max/peak} [119], RHR [119], FAI [119], T [119], SHBG [119], E2 [119], LH [119], FSH [119]	Patten et al. 2020 [121] Kite et al. 2019 [119]
Combined aerobic and resistance training ^b	2; 3; 59	↔ BMI [119, 122], WC [119], HOMA-IR [119, 122], FINS [119], FGL [119], BP [119], TAG [119], TC [119], LDL-C [119], HDL-C [119], RHR [119], T [119, 122], E2 [119], LH [119], FSH [119]	Kite et al. 2019 [119] dos Santos et al. 2020 [122]
High intensity interval training	2; 11; 373	↓ BMI [123], WHR [123], HOMA-IR [123, 124] ↔ BF% [123], BMI [124], BW [124], WC [124], TC [123, 124], LDL-C [123, 124], TAG [124], FINS [123, 124], FGL [124], HDL-C [124], VO _{2max} [124]	Richards et al. 2021 [124] dos Santos et al. 2021 [123]

Abbreviations: ↑ significant increase ($P \leq 0.05$), ↓ significant decrease ($P \leq 0.05$), ↔ no significant change, BF% Percent body fat, BMI Body mass index, BW Body weight, BP Blood pressure, E2 Estradiol, FGL Fasting glucose level, FAI Free androgen index, FINS Fasting insulin, FSH Follicle stimulating hormone, HOMA-IR Homeostatic assessment of insulin resistance, LDL-C Low density lipoprotein cholesterol, LH Luteinizing hormone, PCOS Polycystic ovary syndrome, RHR Resting heart rate, SHBG Sex hormone-binding globulin, T Testosterone, TAG Triglycerides, TC Total cholesterol, VO_{2max} Maximal oxygen uptake, VO_{2peak} Peak oxygen uptake, WC Waist circumference, WHR Waist hip ratio

^a Significant findings from meta-analyses when comparing exercise groups to control

^b Subgroup analyses compared different types of exercise; only 1 study included for combined exercise

interventions were supervised, of a shorter duration (≤ 12 weeks) and were conducted in women who were above a healthy weight [119].

Three more recent systematic reviews have looked at the effects of specific types of exercise on PCOS outcomes [120–122]. These reviews found that vigorous aerobic exercise can improve measures of insulin responsiveness and resistance, including HOMA-IR [121] and the insulin sensitivity index [120]; body composition, including WC [121] and BMI [122]; and cardiorespiratory fitness (VO_{2max}) [121]. High intensity interval training (HIIT) alone may be effective for improving IR and BMI [123], however this has not been consistently shown [124]. Interventions involving a combination of aerobic and resistance exercise [122] or resistance training only [120] did not result in improvements in BMI [122] or weight status [120]. Exercise involving resistance training did result in other beneficial improvements to body composition (reduced body fat, WC and increased lean mass) and strength. This is important, as the degree of

central adiposity predicts responsiveness to weight loss interventions in PCOS [53], and women who achieve greater reductions in central fat show greater symptom improvement with weight loss [45]. Resistance training may also improve androgen levels, though findings are inconsistent and more research is needed to draw definite conclusions [120]. There was insufficient evidence from available data to assess the effects of exercise type on reproductive function [122]. Please see Table 2 for a summary of available evidence from meta-analyses investigating the effects of different types of exercise on PCOS outcomes.

When comparing the effects of exercise and diet combined with diet alone, a systematic review and meta-analysis (three studies) found no differences for any measured outcomes (glucose, insulin HOMA-IR, weight, BMI, WC, body fat, fat free mass, T, SHBG and FAI) [119]. In regards to exercise and diet combined compared to exercise alone, subgroup analysis (including 17 studies) from a large systematic review found that the addition of diet to exercise,

Table 3 Experimental studies investigating the effects of psychological interventions on polycystic ovary syndrome outcomes

References	Study design; study length; N participants	Intervention	Main findings
Abdollahi et al. 2019 [152]	Parallel RCT; 8 wk; 74	I = 8 weekly CBT C = minimal intervention	↑ QoL (PCOSQ) for I compared with C ↓ psychological fatigue (FIS) for I compared with C
Jiskoot et al. 2020 [162] Jiskoot et al. 2020 [154]	Parallel RCT; 1 yr; 183	I = 20 group sessions of CBT combined with nutrition advice and exercise C = usual care	↓ depression (BDI-II) and BW in I compared with C ↑ self-esteem (RSES) in I compared with C
Oberg et al. 2020 [132]	Parallel RCT; 16 wk with a follow-up at 1 yr; 68	I = behavioural modification program C = minimal intervention	↓ anxiety (PGWB) and depressed mood (PGWB) in I compared with C ↑ higher general health (PGWB) in I compared with C
Cooney et al. 2018 [153]	Parallel RCT; 16 wk; 31	I = 8 weekly CBT with lifestyle modification C = no psychological intervention with lifestyle modification	↓ BW in I compared with control ↑ QoL (PCOSQ) in I compared with control
Raja-Khan et al. 2017 [160]	Parallel RCT; 16 wk; 86	I = 8 weekly MBSR C = 8 weekly health education sessions (diet and exercise education)	↑ mindfulness (TMS) in I compared with C ↓ perceived stress (PSS-10) in I compared with C
Stefanaki et al. 2015 [156]	Parallel RCT; 8 wk; 38	I = MBSR C = minimal intervention	↓ depression (DASS21), stress (DASS21) and cortisol in I compared with control
Roessler et al. 2012 [151] ^a Roessler et al. 2013 [163] ^b	Cross-over randomised; 8 wk per arm and 16 wk total; 17	8 wk high-intensity aerobic exercise (including a ramp-up period of two weeks) and 8 wk group counselling in a cross-over design without a wash-out period	Relationships between the participants were important for changes in behaviour, especially relationships which generated helpful peer feedback and reduced social isolation ↓ BW and BMI after 16 wk only in the group who started with group counselling
Rofey et al. 2009 [158]	Single arm experimental; 8 wk; 12	8 one-on-one CBT, 3 family-based CBT and lifestyle goals (diet and exercise)	↓ BW, BMI and depression (CDI) ↑ health-related QoL (IWQoL-K)

Abbreviations: ↑ significant increase ($P \leq 0.05$), ↓ significant decrease ($P \leq 0.05$), *BDI-II* Beck Depression Inventory-II, *BW* Blood pressure, *BMI* Body mass index, *BW* Body weight, *CDI* Children's Depression Inventory, *C* Control, *CBT* Cognitive behavioural therapy, *CES-D* Centre for Epidemiologic Studies – Depression Scale, *DASS21* Depression Anxiety Stress Scales-21, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders (fourth edition), *FGL* Fasting glucose level, *FIS* Fatigue Impact Scale, *I* Intervention, *IWQoL-K* Impact of Weight on Quality of Life Questionnaire—Kids, *HP* Hip circumference, *MBSR* Mindfulness-based stress reduction, *PSS-10* Perceived Stress Scale-10, *PCOS* Polycystic ovary syndrome, *PCOSQ* Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire, *PGWB* Psychological Well-Being Index, *QoL* Quality of life, *RSES* Rosenberg Self Esteem Scale, *RCT* Randomized controlled trial, *STA* State-Trait Anxiety Inventory, *SSP* Swedish Universities Scale of Personalities, *TMS* Toronto Mindfulness Scale, *TSST* Trier Social Stress Test, *WC* Waist circumference

^a Qualitative analysis only

^b Statistical analysis compares order of intervention arms (e.g. counselling followed by exercise versus exercise followed by counselling) and doesn't compare effects of counselling versus exercise

particularly vigorous intensity aerobic exercise, resulted in greater reduction to BMI, WC, FAI and HOMA-IR than exercise only [121]. In regards to exercise (aerobic) alone versus diet alone, one intervention study found that exercise induced weight loss produced greater improvements

in menstrual frequency and ovulation rates [125], with no differences in pregnancy rates [125]. However, this study was not randomised and treatments were self-selected, which may have biased the results and precludes firm conclusions [125].

Table 4 Key observational studies that report non-clinical sleep disruption in polycystic ovary syndrome

Reference	Sample size	Sleep methodology used	Main findings
Moran et al. 2015 [182]	PCOS: n=87 Non-PCOS: n=637	Modified version of the Jenkins Sleep Questionnaire	Women with PCOS were twice as likely to experience sleep disturbance PCOS was associated with difficulty falling asleep and maintaining sleep
Mo et al 2019 [140] ^a	PCOS: n=484 Non-PCOS: n=6094	Sleep duration was self-reported on a work day and non-work day Sleep quality was self-reported through frequency questions about difficulty falling asleep, restless sleep, difficulty sleeping and severe tiredness	Women with/without PCOS had similar sleep duration Women with PCOS had higher prevalence of sleep disturbance, and this relationship maintained even after controlling for BMI, depression, income, marital status, occupation, education status and COB
Bennett et al. 2021 [183] ^a	PCOS: n=464 Non-PCOS: n=5603	Sleep duration was self-reported on a work day and non-work day Sleep quality was self-reported through frequency questions about difficulty falling asleep, restless sleep, difficulty sleeping and severe tiredness	Overall women with PCOS had greater adverse sleep symptoms and higher DGI However, subgroup analysis revealed PCOS was only associated with a higher DGI in women with adequate sleep There was no association between PCOS and DGI in women with poor sleep The higher DGI observed in women with PCOS may only be maintained in women who achieve adequate amounts of good quality sleep
Shreeve et al. 2013 [167]	PCOS: n=15 Non-PCOS: n=18	Actigraphy, PSQI and ESS	Women with PCOS had higher night time melatonin levels Women with PCOS had reduced sleep when compared to controls
Kutanaee et al. 2019 [181]	PCOS: n=201 Non-PCOS: n=199	PSQI	Women with PCOS had lower sleep quality and daytime function Women with PCOS were more likely to utilise medication to assist with sleep

Abbreviations: BMI Body mass index, COB Country of birth, DG Dietary Guidelines Index, ESS Epworth Sleepiness Scale, PCOS Polycystic ovary syndrome, PSQI Pittsburgh Sleep Quality Index

^a Mo et al. [140] and Bennett et al. [183] share the same cohort

Behavioural

The 2018 PCOS guideline promotes the use of behavioural interventions that foster self-efficacy [18]. These include the use of SMART (specific, measurement, achievable, realistic and timely) goals, self-monitoring, stimulus control, problem solving and relapse prevention [18].

Behavioural and cognitive interventions are required to improve sustainability of lifestyle changes, through considering not only the specific behaviour, but also their antecedents, consequences and cognition [126, 127]. Given that women with PCOS show higher rates of weight gain over time [9] and high attrition rates in clinical weight management research [37], there is a clear need to improve adherence to diet and physical activity interventions. However, the majority of research investigating lifestyle change in PCOS involve short-term dietary interventions with/without an exercise element, and there is a paucity of research on behavioural change strategies. As such, guideline development relied heavily on evidence taken from the general population. Only three RCTs in women with PCOS included a ‘behavioural intervention’ [128–130]. While

these studies showed enhanced weight loss [128, 130] and improved androgen and lipid profiles [129] when compared with placebo, the interventions were not well defined, with negligible context provided regarding the theoretic framework or behavioural strategies utilised.

More recently, a cross-sectional study in 501 women with PCOS [131] and two RCTs [44, 132] explored the use of self-management strategies [131] and behavioural modification interventions [44, 132] in PCOS. In the cross-sectional study, implementation of physical activity self-management strategies improved the likelihood of meeting physical activity recommendations, but had no association with BMI. Dietary self-management strategies were associated with reductions in BMI, though were not related to weight or nutritional intake [131]. In the RCTs, only the behavioural modification programme and not the control (general healthy lifestyle recommendations) produced significant weight loss after four months. A significantly greater proportion of women in the intervention group also improved menstrual regularity [44] and psychological well-being (lower anxiety and depressive

symptoms) [132] when compared to the control group. The women who achieved greater weight loss reported higher social desirability and lower embitterment scores on a personality trait assessment measure [132]. These findings are particularly novel, as they provide insight into the influence of personality traits and their contribution to success in following behavioural modifications [132].

Alcohol and smoking

In the clinical setting, smoking and alcohol consumption are often addressed alongside dietary and physical activity changes, employing the same behavioural and cognitive interventions to promote adherence. Hence, alcohol and cigarette use are considered here under traditional lifestyle strategies. The PCOS international guideline highlights the importance of assessing alcohol consumption and cigarette smoking when improving fertility and reproductive outcomes in women with PCOS [18]. Assessment of cigarette use is also recommended when evaluating CVD risk factors and thromboembolism risk associated with oral contraceptive pills [18]. These recommendations are based on existing practice guidelines used for the general population.

There is a paucity of observational research characterising alcohol consumption in women with PCOS. One Swedish study comparing women with PCOS ($n=72$) to healthy controls ($n=30$), demonstrated a lower alcohol intake in the PCOS group [133]. A larger study in Australia comparing women with ($n=409$) and without ($n=7,057$) PCOS, reported no significant difference in alcohol intake [134]. Similarly, a Spanish study ($n=22$ PCOS and $n=59$ controls) and a Chinese study ($n=2,217$ PCOS and $n=279$ controls), found no significant difference in alcohol intake between PCOS and non-PCOS groups [135, 136].

Current evidence on the impact of alcohol intake on anovulatory infertility (a common feature of PCOS) is controversial, with some studies showing adverse effects and others reporting no significant correlation [136, 137]. One prospective study including 18,555 married women from The Nurses' Health Study II, who had no history of infertility, found no clinically significant impact of alcohol intake on anovulatory infertility, after adjusting for parity and other factors [138]. Similarly, a Danish study ($n=6,120$ women aged 21 to 45 years) found no fertility effect with alcohol consumption of less than 14 standard drinks per week [137]. In contrast, a study on 3,833 women who recently gave birth and 1,050 women with infertility, reported an increased risk of anovulatory infertility and endometriosis with increasing alcohol intake [139].

Current observational evidence does not reveal any significant difference in smoking between women with and without PCOS [135, 136, 140], with the exception of one

study in pregnant women which showed a lower smoking rate in women with PCOS ($n=354$) compared to women without PCOS at 15 weeks gestation [3]. However, a significantly higher rate of smoking (including passive and active) is reported in women with PCOS and oligo-anovulation and/or reduced fertility compared to women with PCOS and normal menstruations or healthy controls [141, 142]. Smoking is also associated with PCOS risk independent of BMI and age [142]. A Mendelian randomisation study supports these findings, demonstrating a 38% higher risk of PCOS development in genetically predicted smokers (based on single-nucleotide polymorphisms associated with smoking initiation) compared with those who never smoked [143]. In PCOS, smoking is associated with increased levels of T, DHEAS, TC, LDL-C and FINS [141, 144, 145]. However, the underlying mechanisms are not fully understood and there are inconsistencies in findings from different studies. Furthermore, smoking is associated with lower conception and live birth rates and less favourable ART outcomes in women with PCOS [141, 146].

Psychological

The current guideline highlights the need for awareness, and appropriate assessment (such as stepwise screening) and management, of QoL, depression and anxiety, psychosexual dysfunction, negative body image and disordered eating [18]. The guideline emphasises the importance of clinicians and women working in partnership to address women's individual priorities; understanding that the impact of PCOS on an individual's QoL is key to delivering meaningful outcomes [147, 148]. To assist women to communicate with clinicians about what is important to them, the PCOS Question Prompt List [149] was developed and is consistent with the 2018 guideline. The 2018 guideline recommends screening for risk factors and symptoms of depression and anxiety at time of diagnosis. Women with positive screening results should be supported with further assessment and treatment by appropriately qualified clinicians. To screen for psychosexual dysfunction tools such as the Female Sexual Function Index [150] should be utilised. If negative body image, disordered eating or eating disorders are suspected, the PCOS guideline outlines a stepped approach for screening, and where appropriate promotes the use of psychological therapy offered by trained health professionals, which should be guided by regional clinical practice guidelines [18].

While the PCOS guideline provides justification and summarises evidence for mental health screening and diagnostic assessment, there is also a need for consideration of additional aspects, such as the efficacy of different types of psychological interventions and how

Table 5 Reviews and experimental studies investigating the effects of traditional, complimentary and integrative medicine on polycystic ovary syndrome outcomes

Intervention	N study design	N studies; N participants	Main findings ^a	References
Vitamins				
B-group vitamins (B1, B6, and B12)	1 RCT	1; 60	Counteracted Hcy-increasing effect of metformin ↔ HOMA-IR	Kilicdag et al. 2005 [198]
Folate (vitamin B9)	2 RCT	2; 150	↓ Hcy [199, 200], HOMA-β [199], HOMA-IR [200], FINS [200], TC:HDL-C ratio [200], CRP [199], MDA [199] ↑ TAC [199], GSH [199]	Bahmani et al. 2014 [199] Asemi et al. 2014 [200]
Inositol (vitamin B8)	1 SR/MA	9 RCT; 496	↓ HOMA-IR; ↓ FINS ↔ androstenedione, T, SHBG	Unfer et al. 2017 [191]
Vitamin D	2 SR/MA	23 RCT; 1367	↓ TC [201], LDL [201], TAG [201], HOMA-IR [203], FGL [203], FINS [203], VLDL-C [203] ↑ QUICKI [203] ↔ HDL-C [201]	Guo et al. 2020 [201] Gao et al. 2021 [203]
Vitamin E	1 RCT	1; 86	↓ FGL, HOMA-IR, SHBG, T (only when combined with coenzyme Q10)	Izadi et al. 2019 [205]
Vitamin K	1 RCT	1; 79	↓ WC, FBM, FINS, HOMA-IR, HOMA-β, TAG, FAI, DHT ↑ skeletal muscle mass, SHBG, QUICKI	Tarkesh et al. 2020 [206]
Vitamin-like supplements				
Soy isoflavones	1 pilot pre-post prospective	1; 12	↓ TC, LDL-C, LDL-C:HDL-C ratio, TAG	Romualdi et al. 2018 [208]
Carnitine (L-Carnitine)	1 RCT	1; 60	↓ MDA, MDA:TAC ratio ↑ TAC	Jamilian et al. 2017 [211]
Alpha-lipoic acid	2 pre-post prospective	2; 52	↓ BMI [214], IR [213], LDL-C [213], TAG [213], ovarian cysts [214] ↑ progesterone [214]	Masharani et al. 2010 [213] Cianci et al. 2015 [214]
Minerals				
Vitamin D and calcium	1 SR/MA	6 RCT; 480	↓ FINS, HOMA-IR, FGL, T, TAG, VLDL-C, TC, LDL-C, hirsutism ↑ QUICKI, menstrual regularity	Shojaeian et al. 2019 [219]
Zinc	1 SR	5 RCT; 285	↓ HOMA-IR, HOMA-β, FINS, MDA, CRP, T, FSH, TC, LDL-C, TAG, VLDL-C, DHEAS ↑ TAC, QUICKI	Nasiadek et al. 2020 [220]
Selenium	1 SR	5 RCT; NR	↓ IR, CRP and MDA in some RCTs ↔ (or inconsistent findings) BMI, BW, FGL, blood lipids, androgens, acne, hirsutism	Hajizadeh-Sharafabad et al. 2019 [221]
Magnesium	1 SR	3 RCT; 156	Serum magnesium concentrations were associated with IR but supplementation had inconsistent effects	Hamilton et al. 2019 [222]
Chromium Picolinate	2 SR/MA	11 RCT; 702	↓ BMI [223], FINS [223], IR [224], T [223] ↑ T [224] ↔ BMI [224], FG [223]	Fazelian et al. [223] Tang et al. [224]

Table 5 (continued)

Intervention	N study design	N studies; N participants	Main findings ^a	References
Other supplements				
Omega-3 fatty acids	1 SR/MA	9 RCT; 591	↓ HOMA-IR, TC, LDL-C and TAG. ↔ FINS, FGL, BMI, androgens	Yang et al. 2018 [225]
N-acetyl-cysteine	1 SR/MA	8 RCTS; 910	↑ rates of pregnancy and live births	Thakker et al. 2015 [226]
Coenzyme Q10	1 RCT	1; 60	↓ FGL, FINS, HOMA-IR, HOMA-β, TC, LDL-C ↑ QUICKI	Samimi et al. 2017 [227]
Probiotics	2 SR/MA	19 RCT; 1261	↓ FINS [228], TG [228], VLDL-C [228], FAI [229] ↑ QUICKI [228], SHBG [229] ↔ BW [228], FGL [228], HOMA-IR [228], TC [228], LDL-C [228], HDL-C [228], CRP [228], DHEA [228], T [229]	Liao et al. 2018 [228] Shamasbi et al. 2020 [229]
Quercetin	1 SR	3 RCT; 246	Some improvement in adiponectin-mediated IR ↔ BW, WHR	Pourteymour et al. 2020 [232]
Resveratrol	1 SR/MA	3 RCT; 131	↓ T ↑ high-quality oocytes and embryos ↔ BMI, blood lipids, FGL, pregnancy rate	Shojaei-Zarghani et al. 2021 [233]
Melatonin	1 SR/MA	2 RCT and 1 cell culture; 640	↑ pregnancy rates in assisted reproductive technology	Hu et al. 2020 [172]
Herbal medicine				
Cinnamon	1 SR/MA	5 RCT; 448	↓ HOMA-IR, TC, LDL, FGL, FINS ↑ HDL ↔ BW	Heydarpour et al. 2020 [260]
Curcumin	2 RCT	2; 118	↓ FGL [238], DHEA [238] ↔ FGL [239], FINS [238], blood lipids [239], IR [239]	Heshmati et al. 2021 [238] Sohaei et al. 2019 [239]
Sage	1 RCT	1; 70	↓ BW, BMI, WC, FGL, FINS, HOMA-IR, QUICKI ↔ WHR	Amini et al. 2020 [241]
Fennel and dry cupping	1 RCT	1; 55	↓ BMI, cycle length	Mokaberinejad et.al. 2019 [243]
Licorice	1 pre-post prospective 1 quasi-experimental	2; 41	↓ T [245] Reduce prevalence of side effects related to the diuretic activity of spironolactone [246]	Armanini et al. 2004 [245] Armanini et al. 2007 [246]
Spearmint, ginger, citrus and cinnamon	1 RCT	1; 60	↓ HOMA-IR, FINS, FGL	Ainehchi et al. 2019 [251]
Chinese herbal medicine	1 SR/MA	4 RCT; 414	↑ pregnancy rate when taken with clomiphene (versus clomiphene alone) ↔ pregnancy rate when taken alone (versus clomiphene alone) Insufficient evidence for subfertility	Zhou et al. 2016 [235]

Table 5 (continued)

Intervention	N study design	N studies; N participants	Main findings ^a	References
Other TCIM				
Acupuncture	2 SR/MA	31 RCT; 2846 ^b	↓ BMI [255], LH [254], T [254] ↑ menstrual regularity [254] ↔ FGL [255], FINS [255], live birth [254], pregnancy rate [254], ovulation [254]	Wu et al. 2020 [254] Qu et al. 2016 [255]
Yoga	2 SR [120, 257] 1 SR/MA [258] 1 RCT [259]	21; 1059 ^a	↓ WC [259], HC [259], HOMA-IR [120], FGL [258], FINS [258], T [120], LH [120], DHEA [120], androstenedione [120], adiponectin [120], clinical hyperandrogenism [259] ↑ menstrual regularity [258], menstrual frequency [257] ↓ stress and anxiety [257]	Shele et al. 2020 [120] Thakur et al. 2021 [257] Anita et al. 2021 [258] Mohseni M et al. 2021 [259]

Abbreviations: ↑ significant increase ($P \leq 0.05$), ↓ significant decrease ($P \leq 0.05$), ↔ no significant change, *BMI* Body mass index, *BW* Body weight, *DHEAS* Dehydroepiandrosterone-sulfate, *DHT* Dihydrotestosterone, *FGL* Fasting glucose level, *FINS* Fasting insulin level, *FBM* Fat body mass, *FSH* Follicle stimulating hormone, *FT* Free testosterone, *GSH* Glutathione, *HC* Hip circumference, *Hcy* Homocysteine, *HOMA-IR* Homeostatic assessment of insulin resistance, *HDL-C* High density lipoprotein cholesterol, *IR* Insulin resistance, *QUICKI* Quantitative insulin sensitivity check index, *QoL* Quality of life, *MDA* Malondialdehyde, *MA* Meta-analysis, *NR* Not reported, *OCP* Oral Contraceptive Pill, *RCT* Randomised controlled trial, *SHBG* Sex hormone binding globulin, *SR* Systematic review, *T* Testosterone, *TAC* Total antioxidant capacity, *TC* Total cholesterol, *TAG* Triglycerides, *TCIM* Traditional, complimentary and integrative medicine, *VLDL-C* Very low density lipoprotein cholesterol, *WC* Waist circumference, *WHR* Wait hip ratio

^a Summarises commonly used measures in PCOS research and does not report on all measured outcomes. For prospective pre-post studies significant changes from baseline are reported. For RCTs significant changes between intervention(s) and control are reported

^b Not all participants are included in the findings reported here (e.g. where findings from subgroup analysis are reported)

psychological interventions influence engagement with lifestyle change. This is important, as poorer mental health outcomes at baseline are positively associated with higher rates of attrition in lifestyle interventions [13]. Cognitive behavioural interventions could be considered to improve engagement and adherence to healthy lifestyle in women with PCOS. Research has shown support for a range of different psychological interventions, such as counselling [151], cognitive behavioural therapy (CBT) [152–154] and mindfulness meditation [155, 156], helping to change the way clinicians' approach and deliver optimal PCOS management.

CBT is one of the most widely-researched psychological interventions, and is well-recognised as the most effective psychological treatment for depression and anxiety [157]. One RCT showed that eight weekly group CBT sessions were effective in improving QoL ratings and reducing psychological fatigue in women with PCOS [152]. Another more recent RCT investigated the outcome of a 1 year three-component intervention focusing on CBT, diet and exercise [154] and reported improvements in self-esteem and depressive symptoms as compared to usual care [154]. Similarly, an RCT by Cooney et al. [153], comparing the effects of CBT and lifestyle modification versus lifestyle modification alone, reported the CBT/lifestyle modification group lost more than twice as much weight per week

and had greater improvements in QoL compared to lifestyle only. Depression scores decreased in the overall group and there was no difference between the two groups [153]. Lastly, a pilot intervention study of adolescents with PCOS has shown promising results for the use of CBT in the reduction of weight and improvement in depressive symptoms [158].

Mindfulness meditation programs have gained increasing popularity over the past few decades, and are being included as part of clinical trials to reduce stress and improve psychological wellbeing across a range of medical conditions [159]. Mindfulness meditation can be used to reduce the production of adrenal androgens, activated via the adrenal glands as a direct result of psychological distress [156]. Despite the proposed benefits, there are very few studies investigating the use of mindfulness meditation as a treatment for psychological symptoms associated with PCOS. One RCT ($n=86$) compared the provision of an eight week mindfulness-based stress reduction (MBSR) program, and found that when compared to the control group (health education), the MBSR group produced greater reductions in perceived stress, depressive symptoms and fasting blood glucose [160]. Similarly, another RCT investigating the impact of mindfulness meditation for eight weeks in PCOS showed reduced stress, depression and anxiety symptoms, and increased life satisfaction and QoL in the intervention

group compared to no treatment [156]. In adolescents with PCOS ($n=37$), a pilot RCT reported higher levels of nutrition and physical activity self-efficacy following a mindfulness and self-management program [161]. Mindfulness-based cognitive therapy (MBCT) combines both elements of MBSR and CBT, but as yet there are no trials investigating this intervention in PCOS.

In addition to CBT and mindfulness meditation, there is some evidence to support group counselling sessions as beneficial in conjunction with exercise programs to increase and support weight loss [151]. In one RCT ($n=17$) participants followed a high-intensity aerobic exercise program for eight weeks, followed by eight weeks of group counselling [151]. Qualitative analysis of data taken from the group counselling and physical exercise sessions revealed that development of supportive relationships was important for successful behavioural change. By fostering the exchange of narratives relating to their illness (e.g. effects of PCOS on aspects of everyday life), and generating feedback between group members, counselling sessions helped to reduce social isolation and improve adherence to the exercise intervention [151]. Please see Table 3 for a summary of experimental studies investigating effects of psychological interventions on PCOS outcomes.

Sleep

Women with PCOS have an increased risk of both clinical sleep disorders and non-clinical sleep disturbance, which is mediated by hormone derangement, in particular reduced oestrogen, progesterone and melatonin levels [164]. Oestrogen is required for the metabolism of neurotransmitters (norepinephrine and serotonin) involved in regulating sleep patterns, and plays an important role in maintaining a low body temperature at night [165]. Progesterone has sedative and anxiolytic actions that can support sleep quality, and acts as a respiratory stimulant that lessens airway resistance in obstructive sleep apnoea (OSA) [166]. Melatonin is a neuroendocrine hormone that is widely recognised as crucial in maintaining circadian rhythm regulation. However, melatonin is also involved in ovarian function, with actions including delaying ovarian senescence, promoting follicle formation and improving oocyte quality [167–173].

The current PCOS guideline recognises that OSA is 6.5–8.3 times more likely in women with PCOS [164, 174–177], and promotes routine screening to identify and treat associated symptoms, such as snoring, excessive sleepiness and the potential for fatigue to worsen mood disorders [18]. Screening should include a simple questionnaire, such as the Berlin tool [178], and where appropriate women should be referred onto a specialist for further assessment and

treatment [18]. The guidelines also highlight that treatment of OSA in PCOS should not be used to improve metabolic features. Since guideline inception evidence has emerged reporting weight, PCOS and sleep are interrelated factors that can each contribute to the worsening presentation of one another, whereby sleep disorders and disturbance may worsen the presentation of PCOS related metabolic outcomes and vice versa [179].

Hypersomnia and insomnia are also common clinical sleep disorders in PCOS [164, 177, 180], with prevalence estimated at 11% versus 1% in women with versus those without PCOS [180]. Even in the absence of clinically diagnosed sleep disorders, women with PCOS have a higher prevalence of sleep disturbances, including poor sleep quality [181], issues with sleep initiation [182], severe fatigue [140], restless sleep [140] and difficulty sleeping overnight [140]. The prevalence of sleep disturbances may be up to 20% higher in women with PCOS compared to women without PCOS [183]. Emerging research also suggests that social restrictions arising from the COVID-19 pandemic have worsened sleep disturbances in women with PCOS [177]. Findings from key studies of non-clinical sleep disturbance can be found in Table 4.

In the general population short and disturbed sleep is consistently associated with excess weight [184], IR [185], T2DM [185] and CVD [186]. Similar relationships are observed in PCOS, where OSA and sleep disordered breathing exacerbates risk of IR and metabolic consequences of abnormal glucose tolerance [187, 188]. A cross-sectional study in adolescents with PCOS ($n=103$) reported those with sleep disordered breathing had significantly higher BMI Z-scores, and a higher prevalence of metabolic syndrome (METS) [188]. Similar metabolic consequences are seen in women with PCOS who suffer from non-clinical sleep disturbance [164]. Underlying mechanisms linking sleep disorders and disturbance with worsened metabolic outcomes include amplified sympathetic tone and oxidative stress [164], reduced adipose tissue lipolysis, and an increase in energy intake stemming from heightened hedonic and endocrine appetite signals [189].

Unfavourable effects on energy metabolism and appetite regulation, may explain why women with PCOS who display sleep disturbance have a reduced capacity to maintain dietary interventions [183]. Moreover, depression and anxiety share a bidirectional relationship with disrupted and reduced sleep [190], and as stated previously, interventions that improve mental health can help to increase engagement with dietary and physical activity recommendations [131]. Optimising sleep may therefore be an important consideration when promoting healthy lifestyle change in women with PCOS [183].

Table 6 Current recommendations for clinical practice and research gaps identified by this review

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Effectiveness of lifestyle interventions		
Healthy lifestyle behaviours encompassing healthy eating and regular physical activity should be recommended in all those with PCOS to achieve and/or maintain healthy weight and to optimise hormonal outcomes, general health, and QoL across the life course.	CCR	<ul style="list-style-type: none"> • Improves sustainability of weight loss interventions. • Identifies subgroups who respond to weight loss with clinically relevant metabolic and reproductive improvements (this requires the inclusion of more clinical reproductive outcomes in RCTs). • Defines weight loss thresholds for improvements in different PCOS features (metabolic, reproductive and psychological). • Characterises the degree of metabolic and reproductive improvements related to different lifestyle factors (diet, physical activity and behavioural) independent of weight changes. • Considers effects of weight gain prevention on limiting the progression/worsening of PCOS features. • Investigates how different dietary, physical activity and behavioural interventions affect engagement, adherence and sustainability of lifestyle change. • Investigates efficacy and effectiveness of healthy lifestyle changes independent of weight change.

Table 6 (continued)

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Dietary interventions		
A variety of balanced dietary approaches could be recommended to reduce dietary energy intake and induce weight loss in women with PCOS and overweight and obesity, as per general population recommendations.	CCR	<ul style="list-style-type: none"> Low GI/GL diets may provide benefits in reducing weight and IR in women with PCOS. Further research needs to assess additional risk factors including reproductive function and CVD risk. Identify and define the optimal diet for PCOS management by comparing a range of different dietary approaches (e.g. DASH, Mediterranean or low GI/GL).
General healthy eating principles should be followed for all women with PCOS across the life course, as per general population recommendations.	CCR	
To achieve weight loss in those with excess weight, an energy deficit of 30% or 500 - 750 kcal/day (1,200 to 1,500 kcal/day) could be prescribed for women, also considering individual energy requirements, body weight and physical activity levels.	CPP	
In women with PCOS, there is no or limited evidence that any specific energy equivalent diet type is better than another, or that there is any differential response to weight management intervention, compared to women without PCOS.	CPP	
Tailoring of dietary changes to food preferences, allowing for a flexible and individual approach to reducing energy intake and avoiding unduly restrictive and nutritionally unbalanced diets, are important, as per general population recommendations.	CPP	
Physical activity interventions		
Health professionals should encourage and advise the following for prevention of weight gain and maintenance of health:	CCR	While evidence supports the provision of supervised vigorous aerobic exercise, which may provide greater benefits on PCOS symptoms than other types of exercise (e.g. resistance training), additional larger and longer-term studies are required to: <ul style="list-style-type: none"> Characterise optimal exercise prescription for PCOS management. Identify factors that improve adherence to exercise interventions. Identify subgroups who respond to exercise with clinical improvements.
• in adults from 18 – 64 years; a minimum of 150 min/week of moderate intensity physical activity or 75 min/week of vigorous intensities or an equivalent combination of both, including muscle strengthening activities on 2 non-consecutive days/week;		
• in adolescents, at least 60 minutes of moderate to vigorous intensity physical activity/day, including those that strengthen muscle and bone at least 3 times weekly;		
• activity be performed in at least 10-minute bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days.		
Health professionals should encourage and advise the following for modest weight-loss, prevention of weight-regain and greater health benefits:	CCR	
• a minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensity or an equivalent combination of both, and muscle strengthening activities involving major muscle groups on 2 non-consecutive days/week;		
• minimised sedentary, screen or sitting time.		
Physical activity includes leisure time physical activity, transportation such as walking or cycling, occupational work, household chores, games, sports or planned exercise, in the context of daily, family and community activities.	CPP	
Daily, 10000 steps is ideal, including activities of daily living and 30 minutes of structured physical activity or around 3000 steps.		
Structuring of recommended activities need to consider women's and family routines as well as cultural preferences.		

Table 6 (continued)

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Behavioural interventions		
Lifestyle interventions could include behavioural strategies such as goal-setting, self-monitoring, stimulus control, problem solving, assertiveness training, slower eating, reinforcing changes and relapse prevention, to optimise weight management healthy lifestyle and emotional wellbeing in women with PCOS.	CCR	<ul style="list-style-type: none"> To identify behavioural and cognitive strategies that should be targeted in women with PCOS, more observational research that characterises women's use of self-management strategies is needed. To aid replication and interpretation of findings, RCTs must clearly define the theoretical frameworks and behavioural components used in intervention design.
Comprehensive health behavioural or cognitive behavioural interventions could be considered to increase support, engagement, retention, adherence and maintenance of healthy lifestyle and improve health outcomes in women with PCOS.	CPP	
Assessment and treatment of infertility (as it relates to alcohol and smoking use)		
Cardiovascular disease risk (as it relates to alcohol and smoking use)	CPP	<ul style="list-style-type: none"> Determine whether women with PCOS are at a higher risk of alcohol and smoking-related infertility complications (with a focus on anovulatory infertility) when compared to women without PCOS. Determine whether women with PCOS are at a higher risk of smoking-related CVD complications when compared to women without PCOS.
Factors such as blood glucose, weight, blood pressure, smoking, alcohol, diet, exercise, sleep and mental, emotional and sexual health need to be optimised in women with PCOS, to improve reproductive and obstetric outcomes, aligned with recommendations in the general population.	CCR	
If screening reveals CVD risk factors including obesity, cigarette smoking, dyslipidaemia, hypertension, impaired glucose tolerance and lack of physical activity, women with PCOS should be considered at increased risk of CVD.	CCR	
Quality of life		
Health professionals and women should be aware of the adverse impact of PCOS on quality of life.	CCR	<ul style="list-style-type: none"> Validate QoL tools longitudinally to identify clinically meaningful differences in QoL scores.
Health professionals should capture and consider perceptions of symptoms, impact on quality of life and personal priorities for care to improve patient outcomes.	CCR	
The PCOS quality of life tool (PCOSQ), or the modified PCOSQ, may be useful clinically to highlight PCOS features causing greatest distress, and to evaluate treatment outcomes on women's subjective PCOS health concerns.	CPP	

Table 6 (continued)

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Depression and anxiety symptoms, screening and treatment		
Psychosexual function		
Body image		
Eating disorders and disordered eating		
Health professionals should be aware that in PCOS, there is a high prevalence of moderate to severe anxiety and depressive symptoms in adults; and a likely increased prevalence in adolescents.	CCR	<ul style="list-style-type: none"> To determine accurate prevalence of psychological conditions in PCOS, more adequately powered cross-sectional studies using structured diagnostic interviews administered by appropriately qualified professionals are required. Future research should consider the efficacy of different types of psychological interventions in PCOS, with a focus on how changes to mental health symptoms influence engagement with lifestyle change. In particular, the development of a PCOS specific CBT program, tailored to meet the specific mental health needs of women with PCOS is warrant.
Anxiety and depressive symptoms should be routinely screened in all adolescents and women with PCOS at diagnosis. If the screen for these symptoms and/or other aspects of emotional wellbeing is positive, further assessment and/or referral for assessment and treatment should be completed by suitably qualified health professionals, informed by regional guidelines.	CCR	
If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered in PCOS, informed by regional clinical practice guidelines.	CCR	
Factors including obesity, infertility, hirsutism need consideration along with use of hormonal medications in PCOS, as they may independently exacerbate depressive and anxiety symptoms and other aspects of emotional wellbeing.	CPP	
All health professionals should be aware of the increased prevalence of psychosexual dysfunction and should consider exploring how features of psychohirsutism and body image, impact on sex life and relationships in PCOS.	CCR	
If psychosexual dysfunction is suspected, tools such as the Female Sexual Function Index can be considered.	CCR	
Health professionals and women should be aware that features of PCOS can impact on body image.	CCR	
All health professionals and women should be aware of the increased prevalence of eating disorders and disordered eating associated with PCOS.	CCR	
If eating disorders and disordered eating are suspected, further assessment, referral and treatment, including psychological therapy, could be offered by appropriately trained health professionals, informed by regional clinical practice guidelines.	CCR	

Table 6 (continued)

Recommendation(s) from current guidelines^a

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Obstructive sleep apnoea (OSA)		
Screening should only be considered for OSA in PCOS to identify and alleviate related symptoms, such as snoring, waking unrefreshed from sleep, daytime sleepiness, and the potential for fatigue to contribute to mood disorders. Screening should not be considered with the intention of improving cardiometabolic risk, with inadequate evidence for metabolic benefits of OSA treatment in PCOS and in general populations.	CCR	<ul style="list-style-type: none"> To determine accurate prevalence of subclinical sleep disturbances in PCOS, more adequately powdered cross-sectional studies using validated subjective and objective sleep measures are required. While emerging evidence suggests that disturbed sleep may exacerbate IR via decreasing energy expenditure and increasing adipose tissue deposition, more research in women with PCOS is needed to confirm this hypothesis. Investigate effects of CBT interventions in women with PCOS who have disturbed sleep (outcomes of interest include food intake, metabolic rate, appetite hormones, weight, adherence to lifestyle changes and PCOS features).
A simple screening questionnaire, preferably the Berlin tool [178], could be applied and if positive, referral to a specialist is considered.	CPP	
A positive screen raises the likelihood of OSA, however it does not quantify symptom burden and alone does not justify treatment. If women with PCOS have OSA symptoms and a positive screen, consideration can be given to be referral to a specialist centre for further evaluation.		
Inositol		
Inositol (in any form) should currently be considered an experimental therapy in PCOS, with emerging evidence on efficacy highlighting the need for further research. Women taking inositol and other complementary therapies are encouraged to advise their health professional.	EBR	<ul style="list-style-type: none"> To reduce heterogeneity across studies investigating supplements or herbal medicine, RCTs should focus on specific populations within PCOS (i.e. age, BMI or phenotype) and adopt more consistent approaches to formulation (i.e. limit co-supplementation), dosage, intervention duration and the type of comparator used. Mechanistic studies are needed to investigate herb- or nutrient-drug interactions (with common pharmacological treatments used in PCOS) and other possible interactions with the biological processes underpinning PCOS. Research that characterises the uptake of CIM approaches by women with PCOS, including where they are sourcing information on this topic, will aid health professionals understanding of how to safely navigate the use of adjunct therapies in PCOS management.

Abbreviations: BMI Body mass index, CBT Cognitive behavioural therapy, CI/D Cardiovascular disease, DASH Dietary approaches to stop hypertension, GI Glycaemic index, GL Glycaemic load, IR Insulin resistance, NAC N-acetyl-cysteine, PCOS Polycystic ovary syndrome, RCT Randomised controlled trial, QoL Quality of life

^a Recommendations are taken directly from the 2018 International Evidence-Based Guideline for the Assessment and Management of PCOS [18]. Does not include all recommendations, only those relevant to the findings of this review are presented

^b EBR Evidence based recommendations: Evidence sufficient to inform a recommendation made by the guideline development group. CCR Clinical Consensus Recommendations: In the absence of evidence, a clinical consensus recommendation has been made by the guideline development group. CPP Clinical Practice Points: Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or clinical consensus recommendations

Traditional, complementary and integrative medicine

The 2018 PCOS guideline includes recommendations on inositol supplementation, though do not include evidence regarding the use of other supplements, herbal medicine or other TCIM approaches, including acupuncture and yoga [18].

Vitamins, vitamin-like supplements, minerals and other supplements

The 2018 guideline highlights that inositol (including myo-inositol (MI) and di-chiro inositol) is a nutritional supplement that may be involved in insulin signalling transduction [191]. MI in particular is a key endocrine regulator that displays impaired metabolism in PCOS [191]. MI supplementation has been explored in a meta-analysis of nine RCTs ($n=496$), which showed improved metabolic profiles and reduced hyperandrogenism [191]. These findings are supported by two earlier meta-analyses, reporting improved ovulation, menstrual cyclicity, and hormonal profiles following MI supplementation [192, 193]. The 2018 PCOS guideline recommends that inositol (in any form) should be considered as an experimental therapy in PCOS management. The guideline also recognises that women participating in any form of TCIM should be encouraged to advise their health professional. However, it does not consider emerging evidence for the use of other types of TCIM in PCOS treatment as this was outside of the scope of the 2018 guideline.

Vitamins

B-group vitamins (B₁, B₆ and B₁₂), folic acid (B₉) and vitamins D, E, and K are critical for several biological processes that can affect metabolic and reproductive features of PCOS. B-group vitamins work alongside folic acid (the synthetic form of folate) to regulate homocysteine (Hcy) via re-methylation of Hcy to methionine [194]. Hcy is an amino acid that confers an increased risk of CVD at high levels, and which is often deranged in women with PCOS [195], likely related to a higher prevalence of folate deficiency [196–198]. One RCT explored the use of B-group vitamins combined with folic acid in 60 women with PCOS, and reported a reduction in the Hcy increasing effect of metformin [198]. Folic acid alone has also been examined in two RCTs of women with PCOS ($n=69$ [199] and $n=81$ [200]), improving FINS, HOMA-IR, C-reactive protein, total antioxidant capacity (TAC) and glutathione with doses ≥ 5 mg/day when compared with placebo [199, 200]. Regarding vitamin D supplementation, three large-scale meta-analyses reported improvements in measures of IR (HOMA-IR [201, 202], FINS [201]), fasting glucose [201]), lipid profiles (LDL-C [201–203], TC [203] and TAG [203]) and androgens (T) [202], when compared

with placebo. While vitamin E (or tocopherol) has various reported benefits on fertility outcomes in other populations [204], and has improved androgen profiles when co-supplemented with coenzyme Q10 (CoQ10) in women with PCOS [205], to date no RCTs have examined the use of vitamin E supplements alone in PCOS. Vitamin K also has limited available literature in PCOS, with only one RCT ($n=84$) demonstrating improvements in anthropometry, insulin and androgen profiles following supplementation (90 µg/day Menaquinone-7 for eight weeks), compared with placebo [206].

Vitamin-like supplements

Vitamin-like supplements including bioflavonoids, carnitine and alpha-lipoic acid (α-LA) have well-recognised antioxidant properties and play a role in fatty acid and glucose metabolism, providing possible metabolic benefits in PCOS [207]. Bioflavonoids consist of plant-derived polyphenolic compounds, some of which have been inversely associated with METS in women with PCOS [207]. In a pilot prospective study of 12 women with PCOS, 36 mg/day of the soy isoflavone genistein for six months improved lipid profiles but not anthropometry, IR, hormonal profiles or menstrual cyclicity [208]. Carnitine, particularly the active form L-carnitine, is reported to be lower in women with PCOS and linked with hyperandrogenism, hyperinsulinaemia and reduced oocyte quality [209, 210]. One RCT explored L-carnitine use in PCOS and found beneficial effects on mental health parameters and markers of oxidative stress [211], although the integrity of these have come under scrutiny and hence should be interpreted with caution [122212]. Regarding α-LA, a small pre-post study ($n=6$) administered 1200 mg/day for 16 weeks, and reported improved IR, LDL-C and TAG, though no effects on TAC or plasma oxidation metabolites [213]. Another RCT reported improved anthropometric (BMI), metabolic (FINS and HDL-C) and reproductive (menstrual cyclicity) features in 46 women with PCOS receiving α-LA supplementation (600 mg/day for 180 days) compared with controls [214]. However, as these women were co-supplemented with 1000 mg/day D-chiro-inostiol, findings are not isolated to the effects of α-LA alone [214].

Minerals

Minerals such as calcium, zinc, selenium, magnesium and chromium picolinate (CrP) have been explored in PCOS due to their reported insulin sensitising, antioxidant and anti-inflammatory properties [215–217]. A small number of studies have also reported women with PCOS are at higher risk of being deficient in calcium [218], zinc [215, 217] and selenium [195]. A recent systematic

review (six RCTs) reported that vitamin D and calcium co-supplementation in women with PCOS improved lipid and androgen profiles, follicular health and menstrual cyclicity [219]. While these findings are promising, it is difficult to attribute benefits to calcium alone, given calcium is often co-supplemented with vitamin D due to their complementary mechanisms of action. One systematic review (five RCTs) in PCOS reported zinc (often co-supplemented with other nutrients such as calcium, vitamin D and magnesium), improved HOMA-IR, lipids, T, FSH and DHEAS [220] compared to placebo. Another systematic review (five RCTs) examining selenium supplementation reported reduced IR, oxidative stress and inflammation, while results for anthropometry, lipids, androgens and hirsutism were inconsistent [221]. Regarding magnesium (an intracellular cation involved in insulin metabolism), while supplementation in PCOS has been associated with reduced IR in observational research [222], these findings are not supported by data from RCTs, with considerable inconsistencies between studies [222]. Two meta-analyses examined CrP in women with PCOS [223, 224]. While one reported that CrP supplementation reduced BMI, FINS and free testosterone [223], the other reported decreased IR, but not BMI, and increased levels of T [224].

Other supplements

Other supplements purported to provide a range of antioxidant and anti-inflammatory benefits, including omega-3 fatty acids, N-acetyl-cysteine (NAC), CoQ10, probiotics, quercetin, resveratrol and melatonin have been explored in PCOS. A meta-analysis (nine RCTs) of women with PCOS ($n=591$) receiving omega-3 supplementation reported reductions in HOMA-IR, TC, TAG and LDL-C, though showed no effect on other metabolic parameters or T [225]. In a meta-analysis of eight RCTs ($n=910$) examining NAC supplementation (the acylated form of L-cysteine), researchers reported improved glucose regulation and a greater likelihood of conception and livebirths in women with PCOS compared with placebo [226]. In a single RCT ($n=60$) CoQ10 supplementation (100 mg/day for 12 weeks) improved fasting glucose and insulin, HOMA-IR, insulin sensitivity index and TC, compared with the placebo group [227]. Two meta-analyses reported probiotics improved FAI, SHBG, IR and blood lipids, with no differences in weight or hirsutism between intervention and placebo groups [228, 229]. These findings may be linked to lower microbial diversity and increased intestinal permeability in women with PCOS [230, 231]. In regards to quercetin and resveratrol, which are both food derived polyphenols with a strong antioxidant capacity, one systematic review (three experimental studies, $n=246$ women with PCOS) reported

quercetin supplementation improved measures of IR and testosterone levels, but not anthropometry compared with placebo [232]. Similarly, one RCT in women with PCOS ($n=61$) reported resveratrol (800–1500 mg/day for four days) improved androgen and metabolic profiles and oocyte and embryo quality compared with placebo [233]. Finally, a systematic review (two RCTs and one cell-culture study) investigating the effects of melatonin supplementation in women with PCOS using assisted reproductive technologies reported melatonin significantly increased clinical pregnancy rates but not live birth rates [172]. A more recent RCT ($n=56$) reported improved levels of T, hirsutism, inflammatory and oxidative stress profiles in women receiving 10 g melatonin/day for 12 weeks, compared with placebo [234].

Herbal medicine

To date the most recent and comprehensive review (Cochrane review including five RCTs and $n=414$ women with PCOS) investigating the effects of herbal medicine on reproductive outcomes, reported no difference between the use of Chinese herbal medicine (CHM) and clomiphene for pregnancy rates, and limited evidence of increased pregnancy rate for CHM with clomiphene compared with clomiphene alone [235]. This review concluded that there was inadequate evidence to promote the use of CHM for the treatment of subfertility in women with PCOS [235]. Similarly, a smaller systematic review (five studies) investigating the effects of four herbal medicines (green tea, cinnamon, spearmint and black cohosh) on menstrual regularity in PCOS, found limited high-quality evidence from RCTs to support their clinical use and concluded that evidence for safety was lacking [236].

More recently, a number of small RCTs investigating metabolic and reproductive effects of a range of herbal medicines have been published. Curcumin, an active compound in turmeric (*Curcuma longa*), may exert hypoglycemic effects via a number of mechanisms, including attenuation of circulating levels of tumor necrosis factor- α [237]. One RCT ($n=67$) reported decreased levels of fasting glucose following supplementation compared with placebo [238], while another ($n=51$) which used a lower dose (1000 mg/day versus 1500 mg/day) and shorter duration (six weeks versus 12 weeks), reported no between group differences for fasting glucose, HOMA-IR or lipids [239]. *Salvia officinalis* or sage contains multiple active compounds that display antioxidant effects and therefore effects on glucose metabolism and insulin sensitivity [240]. One RCT ($n=72$) reported consuming sage extract for eight weeks improved IR and reduced BMI, with no effects on WHR or blood pressure [241]. *Foeniculum vulgare*

or fennel may provide protective effects on hormonal abnormalities in PCOS via its actions as a phytoestrogen [242]. One RCT ($n=55$) reported that six months of fennel tea and dry cupping was as effective as metformin for reducing BMI and menstrual cycle length [243]. *Glycyrrhiza glabra* or licorice contains active phytochemicals including isoflavane and glabridin, which have been shown to have antiandrogenic effects [244]. Two experimental studies in healthy women ($n=9$) [245] and women with PCOS ($n=32$) [246] reported that 3.5 g/day of licorice extract decreased T [245] and reduced side effects of spironolactone [246]. *Mentha spicata* (spearmint), *Zingiber officinale Roscoe* (ginger), *Cinnamomum cassia* (cinnamon) and *Citrus sinensis* (citrus) have been shown to exert anti-inflammatory and hypoglycemic effects [247–250]. One RCT in infertile women with PCOS ($n=60$) comparing the effects of a herbal mixture (citrus, ginger, cinnamon and spearmint) with clomiphene citrate (CC), herbal mixture alone, or CC alone reported that the herbal mixture, with or without CC, improved circulating antioxidant levels, IR and fasting blood glucose, but not menstrual regularity when compared to CC alone [251]. While observations from emerging research are promising, to support the safe translation of findings into the clinical setting there is a clear need for larger clinical trials investigating the efficacy and safety of herbal medicine use in PCOS.

Other traditional, complimentary and integrative medicine approaches

Acupuncture may provide beneficial impacts on sympathetic function [252] and ovarian blood flow [253] in women with PCOS. A recent meta-analysis of 22 RCTs ($n=2315$ women with PCOS) reported recovery of the menstrual period in the acupuncture group when compared with placebo, but no evidence for differences between groups in terms of live birth, pregnancy and ovulation [254]. While an earlier meta-analysis reported a significant reduction in BMI following acupuncture use, this was mainly due to one RCT ($n=80$) which compared acupuncture and the oral contraceptive pill to the oral contraceptive pill alone [255]. When this study was removed, the pooled analysis was no longer significant [255].

Yoga gymnastics have been recommended as an example of moderate physical activity in the 2018 evidence-based PCOS guideline [18]. However, as yoga is considered a mind-body therapy that incorporates aspects of meditation, it may provide additional benefits beyond those gained through other forms of exercise [256]. While one systematic review (16 observational and experimental studies, $n=365$ women with

PCOS) reported yoga may provide a range of psychological, reproductive and metabolic benefits, no meta-analysis was performed and a limited summary of included studies made it difficult to confirm findings [257]. A more recent systematic review (11 experimental studies) included a meta-analysis of two RCTs and found that yoga significantly decreased clinical hyperandrogenism, menstrual irregularity and fasting glucose and insulin [258]. Lastly, findings from a recent RCT ($n=67$ women with PCOS) suggests that 90 minutes of yoga per day for six weeks can significantly reduce hirsutism, waist and hip circumference when compared to controls [259]. Please see Table 5 for a summary of available evidence from meta-analyses and experimental studies investigating the effects of TCIM on PCOS outcomes.

Summary of findings and research gaps

The 2018 International Evidence-Based Guideline for the Assessment and Management of PCOS highlights lifestyle (diet, physical activity and/or behavioural) management as the primary initial treatment strategy [18]. It is important to consider that the definition of lifestyle management may warrant expansion consistent with the whole person model of healthcare provision, which may include care addressing psychological and sleep interventions, as well as a range of TCIM approaches [20]. In line with patient interest [31–35], and to assist women and healthcare providers in understanding the evidence to aid safe implementation of adjunct therapies, rigorous assessment of the evidence for these alternative lifestyle strategies in PCOS management is warranted. Using a holistic definition of patient care, this review has summarised evidence to date on the traditional components of lifestyle change (diet, physical activity and behavioural change), psychological interventions and non-pharmacological strategies (sleep, supplements, herbal medicine and other TCIM approaches). Table 6 provides a overview of current guideline recommendations alongside the key findings from this review, summarising the identified research gaps that need to be addressed before evidence-based recommendations for clinical practice can be updated.

With regards to traditional lifestyle treatment, the majority of studies focussed on weight loss as a primary treatment goal. This indicates more research is warranted to understand the role of diet and exercise in lean women and/or in weight gain prevention. RCTs using lifestyle interventions under isocaloric conditions that investigate effects on IR, body composition and androgens independent of weight loss are needed. Given the high risk of failure with long-term weight management [9, 37, 40, 261] and high attrition in weight loss trials in

PCOS [13], exploring interventions that focus on weight neural messaging around dietary quality and physical activity may also aid in optimising engagement, adherence and sustainability of lifestyle interventions. Future research should also identify subgroups who respond more favourably to weight loss [45, 53], to aid provision of a more targeted and personalised treatment approach.

With regards to diet strategies, there is a need for more research understanding the impact of low GI/GL diets on androgen status, as well as the biological mechanisms by which low GI/GL diets may impact reproductive and cardiometabolic outcomes associated with PCOS. With regards to physical activity, additional longer-term studies are required to guide exercise prescription in PCOS, although promising evidence supports the provision of vigorous aerobic exercise performed under supervised conditions (i.e. through referral to an exercise physiologist). While behavioural interventions are essential for long term sustainability of dietary and physical activity change, research in PCOS is scarce and interventions are not well defined. Future research should incorporate appropriate theoretical frameworks and clearly outline behavioural components utilised. This will aid intervention duplication and tailoring of active elements to ensure relevance in women with PCOS.

There is currently a lack of research investigating whether women with PCOS are at a higher risk of alcohol and smoking-related complications. This is particularly relevant given the well-established relationship between higher alcohol and cigarette use and rates of depression and anxiety in the general population [262–265]. There is also a need to better understand the relationship between alcohol intake and reproductive outcomes (particularly anovulatory infertility) [139], as safe alcohol limits in PCOS is currently unknown [139].

With regards to psychological interventions, the current evidence base for prevalence of mental health concerns in PCOS relies heavily on symptom prevalence. More adequately powered, gold standard prevalence studies using structured diagnostic interviews administered by appropriately qualified professionals are needed. While QoL has recently been highlighted as a core outcome in PCOS research [266], the application of QoL tools in clinical care is still unclear, with research yet to validate QoL tools longitudinally or identify clinically meaningful differences in QoL scores. The emerging evidence showing support for the use of CBT in PCOS [152–154] highlights an opportunity for tailoring of this psychological intervention to meet the specific mental health needs of women with PCOS, with a focus on how management of mental health symptoms affect lifestyle modifications. CBT that incorporates elements of

mindfulness-based stress reduction also warrants further investigation.

Future research in PCOS and sleep disorders should include more high-quality research in subclinical disorders using objective sleep measures (polysomnography and actigraphy). Future work should also consider emerging evidence showing that disturbed sleep can detrimentally effect energy expenditure, which may increase adipose tissue deposition and exacerbate IR [164, 184, 186, 267–271], thereby worsening the presentation of PCOS. Further, a consideration of how sleep disturbance can reduce engagement with positive lifestyle changes, for example through the disruption of appetite regulation [272, 273] or via contributing to poor mental health outcomes [190, 274], is warranted. CBT interventions including elements of stimulus control and psychoeducation are effective non-pharmacological treatments for both clinical sleep disorders and sleep disturbances in the general population [275–277]. RCTs in women with PCOS that investigate effects of CBT on dietary intake, energy metabolism, appetite regulation, anthropometry, adherence to lifestyle changes and PCOS features are required.

With regards to TCIM, there is a vast array of literature suggesting some beneficial effects of vitamins (B-group vitamins, folate, vitamins D, E and K), vitamin-like nutrients (bioflavonoids, carnitine and α-LA), minerals (calcium, zinc, selenium, and CrP) and other formulations (such as melatonin, omega-3 fatty acids, probiotics, NAC and cinnamon) in PCOS [278]. However, the quality of evidence across studies ranges from meta-analyses of RCTs (vitamin D, omega-3 fatty acids and NAC) to single retrospective observational studies (vitamin K and carnitine). In addition, heterogeneity in results related to factors including variable PCOS presentation and study methodology make it difficult to draw definite conclusions. Future research should focus on specific populations within PCOS, for example age, BMI or phenotype (factors which substantially affect nutrient sufficiency), and outline more consistent approaches to supplement formulation, dosage, intervention duration and type of comparator used. Mechanistic studies are also needed to investigate herb- or nutrient-drug interactions (with common pharmacological treatments used in PCOS) and other possible interactions with the biological processes underpinning PCOS. In regards to acupuncture and yoga, more sufficiently powered RCTs are needed to determine clinical relevance and integration into PCOS management is not yet warranted.

While current research is not sufficiently robust to support integration of TCIM into routine clinical practice, healthcare providers should broaden their knowledge pertaining to how these therapies can be safely and

appropriately utilised as adjuncts to conventional medical management [279–281]. TCIM is frequently used by women, with uptake of TCIM approaches increasing steadily over the past 10 years [31–35]. In women with PCOS, one cross-sectional study ($n=493$) found that 70% reported use of TCIM, namely nutritional and herbal supplements [282]. The most common reasons for use were to treat PCOS symptoms, improve general wellbeing and reduce depression. Of the women using TCIM, 77% had consulted with a complementary practitioner (acupuncturists, chiropractors, naturopaths and massage therapists) [282]. While the study did not report participants engagement with medical physicians, research in the general population has shown that patients are resistant to discuss TCIM use with their consulting physician [283–288]. Qualified health-care providers should be involved in TCIM discussions to help ensure appropriate use, maximise possible benefits and minimize potential harm [289]. For example, to sustain patient engagement in women who express the desire to experiment with supplementation, health-care providers could consider inositol supplementation, using a nuanced and case-specific approach that encapsulates the variety of pathologies in PCOS.

When considering all of the research summarised here, across traditional lifestyle, psychological, sleep and TCIM interventions, there is a clear need for more real-world PCOS research. This involves the translation of findings from clinical trials (where highly selected populations, intensive treatment protocols and expert multidisciplinary teams provide an ideal research setting), into the heterogeneous situations that face clinicians [290–292]. Health professionals provide care to women from diverse social contexts, are often restrained by finite resources and are required to juggle many competing demands for their time [290–292]. While some barriers to implementation, including time, resource and access issues are considered in the current PCOS guideline, they were generated by the guideline development groups and research is needed to validate and clarify their proposed concerns. Real-world research is required to: a) fully understand whether lifestyle recommendations can be practically integrated into current healthcare settings; b) tailor interventions to meet the unique needs of women with PCOS; and c) generate evidence on clinical outcomes that are of great relevance to patients and clinicians, such as live birth, miscarriage and menstrual regularity, which can be collected through routine care.

It is also important to highlight that while lifestyle management is a first-line treatment for PCOS, the addition of pharmacological therapies to further improve clinical features of hyperandrogenism, menstrual irregularity and infertility are often indicated [293]. In these instances,

prescribing physicians should consider how medical management and lifestyle change can be used in adjunct to optimise treatment. For example, the use of combined oral contraceptive pills may have detrimental effects on weight gain [294] and mental health [295], which can be mitigated by appropriate lifestyle intervention. Further, the combination of lifestyle modification and metformin has been shown to lower BMI, subcutaneous adipose tissue and improve menstruation compared with lifestyle modification alone, and hence may have an additive effect on improving cardio-metabolic outcomes in high risk groups [296].

Conclusion

Using the whole person or holistic definition of health, this review has highlighted emerging areas of research that could be considered for integration into future classifications of lifestyle management in PCOS. When developing lifestyle recommendations for PCOS management, interpreting and communicating evidence not only for diet, physical activity and behavioural interventions, but also psychological, sleep and TCIM approaches, will aid clinicians to deliver patient-centred care by affording women more choice and therefore autonomy over their treatment options. This sentiment aligns with the core objectives underpinning the 2018 PCOS guideline, which sought to understand the unmet needs of women with PCOS through continuing to engage consumers in co-design of guideline development, implementation, translation and dissemination.

Abbreviations

α -LA	Alpha-lipoic acid
BMI	Body mass index
CVD	Cardiovascular disease
CHM	Chinese herbal medicine
CrP	Chromium picolinate
CoQ10	Coenzyme Q10
CBT	Cognitive behavioural therapy
DASH	Dietary Approaches to Stop Hypertension
FINS	Fasting insulin level
FSH	Follicle stimulating hormone
FAI	Free androgen index
GI	Glycaemic index
GL	Glycaemic load
HDL-C	High density lipoprotein cholesterol
Hcy	Homocysteine
IR	Insulin resistance
LDL-C	Low density lipoprotein cholesterol
LH	Luteinizing hormone
$VO_{2\max}$	Maximal rate of oxygen
METS	Metabolic syndrome
MUFA	Monounsaturated fatty acid
MI	Myo-inositol
NAC	N-acetyl-cysteine
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovary syndrome
PUFA	Polyunsaturated fatty acid
RCT	Randomised controlled trial
SHBG	Sex hormone-binding globulin
TAC	Total antioxidant capacity

TC	Total cholesterol
T	Testosterone
TCIM	Traditional, complementary and integrative medicine
TAG	Triglycerides
T2DM	Type 2 diabetes
WC	Waist circumference
WHR	Waist-hip-ratio

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SC, SL, CA, SP, RT, MG, RB, NN, CB, CE, VR, AM, SA and LM reviewed the literature and wrote the first draft of the manuscript. SC, SL, CA, SP, RT, MG, RB, NN, CB, CE, VR, AM, SA and LM revised and edited the manuscript. SC and LM conceptualised and determined the scope of the manuscript and had primary responsibility for the final content. LM supervised the review process. All authors meet ICMJE criteria for authorship and approved the final version for publication.

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REVIEW

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Lifestyle management in polycystic ovary syndrome – beyond diet and physical activity

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Abstract

Polycystic ovary syndrome (PCOS) is a common condition affecting reproductive-aged women with reproductive, metabolic and psychological consequences. Weight and lifestyle (diet, physical activity and behavioural) management are first-line therapy in international evidence-based guidelines for PCOS. While these recommend following population-level diet and physical activity guidelines, there is ongoing interest and research in the potential benefit of including psychological and sleep interventions, as well as a range of traditional, complimentary and integrative medicine (TCIM) approaches, for optimal management of PCOS. There is limited evidence to recommend a specific diet composition for PCOS with approaches including modifying protein, carbohydrate or fat quality or quantity generally having similar effects on the presentations of PCOS. With regards to physical activity, promising evidence supports the provision of vigorous aerobic exercise, which has been shown to improve body composition, cardiorespiratory fitness and insulin resistance. Psychological and sleep interventions are also important considerations, with women displaying poor emotional wellbeing and higher rates of clinical and subclinical sleep disturbance, potentially limiting their ability to make positive lifestyle change. While optimising sleep and emotional wellbeing may aid symptom management in PCOS, research exploring the efficacy of clinical interventions is lacking. Uptake of TCIM approaches, in particular supplement and herbal medicine use, by women with PCOS is growing. However, there is currently insufficient evidence to support integration into routine clinical practice. Research investigating inositol supplementation have produced the most promising findings, showing improved metabolic profiles and reduced hyperandrogenism. Findings for other supplements, herbal medicines, acupuncture and yoga is so far inconsistent, and to reduce heterogeneity more research in specific PCOS populations, (e.g. defined age and BMI ranges) and consistent approaches to intervention delivery, duration and comparators are needed. While there are a range of lifestyle components in addition to population-recommendations for diet and physical activity of potential benefit in PCOS, robust clinical trials are warranted to expand the relatively limited evidence-base regarding holistic lifestyle management. With consumer interest in holistic healthcare rising, healthcare providers will be required to broaden their knowledge pertaining to how these therapies can be safely and appropriately utilised as adjuncts to conventional medical management.

Keywords Polycystic ovary syndrome, diet, guideline, physical activity, sleep, cognitive behavioural therapy, quality of life, complementary medicine

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Introduction

Polycystic ovary syndrome (PCOS) is a common condition affecting up to 13% of reproductive-aged women [1]. It is diagnosed through the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESRHE/ASRM) criteria, requiring two of the following features: polycystic ovaries on ultrasound, oligoovulatory or anovulatory cycles and biochemical or clinical hyperandrogenism [2]. Women with PCOS experience a combination of reproductive (infertility, pregnancy complications) [3], metabolic (risk factors for and conditions of type 2 diabetes (T2DM) and cardiovascular disease (CVD)) [4, 5] and psychological (conditions including anxiety, depression, poor quality of life (QoL), disordered eating) comorbidities [6, 7].

Insulin resistance (IR) is defined as a key pathophysiological feature in PCOS, contributing to hyperandrogenism and worsening the clinical presentation of PCOS. While lean women present with IR in a form that is mechanistically different from IR caused by excess weight, overweight and obesity further exacerbate IR and consequent hyperinsulinaemia [8]. Women with PCOS also display a higher rate of weight gain over time [9] and a greater prevalence of overweight and obesity [10], which can further contribute to this worsening of IR and hence worsening of the presentation of PCOS [11]. The reason for this is unclear, but may be related to differences in intrinsic psychological and biological mechanisms [12–15], or extrinsic lifestyle factors such as diet and physical activity [16, 17]. Improving IR and excess adiposity are therefore key targets in PCOS management.

The International Evidence-Based Guideline for the Assessment and Management of PCOS [18], highlights lifestyle intervention as the primary early management strategy. Lifestyle interventions are traditionally defined as those designed to improve dietary intake or physical activity through appropriate behavioural support. In the 2018 PCOS guideline, lifestyle management is recommended for general health benefits [18]. Given that excess weight is associated with increased IR in PCOS [8], the guideline additionally promotes weight management, defined as: 1) weight gain prevention in all women with PCOS, and 2) achieving and maintaining modest weight loss in women with excess weight [18].

Lifestyle interventions in PCOS management can also be viewed as a broader construct beyond physical health. Since the emergence of the biopsychosocial model of healthcare in 1977, health disciplines have seen a gradual shift away from the classical biomedical model (where health is defined as the ‘absence of disease’) towards whole person or holistic care [19]. This is an approach that reflects many facets of the patient context, via integrating care that addresses biological, psychological, social, spiritual and ecological

aspects [20]. It therefore requires a range of different treatment strategies to improve health. Provision of whole person or holistic care has been identified as a core objective of healthcare reforms internationally [21–23]. In line with these reforms the PCOS guideline recognises the importance of emotional wellbeing to overall health and QoL in women living with PCOS [18]. It also highlights evidence which suggests that the psychological impact associated with PCOS is under-appreciated in clinical care [4, 5], and that few women are satisfied with the mental health support they receive [6, 7]. Recommendations for appropriate screening, assessment and treatment strategies for anxiety, depression, psychosexual dysfunction, eating disorders and poor body image are provided [18]. These specific areas of emotional wellbeing are of particular concern, with research showing a higher prevalence and severity of depression and anxiety [24, 25], lower scores for satisfaction with sex life and feeling sexually attractive [26] and a higher prevalence of disordered eating and eating disorders [7] in women with PCOS. Features of PCOS, in particular hirsutism and increased weight, have also been shown to negatively affect body image [27, 28], with poor body image being strongly related to depression in women with PCOS [29, 30].

While the current PCOS guideline is comprehensive, considering all available evidence at the time of development and providing best-practice recommendations for necessary screening, risk assessment and management, it could not possibly cover all aspects of PCOS care. An International Delphi process was used to prioritise clinical questions, with consensus reached through extensive consultation with both consumers and multidisciplinary clinicians with expertise in PCOS care. Therapies, such as traditional, complementary and integrative medicine (TCIM), supplement use, sleep and meditation interventions are either briefly considered or not at all included in the 2018 PCOS guideline. Many of these therapies are novel and there is a paucity of evidence to support intervention efficacy on PCOS outcomes. However, as patient interest in these types of non-pharmacological interventions are growing [31–35], it is prudent to provide more guidance to healthcare providers in this area on their potential efficacy in PCOS. Whole person or holistic care recognises that the doctor-patient relationship should be one of open dialogue, where healthcare providers involve the patient in negotiating their care and recognises patient’s autonomy to guide treatment (Figure 1) [36].

This review provides an extensive overview of evidence to date on lifestyle strategies used to optimise management of PCOS. Using a holistic definition of patient care, this review considers the traditional components of lifestyle change (diet, physical activity and behavioural change), psychological and sleep interventions, as well as TCIM approaches (supplements, herbal medicine,

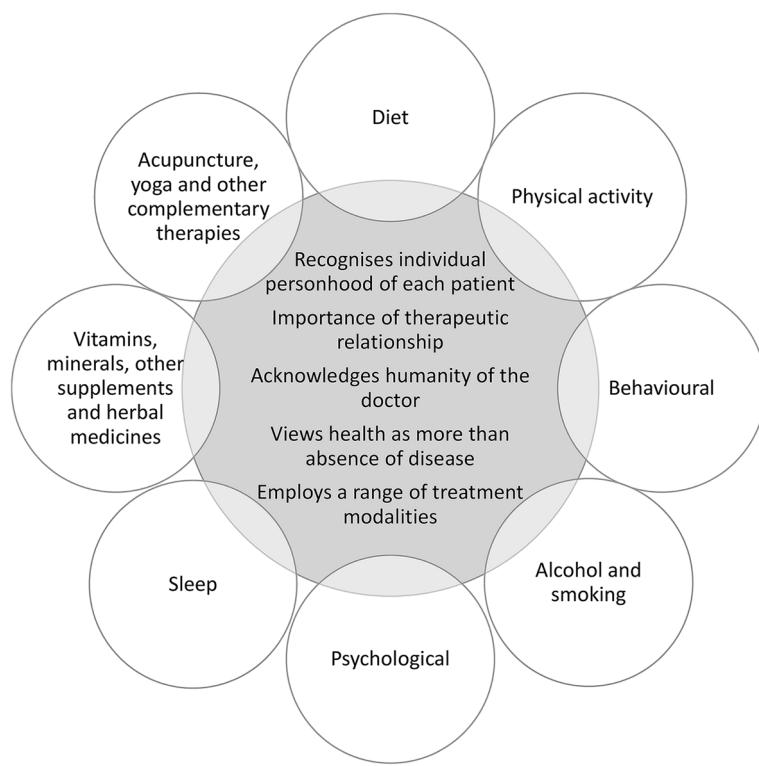


Fig. 1 Viewing lifestyle modifications through a whole person or holistic care lens. The key features of whole person or holistic care listed in the centre of the figure have been adapted from Thomas et al. [20]. ‘Recognises individual personhood’ relates to focusing on the unique needs of the person rather than the disease. ‘Importance of therapeutic relationship’ emphasises patient autonomy and responsibility. ‘Acknowledges humanity of the doctor’ considers the doctors’ ability to self-reflect on how they engage in the care of the patient. ‘Health as more than absence of disease’ incorporates the mental, emotional, physical, environmental and social needs of the patient. ‘Employs a range of treatment modalities’ promotes continuity of care across health disciplines, and while it may include traditional, complementary and integrative medicine (TCIM), TCIM is not holistic if used in isolation and without adequate integration into conventional healthcare

acupuncture and yoga). To improve translation of findings, evidence summaries are accompanied by an overview of relevant recommendations from the existing PCOS guideline. This highlights where emerging evidence supports current recommendations or provides new insights for research. As this is a narrative review, while evidence summaries include peer-reviewed journal articles identified from databases including Medline OVID, this is supplemented by expert opinion of the authors.

Traditional lifestyle and weight management

The PCOS guideline recommends the promotion of healthy lifestyle behaviours in all women with PCOS, to achieve and/or maintain a healthy weight and to optimise general health [18]. In women with excess weight, a weight loss of 5–10% is advised, aiming for an energy deficit of 30% or 500–750 kcal/day (1200–1500 kcal/day). While weight management is seen as a core component of lifestyle interventions, the guideline recognises that a healthy lifestyle provides benefits that occur independent of weight change.

A recent Cochrane review of 15 randomised controlled trials (RCT) and 498 participants, reported that lifestyle interventions compared with minimal intervention or usual care, significantly reduces weight (kg) and body mass index (BMI) and improves secondary reproductive outcomes such as free androgen index (FAI), testosterone (T), sex hormone-binding globulin (SHBG) and hirsutism (Ferriman-Gallwey score) [37]. In terms of metabolic outcomes, lifestyle intervention resulted in significant reductions in total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and fasting insulin (FINS). These findings are largely similar to that of other systematic reviews [38–41]. While no studies in the Cochrane review assessed clinical reproductive outcomes [37], individual trials that were not included in the review have reported that lifestyle interventions resulting in modest weight loss (2–5% total body weight) improve ovulation and menstrual regularity [42–45]. Losing >5% of weight is additionally associated with being able to conceive, having live births, reduction of ovarian volume and reduction in the number of follicles [46–52].

Table 1 Reviews and experimental studies investigating the effects of diet on polycystic ovary syndrome outcomes

Dietary intervention	N study design	N studies; N participants	Main findings ^a	References
Low CHO	2 SR/MA (27 RCT total - 18 RCT using low CHO diet) [56, 85] 1 SR (5 RCT total - 1 RCT using low CHO diet) [16]	14; 901	Low CHO compared with control diets [56]: ↓ BMI, HOMA-IR, TC, LDL-C ↑ SHBG ↔ LH, T, HDL-C Dietary intervention ↓ HOMA-IR, FINS, FGL, BMI, BW, WC compared with minimal intervention, and subgroup analysis showed no additional benefits for low CHO diets [85] Weight loss improved the presentation of PCOS regardless of dietary composition, with no subtle differences observed for low CHO diets [16]	Shang et al. 2020 [85] Zhang et al. 2019 [56] Moran et al. 2013 [16]
Low GI	1 SR/MA (10 RCT total - 8 RCT using low GI diet) [55] 1 SR (5 RCT total - 1 RCT using low GI diet) [16] 4 Pre-post prospective [61, 76, 77, 118] 1 RCT [78]	16 ^b ; 582	High GI compared with low GI diets [55]: ↓ HOMA-IR, FINS, TC, LDL-C, TAG, WC, T ↔ FGL, HDL-C, BW, FAI Low GI diets had greater improvements in IR, TC, HDL-C, fibrinogen, menstrual regularity and QoL [16] Low GI diets followed for ≥ 12 weeks: ↓ BW [76, 77], BMI [76, 77], BFM [77], WC [77], WHR [77], FINS [76, 77], FGL [77], TC [77], LDL-C [77], TAG [77], T [77], LH [77], androstenedione [77], prolactin [77] ↑ insulin sensitivity (HOMA2-IS) [61], synthesis of predominantly anti-inflammatory eicosanoid mediators (e.g. 16(R)/16(S)-HETE, 13(S)-HODE, 9(S)-HODE, 15(S)-HETE, 12(S)-HETE, 5(S)-oxoETE, 5(S)-HETE) [118], fasting glucagon (higher glucagon levels associated with lower levels of self-reported hunger) [78]	Kazemi et al. 2020 [55] Moran et al. 2013 [16] Shishrehgar et al. 2019 [76] Barr et al. 2016 [61] Szczuko et al. 2018 [77] Szczuko et al. 2017 [118] Hoover et al. 2021 [78]
High protein	1 SR (5 RCT total - 3 RCT using high protein diet) [16] 2 Pre-post prospective [73, 74] 6 RCT [92, 94–97]	11; 308	High protein diets improve depression and self-esteem [16] ↓ BFM [74, 97], BW [73, 74, 97], BMI [73, 74], WC [73, 74, 97], WHR [73], FINS [74, 98], FGL [97], HOMA-IR [73, 98], TAG [73], VLDL-C [73], T [73, 98], Ferriman-Gallwey scores [73] High protein and standard/low protein diet ↓ BW [92, 94, 95], BMI [92, 94, 95], BFM [95], WC [92, 94], WHR [94], FINS [95, 96], HOMA-IR [95], TAG [96], LDL-C [98] CRP [96], MPA [96], leptin [95], T [98], DHEAS [98], FAI [98] and there was ↔ between high and standard/low protein diets	Moran et al. 2013 [16] Moran et al. 2010 [96] Moran et al. 2004 [95] Sorensen et al. 2012 [97] Toscani et al. 2011 [92] Nadjarzadeh et al. 2021 [94] Phy et al. 2015 [73] Pohlmeier et al. 2014 [74] Mehrabani et al. 2012 [98]
Low fat	1 SR/MA (19 RCT total - 1 RCT using low fat diet) [85] 1 SR (5 RCT total - 1 RCT using low fat diet) [16] 1 RCT [107]	3; 137	Dietary intervention ↓ HOMA-IR, FINS, FGL, BMI, BW, WC compared with minimal intervention, and subgroup analysis showed no additional benefits for low fat diets [85] Weight loss improved the presentation of PCOS regardless of dietary composition, with no subtle differences observed for low fat diets [16] Low fat (25% E fat) ↓ BW, BFM, BMI though there was ↔ between low fat and standard fat (35% E fat) diets [107]	Shang et al. 2020 [85] Moran et al. 2013 [16] Wong et al. 2016 [107]

Table 1 (continued)

Dietary intervention	N study design	N studies; N participants	Main findings ^a	References
Fatty acids	1 SR (5 RCT total - 1 RCT using MUFA enriched diet) [16] 3 RCT [86, 102, 105] 1 controlled trial (not randomised) [103] ^c	5; 146	MUFA enriched diets may produce greater weight loss when compared to other dietary patterns [16] MUFA enriched compared with PUFA enriched diets ↓ FGL [103], glucose response to OGTT [103], HgBA1 [102] Diets with a higher alpha-linolenic acid, lower omega-6/omega-3 ratio and saturated fat content ↓ TAG, TC/HDL-C, LDL-C-/HDL-C, TAG/HDL-C, and HOMA-IR [105] High total and saturated fat meals compared with high fibre low fat meals produce prolonged ↓ in T [86]	Moran et al. 2013 [16] Yahay et al. 2021 [105] Kalgaonkar et al. 2011 [102] Kasim-Karakas et al. 2004 [103] Katcher et al. 2009 [86]
DASH	1 SR/MA (19 RCT total - 4 RCT using DASH diet) [85]	4; 228	Dietary intervention ↓ HOMA-IR, FINS, FGL, BMI, BW, WC compared with minimal intervention, and subgroup analysis showed DASH diet was more effective at improving insulin sensitivity [85]	Shang et al. 2020 [85]
Plant-based	3 RCT	3; 108	Plant-based (35% animal protein, 35% textured soy protein, 30% vegetable protein) compared to control (70% animal protein, 30% vegetable protein) ↓ BMI, FGL, FINS, TAG, HOMA-IR, T, MDA and ↑ QUICKI [67] Plant-based and control diets (calorie restriction [68] and general dietary recommendations [72]) ↓ BW [68], HOMA-IR [72], T [72], LH/FSH [72] and there was ↔ between plant-based and control diets	Turner-McGrievy et al. 2014 [68] Kazemi et al. 2020 [72] Karamali et al. 2018 [67]
Meal pattern	1 RCT	1; 40	6 meals/day compared with 3 meals/day: ↓ FINS ↑ post-OGTT insulin sensitivity	Papakonstantinou et al. 2016 [111]
Meal timing	1 RCT	1; 60	Consuming a high kilojoule breakfast compared with a high kilojoule dinner: ↓ FGL, FINS, HOMA-IR, T ↑ SHBG	Jakubowicz et al. 2013 [66]

Abbreviations: ↑ significant increase ($P \leq 0.05$), ↓ significant decrease ($P \leq 0.05$), ↔ no significant change, *BFM* Body fat mass, *BMI* Body mass index, *BW* Body weight, *CHO* Carbohydrate, *CRP* C-reactive protein, *DHEAS* Dehydroepiandrosterone-sulfate, *E* Energy, *FAI* Free androgen index, *FBM* Fat body mass, *FGL* Fasting glucose level, *FINS* Fasting insulin level, *FSH* Follicle stimulating hormone, *G* Glycaemic index, *HDL-C* High density lipoprotein cholesterol, *HOMA-B* Homeostatic Model Assessment for Beta Cells, *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance, *IR* Insulin resistance, *LDL-C* Low density lipoprotein cholesterol, *LH* Luteinizing hormone, *MDA* Malondialdehyde, *MUFA* Monounsaturated fatty acid, *OGTT* Oral glucose tolerance test, *PCOS* Polycystic ovary syndrome, *PUFA* Polyunsaturated fatty acid, *QoL* Quality of life, *QUICKI* Quantitative insulin sensitivity check index, *SHBG* Sex hormone-binding globulin, *T* Testosterone, *TAG* Triglycerides, *TC* Total cholesterol, *VLDL-C* Very low density lipoprotein cholesterol, *WC* Waist circumference, *WHR* Waist hip ratio

^a Summarises commonly used measures in PCOS research and does not report on all measured outcomes. For prospective pre-post studies significant changes from baseline are reported. For RCTs significant changes between intervention(s) and control are reported. Only experimental studies not already summarised in included systematic reviews/meta-analysis are presented

^b Shishregar et al. 2019 total study population included 62 women though only findings for the women with PCOS ($n=28$) are included

^c While habitual diet (control) was not enriched with MUFA, nutritional analysis showed that it was rich in oleic acid

Although weight loss has shown clear benefits to PCOS outcomes, including not only on reproductive function, but also glucoregulatory status, androgen status and lipid profiles [42–52], there are varying degrees of responsiveness to weight loss in terms of improvement of PCOS symptoms. One study by Pasquali et al. [53] found that when women achieved similar levels of weight loss (>5% weight) only one-third displayed a full recovery from PCOS, with the remainder showing

only partial or no recovery. Higher waist circumference (WC), waist-hip-ratio (WHR) and androstenedione at baseline were associated with a poorer chance of successful outcomes [53], suggesting that central adiposity and more severe hyperandrogenism may predict responsiveness to weight loss interventions in PCOS. Huber-Buchholz et al. [45] also reported women who achieve greater reductions in central fat and insulin sensitivity show greater symptom improvement with

weight loss. This suggests that lifestyle interventions which simultaneously reduce IR and improve body composition (namely fat distribution), may help to optimise outcomes in PCOS management independent of changes in weight status.

Diet

The 2018 PCOS guideline recognises there is insufficient evidence to suggest that any specific dietary approaches provide greater benefits on health outcomes [18]. Dietary recommendations may take on a variety of balanced dietary strategies according to the individual's lifestyle needs and preferences, as per general population recommendations [18]. This advice is based on a systematic review comparing different dietary compositions (e.g. low carbohydrate, low glycaemic index (GI) and glycaemic load (GL), high protein, monounsaturated fatty acid (MUFA) enriched and fat counting diets) to best manage PCOS, identifying minimal differences between diets on anthropometric outcomes, concluding weight loss improves the presentation of PCOS regardless of dietary composition [16, 54]. There is now an emerging body of evidence that suggests a range of dietary strategies may produce favourable effects on PCOS features that occur independent of weight loss. It is important that the emerging findings from these studies are thoroughly considered to support consumer and health professional interests. To summarise current evidence this review has grouped diets in terms of those that modify carbohydrates, protein and fat, as well as specific dietary patterns.

Carbohydrates

The use of altered carbohydrate composition remains the most researched dietary approach for PCOS management. Two systematic reviews published after guideline inception support altered carbohydrate intake to improve intermediate markers of PCOS [55, 56], finding that altering carbohydrate type, as opposed to content, is preferable to better manage PCOS [55]. RCTs [57–72] and pre-post intervention studies [73–80] demonstrate that following a low GI/GL diet for at least eight weeks significantly reduces WC [55, 73, 74] and BMI when compared to high GI/GL [56] or a regular diet [73–76], although levels of weight loss are generally comparable to other dietary compositions [59, 60, 72, 74]. These reductions are proposed to be a result of decreased hunger, which may reduce energy intake and make it easier to follow dietary recommendations in the long-term [78, 81–84]. Low GI/GL diets also improve insulin sensitivity and reproductive hormones (T, SHBG, FAI) compared to high carbohydrate [16, 55, 57, 79, 85] or control diets [56, 59, 73–76], contributing to improvements in reproductive function, specifically menstrual regularly [60, 79]. Lastly, low GI/GL diets can improve risk factors for T2DM and CVD, including glucose

[86, 87], TC [55, 56, 59, 75, 77], LDL-C [55, 59, 75, 85], TAG [55, 59, 73] and HDL-C [75], when compared to a regular or high GI/GL diet. It must be noted that beneficial effects of low GI/GL diets may also be attributed to proportional increases in protein and/or fat loads.

Protein

In women with PCOS higher protein intakes may be superior at suppressing androgen levels when compared to high carbohydrate diets. Postprandial research has shown that high protein meals can reduce insulin and dehydroepiandrosterone stimulation compared to meals rich in glucose [88]. Research in the general population has also shown that reduced appetite and energy intakes from low GI/GL diets are related to increased protein intakes [89, 90]. RCTs and pre-post intervention studies found that high protein diets (defined here as protein constituting $\geq 25\%$ energy [91]) consumed for at least four weeks reduce weight [12, 73, 74, 92–96], BMI [73, 74, 92, 95], WC [73, 74, 92, 97], WHR [73] and fat mass [74, 92, 97]. These reductions in anthropometric measures are accompanied by improved FINS [12, 74, 95, 98] and HOMA-IR [12, 73, 95, 98], blood lipids [12, 96], T [73, 92, 94] and hirsutism (Ferriman-Gallwey score) [73]. However, only three of these studies were able to show significant improvements in anthropometric measures [97], insulin sensitivity [98] and blood lipids [12] when compared to low/standard protein [12, 97] or control diets [98]. Only one study investigated effects on mental health outcomes and found that a high protein diet reduced depression and improved self-esteem [99].

Fats

Fatty acid composition is also an important consideration as metabolic disorders associated with PCOS can benefit from increased MUFA and polyunsaturated fatty acid (PUFA) intakes [63–65]. Postprandial research in PCOS reported prolonged reductions in T for high fat compared to low fat meals, which likely results from delayed nutrient absorption [86]. Two acute meal studies in lean and obese women with and without PCOS reported that proatherogenic inflammatory markers [100] and oxidative stress [101] were elevated, independent of but augmented by obesity, following saturated fat ingestion with this associated with worsened IR and androgens. Two experimental studies in PCOS investigated the effects of habitual walnut (PUFA rich diet) [102, 103] and almond (MUFA rich diet) [102] intake for at least six weeks and reported no differences in glucoregulatory status, lipids or androgens with the exception of HbA1c significantly decreasing in the walnut relative to the almond group. Kasim-Karakas et al. [103] reported increased fasting and postprandial glucose

(oral glucose tolerance test (OGTT)) for increased walnut intake compared to habitual (control), which they postulated may be related to the control diet being rich in oleic acid. Together these findings suggest minimal benefit for improving dietary PUFA compared to MUFA content. Two RCTs in women with PCOS investigated the effects of diets rich in olive [104, 105], canola [105] and sunflower [105] oil. Yahay et al. [105] reported 25g/day canola oil caused reductions in TAG, TC/HDL-C, LDL-C/HDL-C, TAG/HDL-C and HOMA, but not androgens, compared to 25 g/day olive and sunflower oils [105]. This may be related to the more favourable fatty acid composition of canola oil, with comparable MUFA content to olive oil, higher alpha-linolenic acid, lower omega-6/omega-3 ratio and saturated fat than both olive and sunflower oils. Douglas et al. [104] reported weight and the acute insulin response (OGTT) were lower following a eucaloric low carbohydrate compared to a eucaloric MUFA-enriched olive oil diet, suggesting that reduced carbohydrate intake may have greater glucoregulatory benefits than increased MUFA intake [104]. Lastly, two RCTs compared hypocaloric low-fat diets to a low carbohydrate [106] or low GI [107] diets, with reductions in weight [106], WC [106], body fat [106, 107], FINS [106] and FAI [106] in both groups but no difference between groups.

Dietary and eating patterns

In addition to diets that focus on specific macronutrient manipulations, there are a range of dietary patterns which have been explored in PCOS management. A systematic review (including 19 studies and 1,193 participants) published after guideline development (2020) found that the Dietary Approaches to Stop Hypertension (DASH) diet (rich in fruit, vegetables, wholegrains, nuts, legumes and low-fat dairy and with a predominantly low-GI carbohydrate profile) was the optimal choice for reducing IR [85]. RCTs in PCOS also report beneficial effects on weight [63, 64], BMI [62, 63], IR [62] and hormonal profile, including SHBG [64], androstenedione [64] and FAI [62] for a DASH compared to a control diet after 8–12 weeks. A vegetarian diet also reduced inflammatory markers (CRP, resistin and adiponectin) compared to a meat inclusive diet [80]. A vegan diet improved weight loss at three, but not six months [68], and a pulse-based diet led to similar reductions in weight, insulin sensitivity and reproductive hormones compared to a healthy control diet [72]. All of these dietary patterns are high in fibre and plant proteins, producing favourable effects on microbial diversity and encouraging production of short-chain fatty acids that possess potential anti-inflammatory actions [108, 109]. With mechanistic animal studies suggesting a possible pathophysiological role of gut microbiota in IR and

ovarian dysfunction, it is possible that metabolic and hormonal benefits associated with plant-based dietary patterns in PCOS are related to increased intakes of dietary prebiotics [110]. However, further mechanistic studies exploring the role of gut microbiota in PCOS and RCTs investigating effects of dietary prebiotics on PCOS outcomes are required.

Lastly, particular eating patterns, such as eating smaller more frequent meals across the day [111] and eating a larger breakfast and smaller dinner [66], have also been found to be beneficial for insulin sensitivity [66, 111] and androgen reductions [66]. This is an important finding, as women with PCOS are more likely to either skip breakfast or consume their breakfast and lunch later in the day [112].

Studies examining specific food items in relation to PCOS outcomes, including raw onions [65], concentrated pomegranate juice [69, 113–115] and flaxseed powder [70, 116] have yielded largely inconsistent results. A core limitation of these single food studies is that foods are never consumed alone within the diet, omitting the influence of the dietary matrix and the interactions that occur amongst dietary constituents within meals. These studies provide limited applicability in the context of formulating practical dietary recommendations [117]. Please see Table 1 for a summary of available evidence from reviews and experimental studies investigating the effects of different types of diets on PCOS outcomes.

Physical activity

The 2018 PCOS guideline recommends ≥150 minutes per week of moderate or ≥75 minutes per week of vigorous intensity exercise for weight gain prevention, and ≥250 minutes per week of moderate or ≥150 minutes per week of vigorous intensity exercise for weight loss and weight regain prevention [18]. Minimising sedentary time and the inclusion of strength training exercise for two days per week is also recommended [18].

To date the most comprehensive review in PCOS (including 27 papers from 18 trials up until June 2017) reported that exercise improved FINS, HOMA-IR, TC, LDL-C, TAG, body composition (body fat percentage and WC) and aerobic fitness ($VO_{2\max}$) [119] compared with usual care or control groups. In regards to exercise type, subgroup analysis reported aerobic exercise improved BMI, WC, body fat percentage, FINS, HOMA-IR, TC, TAG and $VO_{2\max}$. In contrast, while resistance training produced unfavourable effects on HDL-C (decrease) and BMI (increase), it improved other measures of anthropometry, including WC. Combined interventions (using both aerobic and resistance training) had no effect on any of the measured markers. Subgroup analysis also found that more outcomes improved when

Table 2 Meta-analyses investigating the effects of different types of exercise on polycystic ovary syndrome outcomes

Physical activity intervention	N reviews; N studies; N participants	Main findings ^a	References
Aerobic exercise	4; 48; 1518	↓ WC [119, 121, 124], BMI [119, 122, 124], BF% [119], HOMA-IR [119, 121, 122, 124], TC [119, 124], FINS [119, 124], TAG [119], LDL-C [119], RHR [119] ↑ VO _{2peak/max} [119, 121, 124] ↔ BMI [121], BW [119, 124], HDL-C [124], LDL-C [124], TAG [124], FGL [119, 124], BP [119], HOMA-IR [122], FAI [119, 121, 122], T [119, 122], SHBG [119], E2 [119], LH [119, 122], FSH [119, 122]	Patten et al. 2020 [121] dos Santos et al. 2020 [122] Richards et al. 2021 [124] Kite et al. 2019 [119]
Resistance training	2; 14; 505	↓ WC [119], HOMA-IR [121], FINS [119], HDL-C [119], FAI [121] ↑ BMI [119] ↔ BW [119], BF% [119], FGL [119], HOMA-IR [119], TAG [119], TC [119], LDL-C [119], VO _{2max/peak} [119], RHR [119], FAI [119], T [119], SHBG [119], E2 [119], LH [119], FSH [119]	Patten et al. 2020 [121] Kite et al. 2019 [119]
Combined aerobic and resistance training ^b	2; 3; 59	↔ BMI [119, 122], WC [119], HOMA-IR [119, 122], FINS [119], FGL [119], BP [119], TAG [119], TC [119], LDL-C [119], HDL-C [119], RHR [119], T [119, 122], E2 [119], LH [119], FSH [119]	Kite et al. 2019 [119] dos Santos et al. 2020 [122]
High intensity interval training	2; 11; 373	↓ BMI [123], WHR [123], HOMA-IR [123, 124] ↔ BF% [123], BMI [124], BW [124], WC [124], TC [123, 124], LDL-C [123, 124], TAG [124], FINS [123, 124], FGL [124], HDL-C [124], VO _{2max} [124]	Richards et al. 2021 [124] dos Santos et al. 2021 [123]

Abbreviations: ↑ significant increase ($P \leq 0.05$), ↓ significant decrease ($P \leq 0.05$), ↔ no significant change, BF% Percent body fat, BMI Body mass index, BW Body weight, BP Blood pressure, E2 Estradiol, FGL Fasting glucose level, FAI Free androgen index, FINS Fasting insulin, FSH Follicle stimulating hormone, HOMA-IR Homeostatic assessment of insulin resistance, LDL-C Low density lipoprotein cholesterol, LH Luteinizing hormone, PCOS Polycystic ovary syndrome, RHR Resting heart rate, SHBG Sex hormone-binding globulin, T Testosterone, TAG Triglycerides, TC Total cholesterol, VO_{2max} Maximal oxygen uptake, VO_{2peak} Peak oxygen uptake, WC Waist circumference, WHR Waist hip ratio

^a Significant findings from meta-analyses when comparing exercise groups to control

^b Subgroup analyses compared different types of exercise; only 1 study included for combined exercise

interventions were supervised, of a shorter duration (≤ 12 weeks) and were conducted in women who were above a healthy weight [119].

Three more recent systematic reviews have looked at the effects of specific types of exercise on PCOS outcomes [120–122]. These reviews found that vigorous aerobic exercise can improve measures of insulin responsiveness and resistance, including HOMA-IR [121] and the insulin sensitivity index [120]; body composition, including WC [121] and BMI [122]; and cardiorespiratory fitness (VO_{2max}) [121]. High intensity interval training (HIIT) alone may be effective for improving IR and BMI [123], however this has not been consistently shown [124]. Interventions involving a combination of aerobic and resistance exercise [122] or resistance training only [120] did not result in improvements in BMI [122] or weight status [120]. Exercise involving resistance training did result in other beneficial improvements to body composition (reduced body fat, WC and increased lean mass) and strength. This is important, as the degree of

central adiposity predicts responsiveness to weight loss interventions in PCOS [53], and women who achieve greater reductions in central fat show greater symptom improvement with weight loss [45]. Resistance training may also improve androgen levels, though findings are inconsistent and more research is needed to draw definite conclusions [120]. There was insufficient evidence from available data to assess the effects of exercise type on reproductive function [122]. Please see Table 2 for a summary of available evidence from meta-analyses investigating the effects of different types of exercise on PCOS outcomes.

When comparing the effects of exercise and diet combined with diet alone, a systematic review and meta-analysis (three studies) found no differences for any measured outcomes (glucose, insulin HOMA-IR, weight, BMI, WC, body fat, fat free mass, T, SHBG and FAI) [119]. In regards to exercise and diet combined compared to exercise alone, subgroup analysis (including 17 studies) from a large systematic review found that the addition of diet to exercise,

Table 3 Experimental studies investigating the effects of psychological interventions on polycystic ovary syndrome outcomes

References	Study design; study length; N participants	Intervention	Main findings
Abdollahi et al. 2019 [152]	Parallel RCT; 8 wk; 74	I = 8 weekly CBT C = minimal intervention	↑ QoL (PCOSQ) for I compared with C ↓ psychological fatigue (FIS) for I compared with C
Jiskoot et al. 2020 [162] Jiskoot et al. 2020 [154]	Parallel RCT; 1 yr; 183	I = 20 group sessions of CBT combined with nutrition advice and exercise C = usual care	↓ depression (BDI-II) and BW in I compared with C ↑ self-esteem (RSES) in I compared with C
Oberg et al. 2020 [132]	Parallel RCT; 16 wk with a follow-up at 1 yr; 68	I = behavioural modification program C = minimal intervention	↓ anxiety (PGWB) and depressed mood (PGWB) in I compared with C ↑ higher general health (PGWB) in I compared with C
Cooney et al. 2018 [153]	Parallel RCT; 16 wk; 31	I = 8 weekly CBT with lifestyle modification C = no psychological intervention with lifestyle modification	↓ BW in I compared with control ↑ QoL (PCOSQ) in I compared with control
Raja-Khan et al. 2017 [160]	Parallel RCT; 16 wk; 86	I = 8 weekly MBSR C = 8 weekly health education sessions (diet and exercise education)	↑ mindfulness (TMS) in I compared with C ↓ perceived stress (PSS-10) in I compared with C
Stefanaki et al. 2015 [156]	Parallel RCT; 8 wk; 38	I = MBSR C = minimal intervention	↓ depression (DASS21), stress (DASS21) and cortisol in I compared with control
Roessler et al. 2012 [151] ^a Roessler et al. 2013 [163] ^b	Cross-over randomised; 8 wk per arm and 16 wk total; 17	8 wk high-intensity aerobic exercise (including a ramp-up period of two weeks) and 8 wk group counselling in a cross-over design without a wash-out period	Relationships between the participants were important for changes in behaviour, especially relationships which generated helpful peer feedback and reduced social isolation ↓ BW and BMI after 16 wk only in the group who started with group counselling
Rofey et al. 2009 [158]	Single arm experimental; 8 wk; 12	8 one-on-one CBT, 3 family-based CBT and lifestyle goals (diet and exercise)	↓ BW, BMI and depression (CDI) ↑ health-related QoL (IWQoL-K)

Abbreviations: ↑ significant increase ($P \leq 0.05$), ↓ significant decrease ($P \leq 0.05$), *BDI-II* Beck Depression Inventory-II, *BW* Blood pressure, *BMI* Body mass index, *BW* Body weight, *CDI* Children's Depression Inventory, *C* Control, *CBT* Cognitive behavioural therapy, *CES-D* Centre for Epidemiologic Studies – Depression Scale, *DASS21* Depression Anxiety Stress Scales-21, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders (fourth edition), *FGL* Fasting glucose level, *FIS* Fatigue Impact Scale, *I* Intervention, *IWQoL-K* Impact of Weight on Quality of Life Questionnaire—Kids, *HP* Hip circumference, *MBSR* Mindfulness-based stress reduction, *PSS-10* Perceived Stress Scale-10, *PCOS* Polycystic ovary syndrome, *PCOSQ* Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire, *PGWB* Psychological Well-Being Index, *QoL* Quality of life, *RSES* Rosenberg Self Esteem Scale, *RCT* Randomized controlled trial, *STA* State-Trait Anxiety Inventory, *SSP* Swedish Universities Scale of Personalities, *TMS* Toronto Mindfulness Scale, *TSST* Trier Social Stress Test, *WC* Waist circumference

^a Qualitative analysis only

^b Statistical analysis compares order of intervention arms (e.g. counselling followed by exercise versus exercise followed by counselling) and doesn't compare effects of counselling versus exercise

particularly vigorous intensity aerobic exercise, resulted in greater reduction to BMI, WC, FAI and HOMA-IR than exercise only [121]. In regards to exercise (aerobic) alone versus diet alone, one intervention study found that exercise induced weight loss produced greater improvements

in menstrual frequency and ovulation rates [125], with no differences in pregnancy rates [125]. However, this study was not randomised and treatments were self-selected, which may have biased the results and precludes firm conclusions [125].

Table 4 Key observational studies that report non-clinical sleep disruption in polycystic ovary syndrome

Reference	Sample size	Sleep methodology used	Main findings
Moran et al. 2015 [182]	PCOS: n=87 Non-PCOS: n=637	Modified version of the Jenkins Sleep Questionnaire	Women with PCOS were twice as likely to experience sleep disturbance PCOS was associated with difficulty falling asleep and maintaining sleep
Mo et al 2019 [140] ^a	PCOS: n=484 Non-PCOS: n=6094	Sleep duration was self-reported on a work day and non-work day Sleep quality was self-reported through frequency questions about difficulty falling asleep, restless sleep, difficulty sleeping and severe tiredness	Women with/without PCOS had similar sleep duration Women with PCOS had higher prevalence of sleep disturbance, and this relationship maintained even after controlling for BMI, depression, income, marital status, occupation, education status and COB
Bennett et al. 2021 [183] ^a	PCOS: n=464 Non-PCOS: n=5603	Sleep duration was self-reported on a work day and non-work day Sleep quality was self-reported through frequency questions about difficulty falling asleep, restless sleep, difficulty sleeping and severe tiredness	Overall women with PCOS had greater adverse sleep symptoms and higher DGI However, subgroup analysis revealed PCOS was only associated with a higher DGI in women with adequate sleep There was no association between PCOS and DGI in women with poor sleep The higher DGI observed in women with PCOS may only be maintained in women who achieve adequate amounts of good quality sleep
Shreeve et al. 2013 [167]	PCOS: n=15 Non-PCOS: n=18	Actigraphy, PSQI and ESS	Women with PCOS had higher night time melatonin levels Women with PCOS had reduced sleep when compared to controls
Kutanaee et al. 2019 [181]	PCOS: n=201 Non-PCOS: n=199	PSQI	Women with PCOS had lower sleep quality and daytime function Women with PCOS were more likely to utilise medication to assist with sleep

Abbreviations: BMI Body mass index, COB Country of birth, DG Dietary Guidelines Index, ESS Epworth Sleepiness Scale, PCOS Polycystic ovary syndrome, PSQI Pittsburgh Sleep Quality Index

^a Mo et al. [140] and Bennett et al. [183] share the same cohort

Behavioural

The 2018 PCOS guideline promotes the use of behavioural interventions that foster self-efficacy [18]. These include the use of SMART (specific, measurement, achievable, realistic and timely) goals, self-monitoring, stimulus control, problem solving and relapse prevention [18].

Behavioural and cognitive interventions are required to improve sustainability of lifestyle changes, through considering not only the specific behaviour, but also their antecedents, consequences and cognition [126, 127]. Given that women with PCOS show higher rates of weight gain over time [9] and high attrition rates in clinical weight management research [37], there is a clear need to improve adherence to diet and physical activity interventions. However, the majority of research investigating lifestyle change in PCOS involve short-term dietary interventions with/without an exercise element, and there is a paucity of research on behavioural change strategies. As such, guideline development relied heavily on evidence taken from the general population. Only three RCTs in women with PCOS included a ‘behavioural intervention’ [128–130]. While

these studies showed enhanced weight loss [128, 130] and improved androgen and lipid profiles [129] when compared with placebo, the interventions were not well defined, with negligible context provided regarding the theoretic framework or behavioural strategies utilised.

More recently, a cross-sectional study in 501 women with PCOS [131] and two RCTs [44, 132] explored the use of self-management strategies [131] and behavioural modification interventions [44, 132] in PCOS. In the cross-sectional study, implementation of physical activity self-management strategies improved the likelihood of meeting physical activity recommendations, but had no association with BMI. Dietary self-management strategies were associated with reductions in BMI, though were not related to weight or nutritional intake [131]. In the RCTs, only the behavioural modification programme and not the control (general healthy lifestyle recommendations) produced significant weight loss after four months. A significantly greater proportion of women in the intervention group also improved menstrual regularity [44] and psychological well-being (lower anxiety and depressive

symptoms) [132] when compared to the control group. The women who achieved greater weight loss reported higher social desirability and lower embitterment scores on a personality trait assessment measure [132]. These findings are particularly novel, as they provide insight into the influence of personality traits and their contribution to success in following behavioural modifications [132].

Alcohol and smoking

In the clinical setting, smoking and alcohol consumption are often addressed alongside dietary and physical activity changes, employing the same behavioural and cognitive interventions to promote adherence. Hence, alcohol and cigarette use are considered here under traditional lifestyle strategies. The PCOS international guideline highlights the importance of assessing alcohol consumption and cigarette smoking when improving fertility and reproductive outcomes in women with PCOS [18]. Assessment of cigarette use is also recommended when evaluating CVD risk factors and thromboembolism risk associated with oral contraceptive pills [18]. These recommendations are based on existing practice guidelines used for the general population.

There is a paucity of observational research characterising alcohol consumption in women with PCOS. One Swedish study comparing women with PCOS ($n=72$) to healthy controls ($n=30$), demonstrated a lower alcohol intake in the PCOS group [133]. A larger study in Australia comparing women with ($n=409$) and without ($n=7,057$) PCOS, reported no significant difference in alcohol intake [134]. Similarly, a Spanish study ($n=22$ PCOS and $n=59$ controls) and a Chinese study ($n=2,217$ PCOS and $n=279$ controls), found no significant difference in alcohol intake between PCOS and non-PCOS groups [135, 136].

Current evidence on the impact of alcohol intake on anovulatory infertility (a common feature of PCOS) is controversial, with some studies showing adverse effects and others reporting no significant correlation [136, 137]. One prospective study including 18,555 married women from The Nurses' Health Study II, who had no history of infertility, found no clinically significant impact of alcohol intake on anovulatory infertility, after adjusting for parity and other factors [138]. Similarly, a Danish study ($n=6,120$ women aged 21 to 45 years) found no fertility effect with alcohol consumption of less than 14 standard drinks per week [137]. In contrast, a study on 3,833 women who recently gave birth and 1,050 women with infertility, reported an increased risk of anovulatory infertility and endometriosis with increasing alcohol intake [139].

Current observational evidence does not reveal any significant difference in smoking between women with and without PCOS [135, 136, 140], with the exception of one

study in pregnant women which showed a lower smoking rate in women with PCOS ($n=354$) compared to women without PCOS at 15 weeks gestation [3]. However, a significantly higher rate of smoking (including passive and active) is reported in women with PCOS and oligo-anovulation and/or reduced fertility compared to women with PCOS and normal menstruations or healthy controls [141, 142]. Smoking is also associated with PCOS risk independent of BMI and age [142]. A Mendelian randomisation study supports these findings, demonstrating a 38% higher risk of PCOS development in genetically predicted smokers (based on single-nucleotide polymorphisms associated with smoking initiation) compared with those who never smoked [143]. In PCOS, smoking is associated with increased levels of T, DHEAS, TC, LDL-C and FINS [141, 144, 145]. However, the underlying mechanisms are not fully understood and there are inconsistencies in findings from different studies. Furthermore, smoking is associated with lower conception and live birth rates and less favourable ART outcomes in women with PCOS [141, 146].

Psychological

The current guideline highlights the need for awareness, and appropriate assessment (such as stepwise screening) and management, of QoL, depression and anxiety, psychosexual dysfunction, negative body image and disordered eating [18]. The guideline emphasises the importance of clinicians and women working in partnership to address women's individual priorities; understanding that the impact of PCOS on an individual's QoL is key to delivering meaningful outcomes [147, 148]. To assist women to communicate with clinicians about what is important to them, the PCOS Question Prompt List [149] was developed and is consistent with the 2018 guideline. The 2018 guideline recommends screening for risk factors and symptoms of depression and anxiety at time of diagnosis. Women with positive screening results should be supported with further assessment and treatment by appropriately qualified clinicians. To screen for psychosexual dysfunction tools such as the Female Sexual Function Index [150] should be utilised. If negative body image, disordered eating or eating disorders are suspected, the PCOS guideline outlines a stepped approach for screening, and where appropriate promotes the use of psychological therapy offered by trained health professionals, which should be guided by regional clinical practice guidelines [18].

While the PCOS guideline provides justification and summarises evidence for mental health screening and diagnostic assessment, there is also a need for consideration of additional aspects, such as the efficacy of different types of psychological interventions and how

Table 5 Reviews and experimental studies investigating the effects of traditional, complimentary and integrative medicine on polycystic ovary syndrome outcomes

Intervention	N study design	N studies; N participants	Main findings ^a	References
Vitamins				
B-group vitamins (B1, B6, and B12)	1 RCT	1; 60	Counteracted Hcy-increasing effect of metformin ↔ HOMA-IR	Kilicdag et al. 2005 [198]
Folate (vitamin B9)	2 RCT	2; 150	↓ Hcy [199, 200], HOMA-β [199], HOMA-IR [200], FINS [200], TC:HDL-C ratio [200], CRP [199], MDA [199] ↑ TAC [199], GSH [199]	Bahmani et al. 2014 [199] Asemi et al. 2014 [200]
Inositol (vitamin B8)	1 SR/MA	9 RCT; 496	↓ HOMA-IR; ↓ FINS ↔ androstenedione, T, SHBG	Unfer et al. 2017 [191]
Vitamin D	2 SR/MA	23 RCT; 1367	↓ TC [201], LDL [201], TAG [201], HOMA-IR [203], FGL [203], FINS [203], VLDL-C [203] ↑ QUICKI [203] ↔ HDL-C [201]	Guo et al. 2020 [201] Gao et al. 2021 [203]
Vitamin E	1 RCT	1; 86	↓ FGL, HOMA-IR, SHBG, T (only when combined with coenzyme Q10)	Izadi et al. 2019 [205]
Vitamin K	1 RCT	1; 79	↓ WC, FBM, FINS, HOMA-IR, HOMA-β, TAG, FAI, DHT ↑ skeletal muscle mass, SHBG, QUICKI	Tarkesh et al. 2020 [206]
Vitamin-like supplements				
Soy isoflavones	1 pilot pre-post prospective	1; 12	↓ TC, LDL-C, LDL-C:HDL-C ratio, TAG	Romualdi et al. 2018 [208]
Carnitine (L-Carnitine)	1 RCT	1; 60	↓ MDA, MDA:TAC ratio ↑ TAC	Jamilian et al. 2017 [211]
Alpha-lipoic acid	2 pre-post prospective	2; 52	↓ BMI [214], IR [213], LDL-C [213], TAG [213], ovarian cysts [214] ↑ progesterone [214]	Masharani et al. 2010 [213] Cianci et al. 2015 [214]
Minerals				
Vitamin D and calcium	1 SR/MA	6 RCT; 480	↓ FINS, HOMA-IR, FGL, T, TAG, VLDL-C, TC, LDL-C, hirsutism ↑ QUICKI, menstrual regularity	Shojaeian et al. 2019 [219]
Zinc	1 SR	5 RCT; 285	↓ HOMA-IR, HOMA-β, FINS, MDA, CRP, T, FSH, TC, LDL-C, TAG, VLDL-C, DHEAS ↑ TAC, QUICKI	Nasiadek et al. 2020 [220]
Selenium	1 SR	5 RCT; NR	↓ IR, CRP and MDA in some RCTs ↔ (or inconsistent findings) BMI, BW, FGL, blood lipids, androgens, acne, hirsutism	Hajizadeh-Sharafabad et al. 2019 [221]
Magnesium	1 SR	3 RCT; 156	Serum magnesium concentrations were associated with IR but supplementation had inconsistent effects	Hamilton et al. 2019 [222]
Chromium Picolinate	2 SR/MA	11 RCT; 702	↓ BMI [223], FINS [223], IR [224], T [223] ↑ T [224] ↔ BMI [224], FG [223]	Fazelian et al. [223] Tang et al. [224]

Table 5 (continued)

Intervention	N study design	N studies; N participants	Main findings ^a	References
Other supplements				
Omega-3 fatty acids	1 SR/MA	9 RCT; 591	↓ HOMA-IR, TC, LDL-C and TAG. ↔ FINS, FGL, BMI, androgens	Yang et al. 2018 [225]
N-acetyl-cysteine	1 SR/MA	8 RCTS; 910	↑ rates of pregnancy and live births	Thakker et al. 2015 [226]
Coenzyme Q10	1 RCT	1; 60	↓ FGL, FINS, HOMA-IR, HOMA-β, TC, LDL-C ↑ QUICKI	Samimi et al. 2017 [227]
Probiotics	2 SR/MA	19 RCT; 1261	↓ FINS [228], TG [228], VLDL-C [228], FAI [229] ↑ QUICKI [228], SHBG [229] ↔ BW [228], FGL [228], HOMA-IR [228], TC [228], LDL-C [228], HDL-C [228], CRP [228], DHEA [228], T [229]	Liao et al. 2018 [228] Shamasbi et al. 2020 [229]
Quercetin	1 SR	3 RCT; 246	Some improvement in adiponectin-mediated IR ↔ BW, WHR	Pourteymour et al. 2020 [232]
Resveratrol	1 SR/MA	3 RCT; 131	↓ T ↑ high-quality oocytes and embryos ↔ BMI, blood lipids, FGL, pregnancy rate	Shojaei-Zarghani et al. 2021 [233]
Melatonin	1 SR/MA	2 RCT and 1 cell culture; 640	↑ pregnancy rates in assisted reproductive technology	Hu et al. 2020 [172]
Herbal medicine				
Cinnamon	1 SR/MA	5 RCT; 448	↓ HOMA-IR, TC, LDL, FGL, FINS ↑ HDL ↔ BW	Heydarpour et al. 2020 [260]
Curcumin	2 RCT	2; 118	↓ FGL [238], DHEA [238] ↔ FGL [239], FINS [238], blood lipids [239], IR [239]	Heshmati et al. 2021 [238] Sohaei et al. 2019 [239]
Sage	1 RCT	1; 70	↓ BW, BMI, WC, FGL, FINS, HOMA-IR, QUICKI ↔ WHR	Amini et al. 2020 [241]
Fennel and dry cupping	1 RCT	1; 55	↓ BMI, cycle length	Mokaberinejad et.al. 2019 [243]
Licorice	1 pre-post prospective 1 quasi-experimental	2; 41	↓ T [245] Reduce prevalence of side effects related to the diuretic activity of spironolactone [246]	Armanini et al. 2004 [245] Armanini et al. 2007 [246]
Spearmint, ginger, citrus and cinnamon	1 RCT	1; 60	↓ HOMA-IR, FINS, FGL	Ainehchi et al. 2019 [251]
Chinese herbal medicine	1 SR/MA	4 RCT; 414	↑ pregnancy rate when taken with clomiphene (versus clomiphene alone) ↔ pregnancy rate when taken alone (versus clomiphene alone) Insufficient evidence for subfertility	Zhou et al. 2016 [235]

Table 5 (continued)

Intervention	N study design	N studies; N participants	Main findings ^a	References
Other TCIM				
Acupuncture	2 SR/MA	31 RCT; 2846 ^b	↓ BMI [255], LH [254], T [254] ↑ menstrual regularity [254] ↔ FGL [255], FINS [255], live birth [254], pregnancy rate [254], ovulation [254]	Wu et al. 2020 [254] Qu et al. 2016 [255]
Yoga	2 SR [120, 257] 1 SR/MA [258] 1 RCT [259]	21; 1059 ^a	↓ WC [259], HC [259], HOMA-IR [120], FGL [258], FINS [258], T [120], LH [120], DHEA [120], androsterone [120], adiponectin [120], clinical hyperandrogenism [259] ↑ menstrual regularity [258], menstrual frequency [257] ↓ stress and anxiety [257]	Shele et al. 2020 [120] Thakur et al. 2021 [257] Anita et al. 2021 [258] Mohseni M et al. 2021 [259]

Abbreviations: ↑ significant increase ($P \leq 0.05$), ↓ significant decrease ($P \leq 0.05$), ↔ no significant change, *BMI* Body mass index, *BW* Body weight, *DHEAS* Dehydroepiandrosterone-sulfate, *DHT* Dihydrotestosterone, *FGL* Fasting glucose level, *FINS* Fasting insulin level, *FBM* Fat body mass, *FSH* Follicle stimulating hormone, *FT* Free testosterone, *GSH* Glutathione, *HC* Hip circumference, *Hcy* Homocysteine, *HOMA-IR* Homeostatic assessment of insulin resistance, *HDL-C* High density lipoprotein cholesterol, *IR* Insulin resistance, *QUICKI* Quantitative insulin sensitivity check index, *QoL* Quality of life, *MDA* Malondialdehyde, *MA* Meta-analysis, *NR* Not reported, *OCP* Oral Contraceptive Pill, *RCT* Randomised controlled trial, *SHBG* Sex hormone binding globulin, *SR* Systematic review, *T* Testosterone, *TAC* Total antioxidant capacity, *TC* Total cholesterol, *TAG* Triglycerides, *TCIM* Traditional, complimentary and integrative medicine, *VLDL-C* Very low density lipoprotein cholesterol, *WC* Waist circumference, *WHR* Wait hip ratio

^a Summarises commonly used measures in PCOS research and does not report on all measured outcomes. For prospective pre-post studies significant changes from baseline are reported. For RCTs significant changes between intervention(s) and control are reported

^b Not all participants are included in the findings reported here (e.g. where findings from subgroup analysis are reported)

psychological interventions influence engagement with lifestyle change. This is important, as poorer mental health outcomes at baseline are positively associated with higher rates of attrition in lifestyle interventions [13]. Cognitive behavioural interventions could be considered to improve engagement and adherence to healthy lifestyle in women with PCOS. Research has shown support for a range of different psychological interventions, such as counselling [151], cognitive behavioural therapy (CBT) [152–154] and mindfulness meditation [155, 156], helping to change the way clinicians' approach and deliver optimal PCOS management.

CBT is one of the most widely-researched psychological interventions, and is well-recognised as the most effective psychological treatment for depression and anxiety [157]. One RCT showed that eight weekly group CBT sessions were effective in improving QoL ratings and reducing psychological fatigue in women with PCOS [152]. Another more recent RCT investigated the outcome of a 1 year three-component intervention focusing on CBT, diet and exercise [154] and reported improvements in self-esteem and depressive symptoms as compared to usual care [154]. Similarly, an RCT by Cooney et al. [153], comparing the effects of CBT and lifestyle modification versus lifestyle modification alone, reported the CBT/lifestyle modification group lost more than twice as much weight per week

and had greater improvements in QoL compared to lifestyle only. Depression scores decreased in the overall group and there was no difference between the two groups [153]. Lastly, a pilot intervention study of adolescents with PCOS has shown promising results for the use of CBT in the reduction of weight and improvement in depressive symptoms [158].

Mindfulness meditation programs have gained increasing popularity over the past few decades, and are being included as part of clinical trials to reduce stress and improve psychological wellbeing across a range of medical conditions [159]. Mindfulness meditation can be used to reduce the production of adrenal androgens, activated via the adrenal glands as a direct result of psychological distress [156]. Despite the proposed benefits, there are very few studies investigating the use of mindfulness meditation as a treatment for psychological symptoms associated with PCOS. One RCT ($n=86$) compared the provision of an eight week mindfulness-based stress reduction (MBSR) program, and found that when compared to the control group (health education), the MBSR group produced greater reductions in perceived stress, depressive symptoms and fasting blood glucose [160]. Similarly, another RCT investigating the impact of mindfulness meditation for eight weeks in PCOS showed reduced stress, depression and anxiety symptoms, and increased life satisfaction and QoL in the intervention

group compared to no treatment [156]. In adolescents with PCOS ($n=37$), a pilot RCT reported higher levels of nutrition and physical activity self-efficacy following a mindfulness and self-management program [161]. Mindfulness-based cognitive therapy (MBCT) combines both elements of MBSR and CBT, but as yet there are no trials investigating this intervention in PCOS.

In addition to CBT and mindfulness meditation, there is some evidence to support group counselling sessions as beneficial in conjunction with exercise programs to increase and support weight loss [151]. In one RCT ($n=17$) participants followed a high-intensity aerobic exercise program for eight weeks, followed by eight weeks of group counselling [151]. Qualitative analysis of data taken from the group counselling and physical exercise sessions revealed that development of supportive relationships was important for successful behavioural change. By fostering the exchange of narratives relating to their illness (e.g. effects of PCOS on aspects of everyday life), and generating feedback between group members, counselling sessions helped to reduce social isolation and improve adherence to the exercise intervention [151]. Please see Table 3 for a summary of experimental studies investigating effects of psychological interventions on PCOS outcomes.

Sleep

Women with PCOS have an increased risk of both clinical sleep disorders and non-clinical sleep disturbance, which is mediated by hormone derangement, in particular reduced oestrogen, progesterone and melatonin levels [164]. Oestrogen is required for the metabolism of neurotransmitters (norepinephrine and serotonin) involved in regulating sleep patterns, and plays an important role in maintaining a low body temperature at night [165]. Progesterone has sedative and anxiolytic actions that can support sleep quality, and acts as a respiratory stimulant that lessens airway resistance in obstructive sleep apnoea (OSA) [166]. Melatonin is a neuroendocrine hormone that is widely recognised as crucial in maintaining circadian rhythm regulation. However, melatonin is also involved in ovarian function, with actions including delaying ovarian senescence, promoting follicle formation and improving oocyte quality [167–173].

The current PCOS guideline recognises that OSA is 6.5–8.3 times more likely in women with PCOS [164, 174–177], and promotes routine screening to identify and treat associated symptoms, such as snoring, excessive sleepiness and the potential for fatigue to worsen mood disorders [18]. Screening should include a simple questionnaire, such as the Berlin tool [178], and where appropriate women should be referred onto a specialist for further assessment and

treatment [18]. The guidelines also highlight that treatment of OSA in PCOS should not be used to improve metabolic features. Since guideline inception evidence has emerged reporting weight, PCOS and sleep are interrelated factors that can each contribute to the worsening presentation of one another, whereby sleep disorders and disturbance may worsen the presentation of PCOS related metabolic outcomes and vice versa [179].

Hypersomnia and insomnia are also common clinical sleep disorders in PCOS [164, 177, 180], with prevalence estimated at 11% versus 1% in women with versus those without PCOS [180]. Even in the absence of clinically diagnosed sleep disorders, women with PCOS have a higher prevalence of sleep disturbances, including poor sleep quality [181], issues with sleep initiation [182], severe fatigue [140], restless sleep [140] and difficulty sleeping overnight [140]. The prevalence of sleep disturbances may be up to 20% higher in women with PCOS compared to women without PCOS [183]. Emerging research also suggests that social restrictions arising from the COVID-19 pandemic have worsened sleep disturbances in women with PCOS [177]. Findings from key studies of non-clinical sleep disturbance can be found in Table 4.

In the general population short and disturbed sleep is consistently associated with excess weight [184], IR [185], T2DM [185] and CVD [186]. Similar relationships are observed in PCOS, where OSA and sleep disordered breathing exacerbates risk of IR and metabolic consequences of abnormal glucose tolerance [187, 188]. A cross-sectional study in adolescents with PCOS ($n=103$) reported those with sleep disordered breathing had significantly higher BMI Z-scores, and a higher prevalence of metabolic syndrome (METS) [188]. Similar metabolic consequences are seen in women with PCOS who suffer from non-clinical sleep disturbance [164]. Underlying mechanisms linking sleep disorders and disturbance with worsened metabolic outcomes include amplified sympathetic tone and oxidative stress [164], reduced adipose tissue lipolysis, and an increase in energy intake stemming from heightened hedonic and endocrine appetite signals [189].

Unfavourable effects on energy metabolism and appetite regulation, may explain why women with PCOS who display sleep disturbance have a reduced capacity to maintain dietary interventions [183]. Moreover, depression and anxiety share a bidirectional relationship with disrupted and reduced sleep [190], and as stated previously, interventions that improve mental health can help to increase engagement with dietary and physical activity recommendations [131]. Optimising sleep may therefore be an important consideration when promoting healthy lifestyle change in women with PCOS [183].

Table 6 Current recommendations for clinical practice and research gaps identified by this review

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Effectiveness of lifestyle interventions		
Healthy lifestyle behaviours encompassing healthy eating and regular physical activity should be recommended in all those with PCOS to achieve and/or maintain healthy weight and to optimise hormonal outcomes, general health, and QoL across the life course. Lifestyle intervention (preferably multicomponent including diet, exercise and behavioural strategies) should be recommended in all those with PCOS and excess weight, for reductions in weight, central obesity and IR.	CCR EBR	<ul style="list-style-type: none"> • Improves sustainability of weight loss interventions. • Identifies subgroups who respond to weight loss with clinically relevant metabolic and reproductive improvements (this requires the inclusion of more clinical reproductive outcomes in RCTs). • Defines weight loss thresholds for improvements in different PCOS features (metabolic, reproductive and psychological). • Characterises the degree of metabolic and reproductive improvements related to different lifestyle factors (diet, physical activity and behavioural) independent of weight changes. • Considers effects of weight gain prevention on limiting the progression/worsening of PCOS features. • Investigates how different dietary, physical activity and behavioural interventions affect engagement, adherence and sustainability of lifestyle change. • Investigates efficacy and effectiveness of healthy lifestyle changes independent of weight change.

Table 6 (continued)

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Dietary interventions		
A variety of balanced dietary approaches could be recommended to reduce dietary energy intake and induce weight loss in women with PCOS and overweight and obesity, as per general population recommendations.	CCR	<ul style="list-style-type: none"> Low GI/GL diets may provide benefits in reducing weight and IR in women with PCOS. Further research needs to assess additional risk factors including reproductive function and CVD risk. Identify and define the optimal diet for PCOS management by comparing a range of different dietary approaches (e.g. DASH, Mediterranean or low GI/GL).
General healthy eating principles should be followed for all women with PCOS across the life course, as per general population recommendations.	CCR	
To achieve weight loss in those with excess weight, an energy deficit of 30% or 500 - 750 kcal/day (1,200 to 1,500 kcal/day) could be prescribed for women, also considering individual energy requirements, body weight and physical activity levels.	CPP	
In women with PCOS, there is no or limited evidence that any specific energy equivalent diet type is better than another, or that there is any differential response to weight management intervention, compared to women without PCOS.	CPP	
Tailoring of dietary changes to food preferences, allowing for a flexible and individual approach to reducing energy intake and avoiding unduly restrictive and nutritionally unbalanced diets, are important, as per general population recommendations.	CPP	
Physical activity interventions		
Health professionals should encourage and advise the following for prevention of weight gain and maintenance of health:	CCR	While evidence supports the provision of supervised vigorous aerobic exercise, which may provide greater benefits on PCOS symptoms than other types of exercise (e.g. resistance training), additional larger and longer-term studies are required to: <ul style="list-style-type: none"> Characterise optimal exercise prescription for PCOS management. Identify factors that improve adherence to exercise interventions. Identify subgroups who respond to exercise with clinical improvements.
• in adults from 18 – 64 years; a minimum of 150 min/week of moderate intensity physical activity or 75 min/week of vigorous intensities or an equivalent combination of both, including muscle strengthening activities on 2 non-consecutive days/week;		
• in adolescents, at least 60 minutes of moderate to vigorous intensity physical activity/day, including those that strengthen muscle and bone at least 3 times weekly;		
• activity be performed in at least 10-minute bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days.		
Health professionals should encourage and advise the following for modest weight-loss, prevention of weight-regain and greater health benefits:	CCR	
• a minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensity or an equivalent combination of both, and muscle strengthening activities involving major muscle groups on 2 non-consecutive days/week;		
• minimised sedentary, screen or sitting time.		
Physical activity includes leisure time physical activity, transportation such as walking or cycling, occupational work, household chores, games, sports or planned exercise, in the context of daily, family and community activities.	CPP	
Daily, 10000 steps is ideal, including activities of daily living and 30 minutes of structured physical activity or around 3000 steps.		
Structuring of recommended activities need to consider women's and family routines as well as cultural preferences.		

Table 6 (continued)

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Behavioural interventions		
Lifestyle interventions could include behavioural strategies such as goal-setting, self-monitoring, stimulus control, problem solving, assertiveness training, slower eating, reinforcing changes and relapse prevention, to optimise weight management healthy lifestyle and emotional wellbeing in women with PCOS.	CCR	<ul style="list-style-type: none"> To identify behavioural and cognitive strategies that should be targeted in women with PCOS, more observational research that characterises women's use of self-management strategies is needed. To aid replication and interpretation of findings, RCTs must clearly define the theoretical frameworks and behavioural components used in intervention design.
Comprehensive health behavioural or cognitive behavioural interventions could be considered to increase support, engagement, retention, adherence and maintenance of healthy lifestyle and improve health outcomes in women with PCOS.	CPP	
Assessment and treatment of infertility (as it relates to alcohol and smoking use)		
Cardiovascular disease risk (as it relates to alcohol and smoking use)	CPP	<ul style="list-style-type: none"> Determine whether women with PCOS are at a higher risk of alcohol and smoking-related infertility complications (with a focus on anovulatory infertility) when compared to women without PCOS. Determine whether women with PCOS are at a higher risk of smoking-related CVD complications when compared to women without PCOS.
Factors such as blood glucose, weight, blood pressure, smoking, alcohol, diet, exercise, sleep and mental, emotional and sexual health need to be optimised in women with PCOS, to improve reproductive and obstetric outcomes, aligned with recommendations in the general population.	CCR	
If screening reveals CVD risk factors including obesity, cigarette smoking, dyslipidaemia, hypertension, impaired glucose tolerance and lack of physical activity, women with PCOS should be considered at increased risk of CVD.	CCR	
Quality of life		
Health professionals and women should be aware of the adverse impact of PCOS on quality of life.	CCR	<ul style="list-style-type: none"> Validate QoL tools longitudinally to identify clinically meaningful differences in QoL scores.
Health professionals should capture and consider perceptions of symptoms, impact on quality of life and personal priorities for care to improve patient outcomes.	CCR	
The PCOS quality of life tool (PCOSQ), or the modified PCOSQ, may be useful clinically to highlight PCOS features causing greatest distress, and to evaluate treatment outcomes on women's subjective PCOS health concerns.	CPP	

Table 6 (continued)

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Depression and anxiety symptoms, screening and treatment		
Psychosexual function		
Body image		
Eating disorders and disordered eating		
Health professionals should be aware that in PCOS, there is a high prevalence of moderate to severe anxiety and depressive symptoms in adults; and a likely increased prevalence in adolescents.	CCR	<ul style="list-style-type: none"> To determine accurate prevalence of psychological conditions in PCOS, more adequately powered cross-sectional studies using structured diagnostic interviews administered by appropriately qualified professionals are required. Future research should consider the efficacy of different types of psychological interventions in PCOS, with a focus on how changes to mental health symptoms influence engagement with lifestyle change. In particular, the development of a PCOS specific CBT program, tailored to meet the specific mental health needs of women with PCOS is warrant.
Anxiety and depressive symptoms should be routinely screened in all adolescents and women with PCOS at diagnosis. If the screen for these symptoms and/or other aspects of emotional wellbeing is positive, further assessment and/or referral for assessment and treatment should be completed by suitably qualified health professionals, informed by regional guidelines.	CCR	
If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered in PCOS, informed by regional clinical practice guidelines.	CCR	
Factors including obesity, infertility, hirsutism need consideration along with use of hormonal medications in PCOS, as they may independently exacerbate depressive and anxiety symptoms and other aspects of emotional wellbeing.	CPP	
All health professionals should be aware of the increased prevalence of psychosexual dysfunction and should consider exploring how features of psychohirsutism and body image, impact on sex life and relationships in PCOS.	CCR	
If psychosexual dysfunction is suspected, tools such as the Female Sexual Function Index can be considered.	CCR	
Health professionals and women should be aware that features of PCOS can impact on body image.	CCR	
All health professionals and women should be aware of the increased prevalence of eating disorders and disordered eating associated with PCOS.	CCR	
If eating disorders and disordered eating are suspected, further assessment, referral and treatment, including psychological therapy, could be offered by appropriately trained health professionals, informed by regional clinical practice guidelines.	CCR	

Table 6 (continued)
Recommendation(s) from current guidelines^a

Category of recommendation ^b	Research gaps
Obstructive sleep apnoea (OSA)	<ul style="list-style-type: none"> To determine accurate prevalence of subclinical sleep disturbances in PCOS, more adequately powdered cross-sectional studies using validated subjective and objective sleep measures are required. While emerging evidence suggests that disturbed sleep may exacerbate IR via decreasing energy expenditure and increasing adipose tissue deposition, more research in women with PCOS is needed to confirm this hypothesis. Investigate effects of CBT interventions in women with PCOS who have disturbed sleep (outcomes of interest include food intake, metabolic rate, appetite hormones, weight, adherence to lifestyle changes and PCOS features).
Inositol	<ul style="list-style-type: none"> To reduce heterogeneity across studies investigating supplements or herbal medicine, RCTs should focus on specific populations within PCOS (i.e. age, BMI or phenotype) and adopt more consistent approaches to formulation (i.e. limit co-supplementation), dosage, intervention duration and the type of comparator used. Mechanistic studies are needed to investigate herb- or nutrient-drug interactions (with common pharmacological treatments used in PCOS) and other possible interactions with the biological processes underpinning PCOS. Research that characterises the uptake of CIM approaches by women with PCOS, including where they are sourcing information on this topic, will aid health professionals understanding of how to safely navigate the use of adjunct therapies in PCOS management.

Abbreviations: BMI Body mass index, CBT Cognitive behavioural therapy, CI/D Cardiovascular disease, DS/H Dietary approaches to stop hypertension, GI Glycaemic index, GL Glycaemic load, IR Insulin resistance, NAC N-acetyl-cysteine, PCOS Polycystic ovary syndrome, RCT Randomised controlled trial, QoL Quality of life

^a Recommendations are taken directly from the 2018 International Evidence-Based Guideline for the Assessment and Management of PCOS [18]. Does not include all recommendations, only those relevant to the findings of this review are presented

^b EBR Evidence based recommendations: Evidence sufficient to inform a recommendation made by the guideline development group. CCR Clinical Consensus Recommendations: In the absence of evidence, a clinical consensus recommendation has been made by the guideline development group. CPP Clinical Practice Points: Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or clinical consensus recommendations

Traditional, complementary and integrative medicine

The 2018 PCOS guideline includes recommendations on inositol supplementation, though do not include evidence regarding the use of other supplements, herbal medicine or other TCIM approaches, including acupuncture and yoga [18].

Vitamins, vitamin-like supplements, minerals and other supplements

The 2018 guideline highlights that inositol (including myo-inositol (MI) and di-chiro inositol) is a nutritional supplement that may be involved in insulin signalling transduction [191]. MI in particular is a key endocrine regulator that displays impaired metabolism in PCOS [191]. MI supplementation has been explored in a meta-analysis of nine RCTs ($n=496$), which showed improved metabolic profiles and reduced hyperandrogenism [191]. These findings are supported by two earlier meta-analyses, reporting improved ovulation, menstrual cyclicity, and hormonal profiles following MI supplementation [192, 193]. The 2018 PCOS guideline recommends that inositol (in any form) should be considered as an experimental therapy in PCOS management. The guideline also recognises that women participating in any form of TCIM should be encouraged to advise their health professional. However, it does not consider emerging evidence for the use of other types of TCIM in PCOS treatment as this was outside of the scope of the 2018 guideline.

Vitamins

B-group vitamins (B₁, B₆ and B₁₂), folic acid (B₉) and vitamins D, E, and K are critical for several biological processes that can affect metabolic and reproductive features of PCOS. B-group vitamins work alongside folic acid (the synthetic form of folate) to regulate homocysteine (Hcy) via re-methylation of Hcy to methionine [194]. Hcy is an amino acid that confers an increased risk of CVD at high levels, and which is often deranged in women with PCOS [195], likely related to a higher prevalence of folate deficiency [196–198]. One RCT explored the use of B-group vitamins combined with folic acid in 60 women with PCOS, and reported a reduction in the Hcy increasing effect of metformin [198]. Folic acid alone has also been examined in two RCTs of women with PCOS ($n=69$ [199] and $n=81$ [200]), improving FINS, HOMA-IR, C-reactive protein, total antioxidant capacity (TAC) and glutathione with doses ≥ 5 mg/day when compared with placebo [199, 200]. Regarding vitamin D supplementation, three large-scale meta-analyses reported improvements in measures of IR (HOMA-IR [201, 202], FINS [201]), fasting glucose [201]), lipid profiles (LDL-C [201–203], TC [203] and TAG [203]) and androgens (T) [202], when compared

with placebo. While vitamin E (or tocopherol) has various reported benefits on fertility outcomes in other populations [204], and has improved androgen profiles when co-supplemented with coenzyme Q10 (CoQ10) in women with PCOS [205], to date no RCTs have examined the use of vitamin E supplements alone in PCOS. Vitamin K also has limited available literature in PCOS, with only one RCT ($n=84$) demonstrating improvements in anthropometry, insulin and androgen profiles following supplementation (90 µg/day Menaquinone-7 for eight weeks), compared with placebo [206].

Vitamin-like supplements

Vitamin-like supplements including bioflavonoids, carnitine and alpha-lipoic acid (α-LA) have well-recognised antioxidant properties and play a role in fatty acid and glucose metabolism, providing possible metabolic benefits in PCOS [207]. Bioflavonoids consist of plant-derived polyphenolic compounds, some of which have been inversely associated with METS in women with PCOS [207]. In a pilot prospective study of 12 women with PCOS, 36 mg/day of the soy isoflavone genistein for six months improved lipid profiles but not anthropometry, IR, hormonal profiles or menstrual cyclicity [208]. Carnitine, particularly the active form L-carnitine, is reported to be lower in women with PCOS and linked with hyperandrogenism, hyperinsulinaemia and reduced oocyte quality [209, 210]. One RCT explored L-carnitine use in PCOS and found beneficial effects on mental health parameters and markers of oxidative stress [211], although the integrity of these have come under scrutiny and hence should be interpreted with caution [122212]. Regarding α-LA, a small pre-post study ($n=6$) administered 1200 mg/day for 16 weeks, and reported improved IR, LDL-C and TAG, though no effects on TAC or plasma oxidation metabolites [213]. Another RCT reported improved anthropometric (BMI), metabolic (FINS and HDL-C) and reproductive (menstrual cyclicity) features in 46 women with PCOS receiving α-LA supplementation (600 mg/day for 180 days) compared with controls [214]. However, as these women were co-supplemented with 1000 mg/day D-chiro-inostiol, findings are not isolated to the effects of α-LA alone [214].

Minerals

Minerals such as calcium, zinc, selenium, magnesium and chromium picolinate (CrP) have been explored in PCOS due to their reported insulin sensitising, antioxidant and anti-inflammatory properties [215–217]. A small number of studies have also reported women with PCOS are at higher risk of being deficient in calcium [218], zinc [215, 217] and selenium [195]. A recent systematic

review (six RCTs) reported that vitamin D and calcium co-supplementation in women with PCOS improved lipid and androgen profiles, follicular health and menstrual cyclicity [219]. While these findings are promising, it is difficult to attribute benefits to calcium alone, given calcium is often co-supplemented with vitamin D due to their complementary mechanisms of action. One systematic review (five RCTs) in PCOS reported zinc (often co-supplemented with other nutrients such as calcium, vitamin D and magnesium), improved HOMA-IR, lipids, T, FSH and DHEAS [220] compared to placebo. Another systematic review (five RCTs) examining selenium supplementation reported reduced IR, oxidative stress and inflammation, while results for anthropometry, lipids, androgens and hirsutism were inconsistent [221]. Regarding magnesium (an intracellular cation involved in insulin metabolism), while supplementation in PCOS has been associated with reduced IR in observational research [222], these findings are not supported by data from RCTs, with considerable inconsistencies between studies [222]. Two meta-analyses examined CrP in women with PCOS [223, 224]. While one reported that CrP supplementation reduced BMI, FINS and free testosterone [223], the other reported decreased IR, but not BMI, and increased levels of T [224].

Other supplements

Other supplements purported to provide a range of antioxidant and anti-inflammatory benefits, including omega-3 fatty acids, N-acetyl-cysteine (NAC), CoQ10, probiotics, quercetin, resveratrol and melatonin have been explored in PCOS. A meta-analysis (nine RCTs) of women with PCOS ($n=591$) receiving omega-3 supplementation reported reductions in HOMA-IR, TC, TAG and LDL-C, though showed no effect on other metabolic parameters or T [225]. In a meta-analysis of eight RCTs ($n=910$) examining NAC supplementation (the acylated form of L-cysteine), researchers reported improved glucose regulation and a greater likelihood of conception and livebirths in women with PCOS compared with placebo [226]. In a single RCT ($n=60$) CoQ10 supplementation (100 mg/day for 12 weeks) improved fasting glucose and insulin, HOMA-IR, insulin sensitivity index and TC, compared with the placebo group [227]. Two meta-analyses reported probiotics improved FAI, SHBG, IR and blood lipids, with no differences in weight or hirsutism between intervention and placebo groups [228, 229]. These findings may be linked to lower microbial diversity and increased intestinal permeability in women with PCOS [230, 231]. In regards to quercetin and resveratrol, which are both food derived polyphenols with a strong antioxidant capacity, one systematic review (three experimental studies, $n=246$ women with PCOS) reported

quercetin supplementation improved measures of IR and testosterone levels, but not anthropometry compared with placebo [232]. Similarly, one RCT in women with PCOS ($n=61$) reported resveratrol (800–1500 mg/day for four days) improved androgen and metabolic profiles and oocyte and embryo quality compared with placebo [233]. Finally, a systematic review (two RCTs and one cell-culture study) investigating the effects of melatonin supplementation in women with PCOS using assisted reproductive technologies reported melatonin significantly increased clinical pregnancy rates but not live birth rates [172]. A more recent RCT ($n=56$) reported improved levels of T, hirsutism, inflammatory and oxidative stress profiles in women receiving 10 g melatonin/day for 12 weeks, compared with placebo [234].

Herbal medicine

To date the most recent and comprehensive review (Cochrane review including five RCTs and $n=414$ women with PCOS) investigating the effects of herbal medicine on reproductive outcomes, reported no difference between the use of Chinese herbal medicine (CHM) and clomiphene for pregnancy rates, and limited evidence of increased pregnancy rate for CHM with clomiphene compared with clomiphene alone [235]. This review concluded that there was inadequate evidence to promote the use of CHM for the treatment of subfertility in women with PCOS [235]. Similarly, a smaller systematic review (five studies) investigating the effects of four herbal medicines (green tea, cinnamon, spearmint and black cohosh) on menstrual regularity in PCOS, found limited high-quality evidence from RCTs to support their clinical use and concluded that evidence for safety was lacking [236].

More recently, a number of small RCTs investigating metabolic and reproductive effects of a range of herbal medicines have been published. Curcumin, an active compound in turmeric (*Curcuma longa*), may exert hypoglycemic effects via a number of mechanisms, including attenuation of circulating levels of tumor necrosis factor- α [237]. One RCT ($n=67$) reported decreased levels of fasting glucose following supplementation compared with placebo [238], while another ($n=51$) which used a lower dose (1000 mg/day versus 1500 mg/day) and shorter duration (six weeks versus 12 weeks), reported no between group differences for fasting glucose, HOMA-IR or lipids [239]. *Salvia officinalis* or sage contains multiple active compounds that display antioxidant effects and therefore effects on glucose metabolism and insulin sensitivity [240]. One RCT ($n=72$) reported consuming sage extract for eight weeks improved IR and reduced BMI, with no effects on WHR or blood pressure [241]. *Foeniculum vulgare*

or fennel may provide protective effects on hormonal abnormalities in PCOS via its actions as a phytoestrogen [242]. One RCT ($n=55$) reported that six months of fennel tea and dry cupping was as effective as metformin for reducing BMI and menstrual cycle length [243]. *Glycyrrhiza glabra* or licorice contains active phytochemicals including isoflavane and glabridin, which have been shown to have antiandrogenic effects [244]. Two experimental studies in healthy women ($n=9$) [245] and women with PCOS ($n=32$) [246] reported that 3.5 g/day of licorice extract decreased T [245] and reduced side effects of spironolactone [246]. *Mentha spicata* (spearmint), *Zingiber officinale Roscoe* (ginger), *Cinnamomum cassia* (cinnamon) and *Citrus sinensis* (citrus) have been shown to exert anti-inflammatory and hypoglycemic effects [247–250]. One RCT in infertile women with PCOS ($n=60$) comparing the effects of a herbal mixture (citrus, ginger, cinnamon and spearmint) with clomiphene citrate (CC), herbal mixture alone, or CC alone reported that the herbal mixture, with or without CC, improved circulating antioxidant levels, IR and fasting blood glucose, but not menstrual regularity when compared to CC alone [251]. While observations from emerging research are promising, to support the safe translation of findings into the clinical setting there is a clear need for larger clinical trials investigating the efficacy and safety of herbal medicine use in PCOS.

Other traditional, complimentary and integrative medicine approaches

Acupuncture may provide beneficial impacts on sympathetic function [252] and ovarian blood flow [253] in women with PCOS. A recent meta-analysis of 22 RCTs ($n=2315$ women with PCOS) reported recovery of the menstrual period in the acupuncture group when compared with placebo, but no evidence for differences between groups in terms of live birth, pregnancy and ovulation [254]. While an earlier meta-analysis reported a significant reduction in BMI following acupuncture use, this was mainly due to one RCT ($n=80$) which compared acupuncture and the oral contraceptive pill to the oral contraceptive pill alone [255]. When this study was removed, the pooled analysis was no longer significant [255].

Yoga gymnastics have been recommended as an example of moderate physical activity in the 2018 evidence-based PCOS guideline [18]. However, as yoga is considered a mind-body therapy that incorporates aspects of meditation, it may provide additional benefits beyond those gained through other forms of exercise [256]. While one systematic review (16 observational and experimental studies, $n=365$ women with

PCOS) reported yoga may provide a range of psychological, reproductive and metabolic benefits, no meta-analysis was performed and a limited summary of included studies made it difficult to confirm findings [257]. A more recent systematic review (11 experimental studies) included a meta-analysis of two RCTs and found that yoga significantly decreased clinical hyperandrogenism, menstrual irregularity and fasting glucose and insulin [258]. Lastly, findings from a recent RCT ($n=67$ women with PCOS) suggests that 90 minutes of yoga per day for six weeks can significantly reduce hirsutism, waist and hip circumference when compared to controls [259]. Please see Table 5 for a summary of available evidence from meta-analyses and experimental studies investigating the effects of TCIM on PCOS outcomes.

Summary of findings and research gaps

The 2018 International Evidence-Based Guideline for the Assessment and Management of PCOS highlights lifestyle (diet, physical activity and/or behavioural) management as the primary initial treatment strategy [18]. It is important to consider that the definition of lifestyle management may warrant expansion consistent with the whole person model of healthcare provision, which may include care addressing psychological and sleep interventions, as well as a range of TCIM approaches [20]. In line with patient interest [31–35], and to assist women and healthcare providers in understanding the evidence to aid safe implementation of adjunct therapies, rigorous assessment of the evidence for these alternative lifestyle strategies in PCOS management is warranted. Using a holistic definition of patient care, this review has summarised evidence to date on the traditional components of lifestyle change (diet, physical activity and behavioural change), psychological interventions and non-pharmacological strategies (sleep, supplements, herbal medicine and other TCIM approaches). Table 6 provides a overview of current guideline recommendations alongside the key findings from this review, summarising the identified research gaps that need to be addressed before evidence-based recommendations for clinical practice can be updated.

With regards to traditional lifestyle treatment, the majority of studies focussed on weight loss as a primary treatment goal. This indicates more research is warranted to understand the role of diet and exercise in lean women and/or in weight gain prevention. RCTs using lifestyle interventions under isocaloric conditions that investigate effects on IR, body composition and androgens independent of weight loss are needed. Given the high risk of failure with long-term weight management [9, 37, 40, 261] and high attrition in weight loss trials in

PCOS [13], exploring interventions that focus on weight neural messaging around dietary quality and physical activity may also aid in optimising engagement, adherence and sustainability of lifestyle interventions. Future research should also identify subgroups who respond more favourably to weight loss [45, 53], to aid provision of a more targeted and personalised treatment approach.

With regards to diet strategies, there is a need for more research understanding the impact of low GI/GL diets on androgen status, as well as the biological mechanisms by which low GI/GL diets may impact reproductive and cardiometabolic outcomes associated with PCOS. With regards to physical activity, additional longer-term studies are required to guide exercise prescription in PCOS, although promising evidence supports the provision of vigorous aerobic exercise performed under supervised conditions (i.e. through referral to an exercise physiologist). While behavioural interventions are essential for long term sustainability of dietary and physical activity change, research in PCOS is scarce and interventions are not well defined. Future research should incorporate appropriate theoretical frameworks and clearly outline behavioural components utilised. This will aid intervention duplication and tailoring of active elements to ensure relevance in women with PCOS.

There is currently a lack of research investigating whether women with PCOS are at a higher risk of alcohol and smoking-related complications. This is particularly relevant given the well-established relationship between higher alcohol and cigarette use and rates of depression and anxiety in the general population [262–265]. There is also a need to better understand the relationship between alcohol intake and reproductive outcomes (particularly anovulatory infertility) [139], as safe alcohol limits in PCOS is currently unknown [139].

With regards to psychological interventions, the current evidence base for prevalence of mental health concerns in PCOS relies heavily on symptom prevalence. More adequately powered, gold standard prevalence studies using structured diagnostic interviews administered by appropriately qualified professionals are needed. While QoL has recently been highlighted as a core outcome in PCOS research [266], the application of QoL tools in clinical care is still unclear, with research yet to validate QoL tools longitudinally or identify clinically meaningful differences in QoL scores. The emerging evidence showing support for the use of CBT in PCOS [152–154] highlights an opportunity for tailoring of this psychological intervention to meet the specific mental health needs of women with PCOS, with a focus on how management of mental health symptoms affect lifestyle modifications. CBT that incorporates elements of

mindfulness-based stress reduction also warrants further investigation.

Future research in PCOS and sleep disorders should include more high-quality research in subclinical disorders using objective sleep measures (polysomnography and actigraphy). Future work should also consider emerging evidence showing that disturbed sleep can detrimentally effect energy expenditure, which may increase adipose tissue deposition and exacerbate IR [164, 184, 186, 267–271], thereby worsening the presentation of PCOS. Further, a consideration of how sleep disturbance can reduce engagement with positive lifestyle changes, for example through the disruption of appetite regulation [272, 273] or via contributing to poor mental health outcomes [190, 274], is warranted. CBT interventions including elements of stimulus control and psychoeducation are effective non-pharmacological treatments for both clinical sleep disorders and sleep disturbances in the general population [275–277]. RCTs in women with PCOS that investigate effects of CBT on dietary intake, energy metabolism, appetite regulation, anthropometry, adherence to lifestyle changes and PCOS features are required.

With regards to TCIM, there is a vast array of literature suggesting some beneficial effects of vitamins (B-group vitamins, folate, vitamins D, E and K), vitamin-like nutrients (bioflavonoids, carnitine and α-LA), minerals (calcium, zinc, selenium, and CrP) and other formulations (such as melatonin, omega-3 fatty acids, probiotics, NAC and cinnamon) in PCOS [278]. However, the quality of evidence across studies ranges from meta-analyses of RCTs (vitamin D, omega-3 fatty acids and NAC) to single retrospective observational studies (vitamin K and carnitine). In addition, heterogeneity in results related to factors including variable PCOS presentation and study methodology make it difficult to draw definite conclusions. Future research should focus on specific populations within PCOS, for example age, BMI or phenotype (factors which substantially affect nutrient sufficiency), and outline more consistent approaches to supplement formulation, dosage, intervention duration and type of comparator used. Mechanistic studies are also needed to investigate herb- or nutrient-drug interactions (with common pharmacological treatments used in PCOS) and other possible interactions with the biological processes underpinning PCOS. In regards to acupuncture and yoga, more sufficiently powered RCTs are needed to determine clinical relevance and integration into PCOS management is not yet warranted.

While current research is not sufficiently robust to support integration of TCIM into routine clinical practice, healthcare providers should broaden their knowledge pertaining to how these therapies can be safely and

appropriately utilised as adjuncts to conventional medical management [279–281]. TCIM is frequently used by women, with uptake of TCIM approaches increasing steadily over the past 10 years [31–35]. In women with PCOS, one cross-sectional study ($n=493$) found that 70% reported use of TCIM, namely nutritional and herbal supplements [282]. The most common reasons for use were to treat PCOS symptoms, improve general wellbeing and reduce depression. Of the women using TCIM, 77% had consulted with a complementary practitioner (acupuncturists, chiropractors, naturopaths and massage therapists) [282]. While the study did not report participants engagement with medical physicians, research in the general population has shown that patients are resistant to discuss TCIM use with their consulting physician [283–288]. Qualified health-care providers should be involved in TCIM discussions to help ensure appropriate use, maximise possible benefits and minimize potential harm [289]. For example, to sustain patient engagement in women who express the desire to experiment with supplementation, health-care providers could consider inositol supplementation, using a nuanced and case-specific approach that encapsulates the variety of pathologies in PCOS.

When considering all of the research summarised here, across traditional lifestyle, psychological, sleep and TCIM interventions, there is a clear need for more real-world PCOS research. This involves the translation of findings from clinical trials (where highly selected populations, intensive treatment protocols and expert multidisciplinary teams provide an ideal research setting), into the heterogeneous situations that face clinicians [290–292]. Health professionals provide care to women from diverse social contexts, are often restrained by finite resources and are required to juggle many competing demands for their time [290–292]. While some barriers to implementation, including time, resource and access issues are considered in the current PCOS guideline, they were generated by the guideline development groups and research is needed to validate and clarify their proposed concerns. Real-world research is required to: a) fully understand whether lifestyle recommendations can be practically integrated into current healthcare settings; b) tailor interventions to meet the unique needs of women with PCOS; and c) generate evidence on clinical outcomes that are of great relevance to patients and clinicians, such as live birth, miscarriage and menstrual regularity, which can be collected through routine care.

It is also important to highlight that while lifestyle management is a first-line treatment for PCOS, the addition of pharmacological therapies to further improve clinical features of hyperandrogenism, menstrual irregularity and infertility are often indicated [293]. In these instances,

prescribing physicians should consider how medical management and lifestyle change can be used in adjunct to optimise treatment. For example, the use of combined oral contraceptive pills may have detrimental effects on weight gain [294] and mental health [295], which can be mitigated by appropriate lifestyle intervention. Further, the combination of lifestyle modification and metformin has been shown to lower BMI, subcutaneous adipose tissue and improve menstruation compared with lifestyle modification alone, and hence may have an additive effect on improving cardio-metabolic outcomes in high risk groups [296].

Conclusion

Using the whole person or holistic definition of health, this review has highlighted emerging areas of research that could be considered for integration into future classifications of lifestyle management in PCOS. When developing lifestyle recommendations for PCOS management, interpreting and communicating evidence not only for diet, physical activity and behavioural interventions, but also psychological, sleep and TCIM approaches, will aid clinicians to deliver patient-centred care by affording women more choice and therefore autonomy over their treatment options. This sentiment aligns with the core objectives underpinning the 2018 PCOS guideline, which sought to understand the unmet needs of women with PCOS through continuing to engage consumers in co-design of guideline development, implementation, translation and dissemination.

Abbreviations

α -LA	Alpha-lipoic acid
BMI	Body mass index
CVD	Cardiovascular disease
CHM	Chinese herbal medicine
CrP	Chromium picolinate
CoQ10	Coenzyme Q10
CBT	Cognitive behavioural therapy
DASH	Dietary Approaches to Stop Hypertension
FINS	Fasting insulin level
FSH	Follicle stimulating hormone
FAI	Free androgen index
GI	Glycaemic index
GL	Glycaemic load
HDL-C	High density lipoprotein cholesterol
Hcy	Homocysteine
IR	Insulin resistance
LDL-C	Low density lipoprotein cholesterol
LH	Luteinizing hormone
$VO_{2\max}$	Maximal rate of oxygen
METS	Metabolic syndrome
MUFA	Monounsaturated fatty acid
MI	Myo-inositol
NAC	N-acetyl-cysteine
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovary syndrome
PUFA	Polyunsaturated fatty acid
RCT	Randomised controlled trial
SHBG	Sex hormone-binding globulin
TAC	Total antioxidant capacity

TC	Total cholesterol
T	Testosterone
TCIM	Traditional, complementary and integrative medicine
TAG	Triglycerides
T2DM	Type 2 diabetes
WC	Waist circumference
WHR	Waist-hip-ratio

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SC, SL, CA, SP, RT, MG, RB, NN, CB, CE, VR, AM, SA and LM reviewed the literature and wrote the first draft of the manuscript. SC, SL, CA, SP, RT, MG, RB, NN, CB, CE, VR, AM, SA and LM revised and edited the manuscript. SC and LM conceptualised and determined the scope of the manuscript and had primary responsibility for the final content. LM supervised the review process. All authors meet ICMJE criteria for authorship and approved the final version for publication.

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REVIEW

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Lifestyle management in polycystic ovary syndrome – beyond diet and physical activity

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Abstract

Polycystic ovary syndrome (PCOS) is a common condition affecting reproductive-aged women with reproductive, metabolic and psychological consequences. Weight and lifestyle (diet, physical activity and behavioural) management are first-line therapy in international evidence-based guidelines for PCOS. While these recommend following population-level diet and physical activity guidelines, there is ongoing interest and research in the potential benefit of including psychological and sleep interventions, as well as a range of traditional, complimentary and integrative medicine (TCIM) approaches, for optimal management of PCOS. There is limited evidence to recommend a specific diet composition for PCOS with approaches including modifying protein, carbohydrate or fat quality or quantity generally having similar effects on the presentations of PCOS. With regards to physical activity, promising evidence supports the provision of vigorous aerobic exercise, which has been shown to improve body composition, cardiorespiratory fitness and insulin resistance. Psychological and sleep interventions are also important considerations, with women displaying poor emotional wellbeing and higher rates of clinical and subclinical sleep disturbance, potentially limiting their ability to make positive lifestyle change. While optimising sleep and emotional wellbeing may aid symptom management in PCOS, research exploring the efficacy of clinical interventions is lacking. Uptake of TCIM approaches, in particular supplement and herbal medicine use, by women with PCOS is growing. However, there is currently insufficient evidence to support integration into routine clinical practice. Research investigating inositol supplementation have produced the most promising findings, showing improved metabolic profiles and reduced hyperandrogenism. Findings for other supplements, herbal medicines, acupuncture and yoga is so far inconsistent, and to reduce heterogeneity more research in specific PCOS populations, (e.g. defined age and BMI ranges) and consistent approaches to intervention delivery, duration and comparators are needed. While there are a range of lifestyle components in addition to population-recommendations for diet and physical activity of potential benefit in PCOS, robust clinical trials are warranted to expand the relatively limited evidence-base regarding holistic lifestyle management. With consumer interest in holistic healthcare rising, healthcare providers will be required to broaden their knowledge pertaining to how these therapies can be safely and appropriately utilised as adjuncts to conventional medical management.

Keywords Polycystic ovary syndrome, diet, guideline, physical activity, sleep, cognitive behavioural therapy, quality of life, complementary medicine

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Introduction

Polycystic ovary syndrome (PCOS) is a common condition affecting up to 13% of reproductive-aged women [1]. It is diagnosed through the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESRHE/ASRM) criteria, requiring two of the following features: polycystic ovaries on ultrasound, oligoovulatory or anovulatory cycles and biochemical or clinical hyperandrogenism [2]. Women with PCOS experience a combination of reproductive (infertility, pregnancy complications) [3], metabolic (risk factors for and conditions of type 2 diabetes (T2DM) and cardiovascular disease (CVD)) [4, 5] and psychological (conditions including anxiety, depression, poor quality of life (QoL), disordered eating) comorbidities [6, 7].

Insulin resistance (IR) is defined as a key pathophysiological feature in PCOS, contributing to hyperandrogenism and worsening the clinical presentation of PCOS. While lean women present with IR in a form that is mechanistically different from IR caused by excess weight, overweight and obesity further exacerbate IR and consequent hyperinsulinaemia [8]. Women with PCOS also display a higher rate of weight gain over time [9] and a greater prevalence of overweight and obesity [10], which can further contribute to this worsening of IR and hence worsening of the presentation of PCOS [11]. The reason for this is unclear, but may be related to differences in intrinsic psychological and biological mechanisms [12–15], or extrinsic lifestyle factors such as diet and physical activity [16, 17]. Improving IR and excess adiposity are therefore key targets in PCOS management.

The International Evidence-Based Guideline for the Assessment and Management of PCOS [18], highlights lifestyle intervention as the primary early management strategy. Lifestyle interventions are traditionally defined as those designed to improve dietary intake or physical activity through appropriate behavioural support. In the 2018 PCOS guideline, lifestyle management is recommended for general health benefits [18]. Given that excess weight is associated with increased IR in PCOS [8], the guideline additionally promotes weight management, defined as: 1) weight gain prevention in all women with PCOS, and 2) achieving and maintaining modest weight loss in women with excess weight [18].

Lifestyle interventions in PCOS management can also be viewed as a broader construct beyond physical health. Since the emergence of the biopsychosocial model of healthcare in 1977, health disciplines have seen a gradual shift away from the classical biomedical model (where health is defined as the ‘absence of disease’) towards whole person or holistic care [19]. This is an approach that reflects many facets of the patient context, via integrating care that addresses biological, psychological, social, spiritual and ecological

aspects [20]. It therefore requires a range of different treatment strategies to improve health. Provision of whole person or holistic care has been identified as a core objective of healthcare reforms internationally [21–23]. In line with these reforms the PCOS guideline recognises the importance of emotional wellbeing to overall health and QoL in women living with PCOS [18]. It also highlights evidence which suggests that the psychological impact associated with PCOS is under-appreciated in clinical care [4, 5], and that few women are satisfied with the mental health support they receive [6, 7]. Recommendations for appropriate screening, assessment and treatment strategies for anxiety, depression, psychosexual dysfunction, eating disorders and poor body image are provided [18]. These specific areas of emotional wellbeing are of particular concern, with research showing a higher prevalence and severity of depression and anxiety [24, 25], lower scores for satisfaction with sex life and feeling sexually attractive [26] and a higher prevalence of disordered eating and eating disorders [7] in women with PCOS. Features of PCOS, in particular hirsutism and increased weight, have also been shown to negatively affect body image [27, 28], with poor body image being strongly related to depression in women with PCOS [29, 30].

While the current PCOS guideline is comprehensive, considering all available evidence at the time of development and providing best-practice recommendations for necessary screening, risk assessment and management, it could not possibly cover all aspects of PCOS care. An International Delphi process was used to prioritise clinical questions, with consensus reached through extensive consultation with both consumers and multidisciplinary clinicians with expertise in PCOS care. Therapies, such as traditional, complementary and integrative medicine (TCIM), supplement use, sleep and meditation interventions are either briefly considered or not at all included in the 2018 PCOS guideline. Many of these therapies are novel and there is a paucity of evidence to support intervention efficacy on PCOS outcomes. However, as patient interest in these types of non-pharmacological interventions are growing [31–35], it is prudent to provide more guidance to healthcare providers in this area on their potential efficacy in PCOS. Whole person or holistic care recognises that the doctor-patient relationship should be one of open dialogue, where healthcare providers involve the patient in negotiating their care and recognises patient’s autonomy to guide treatment (Figure 1) [36].

This review provides an extensive overview of evidence to date on lifestyle strategies used to optimise management of PCOS. Using a holistic definition of patient care, this review considers the traditional components of lifestyle change (diet, physical activity and behavioural change), psychological and sleep interventions, as well as TCIM approaches (supplements, herbal medicine,

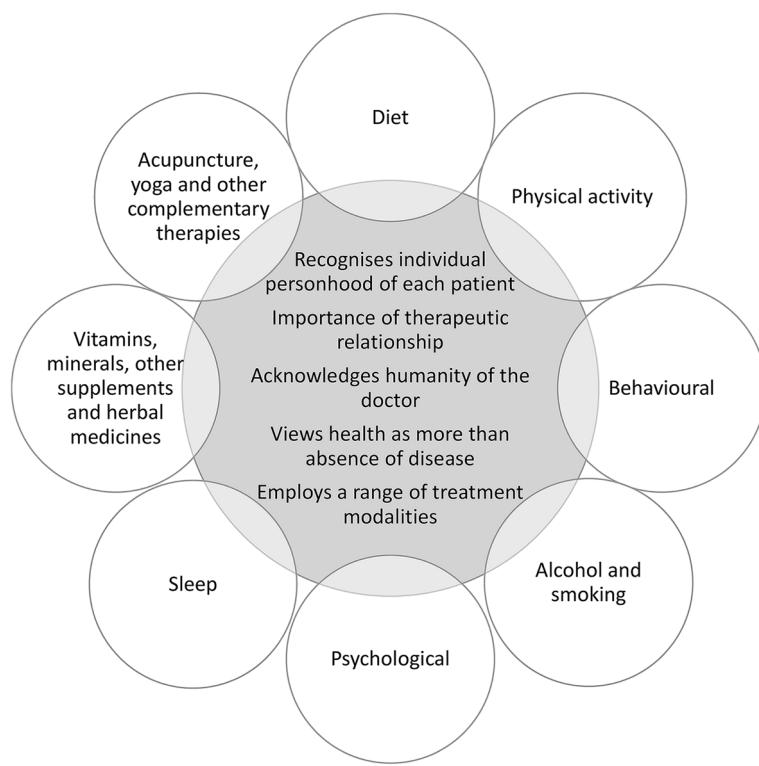


Fig. 1 Viewing lifestyle modifications through a whole person or holistic care lens. The key features of whole person or holistic care listed in the centre of the figure have been adapted from Thomas et al. [20]. ‘Recognises individual personhood’ relates to focusing on the unique needs of the person rather than the disease. ‘Importance of therapeutic relationship’ emphasises patient autonomy and responsibility. ‘Acknowledges humanity of the doctor’ considers the doctors’ ability to self-reflect on how they engage in the care of the patient. ‘Health as more than absence of disease’ incorporates the mental, emotional, physical, environmental and social needs of the patient. ‘Employs a range of treatment modalities’ promotes continuity of care across health disciplines, and while it may include traditional, complementary and integrative medicine (TCIM), TCIM is not holistic if used in isolation and without adequate integration into conventional healthcare

acupuncture and yoga). To improve translation of findings, evidence summaries are accompanied by an overview of relevant recommendations from the existing PCOS guideline. This highlights where emerging evidence supports current recommendations or provides new insights for research. As this is a narrative review, while evidence summaries include peer-reviewed journal articles identified from databases including Medline OVID, this is supplemented by expert opinion of the authors.

Traditional lifestyle and weight management

The PCOS guideline recommends the promotion of healthy lifestyle behaviours in all women with PCOS, to achieve and/or maintain a healthy weight and to optimise general health [18]. In women with excess weight, a weight loss of 5–10% is advised, aiming for an energy deficit of 30% or 500–750 kcal/day (1200–1500 kcal/day). While weight management is seen as a core component of lifestyle interventions, the guideline recognises that a healthy lifestyle provides benefits that occur independent of weight change.

A recent Cochrane review of 15 randomised controlled trials (RCT) and 498 participants, reported that lifestyle interventions compared with minimal intervention or usual care, significantly reduces weight (kg) and body mass index (BMI) and improves secondary reproductive outcomes such as free androgen index (FAI), testosterone (T), sex hormone-binding globulin (SHBG) and hirsutism (Ferriman-Gallwey score) [37]. In terms of metabolic outcomes, lifestyle intervention resulted in significant reductions in total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and fasting insulin (FINS). These findings are largely similar to that of other systematic reviews [38–41]. While no studies in the Cochrane review assessed clinical reproductive outcomes [37], individual trials that were not included in the review have reported that lifestyle interventions resulting in modest weight loss (2–5% total body weight) improve ovulation and menstrual regularity [42–45]. Losing >5% of weight is additionally associated with being able to conceive, having live births, reduction of ovarian volume and reduction in the number of follicles [46–52].

Table 1 Reviews and experimental studies investigating the effects of diet on polycystic ovary syndrome outcomes

Dietary intervention	N study design	N studies; N participants	Main findings ^a	References
Low CHO	2 SR/MA (27 RCT total - 18 RCT using low CHO diet) [56, 85] 1 SR (5 RCT total - 1 RCT using low CHO diet) [16]	14; 901	Low CHO compared with control diets [56]: ↓ BMI, HOMA-IR, TC, LDL-C ↑ SHBG ↔ LH, T, HDL-C Dietary intervention ↓ HOMA-IR, FINS, FGL, BMI, BW, WC compared with minimal intervention, and subgroup analysis showed no additional benefits for low CHO diets [85] Weight loss improved the presentation of PCOS regardless of dietary composition, with no subtle differences observed for low CHO diets [16]	Shang et al. 2020 [85] Zhang et al. 2019 [56] Moran et al. 2013 [16]
Low GI	1 SR/MA (10 RCT total - 8 RCT using low GI diet) [55] 1 SR (5 RCT total - 1 RCT using low GI diet) [16] 4 Pre-post prospective [61, 76, 77, 118] 1 RCT [78]	16 ^b ; 582	High GI compared with low GI diets [55]: ↓ HOMA-IR, FINS, TC, LDL-C, TAG, WC, T ↔ FGL, HDL-C, BW, FAI Low GI diets had greater improvements in IR, TC, HDL-C, fibrinogen, menstrual regularity and QoL [16] Low GI diets followed for ≥ 12 weeks: ↓ BW [76, 77], BMI [76, 77], BFM [77], WC [77], WHR [77], FINS [76, 77], FGL [77], TC [77], LDL-C [77], TAG [77], T [77], LH [77], androstenedione [77], prolactin [77] ↑ insulin sensitivity (HOMA2-IS) [61], synthesis of predominantly anti-inflammatory eicosanoid mediators (e.g. 16(R)/16(S)-HETE, 13(S)-HODE, 9(S)-HODE, 15(S)-HETE, 12(S)-HETE, 5(S)-oxoETE, 5(S)-HETE) [118], fasting glucagon (higher glucagon levels associated with lower levels of self-reported hunger) [78]	Kazemi et al. 2020 [55] Moran et al. 2013 [16] Shishrehgar et al. 2019 [76] Barr et al. 2016 [61] Szczuko et al. 2018 [77] Szczuko et al. 2017 [118] Hoover et al. 2021 [78]
High protein	1 SR (5 RCT total - 3 RCT using high protein diet) [16] 2 Pre-post prospective [73, 74] 6 RCT [92, 94–97]	11; 308	High protein diets improve depression and self-esteem [16] ↓ BFM [74, 97], BW [73, 74, 97], BMI [73, 74], WC [73, 74, 97], WHR [73], FINS [74, 98], FGL [97], HOMA-IR [73, 98], TAG [73], VLDL-C [73], T [73, 98], Ferriman-Gallwey scores [73] High protein and standard/low protein diet ↓ BW [92, 94, 95], BMI [92, 94, 95], BFM [95], WC [92, 94], WHR [94], FINS [95, 96], HOMA-IR [95], TAG [96], LDL-C [98] CRP [96], MPA [96], leptin [95], T [98], DHEAS [98], FAI [98] and there was ↔ between high and standard/low protein diets	Moran et al. 2013 [16] Moran et al. 2010 [96] Moran et al. 2004 [95] Sorensen et al. 2012 [97] Toscani et al. 2011 [92] Nadjarzadeh et al. 2021 [94] Phy et al. 2015 [73] Pohlmeier et al. 2014 [74] Mehrabani et al. 2012 [98]
Low fat	1 SR/MA (19 RCT total - 1 RCT using low fat diet) [85] 1 SR (5 RCT total - 1 RCT using low fat diet) [16] 1 RCT [107]	3; 137	Dietary intervention ↓ HOMA-IR, FINS, FGL, BMI, BW, WC compared with minimal intervention, and subgroup analysis showed no additional benefits for low fat diets [85] Weight loss improved the presentation of PCOS regardless of dietary composition, with no subtle differences observed for low fat diets [16] Low fat (25% E fat) ↓ BW, BFM, BMI though there was ↔ between low fat and standard fat (35% E fat) diets [107]	Shang et al. 2020 [85] Moran et al. 2013 [16] Wong et al. 2016 [107]

Table 1 (continued)

Dietary intervention	N study design	N studies; N participants	Main findings ^a	References
Fatty acids	1 SR (5 RCT total - 1 RCT using MUFA enriched diet) [16] 3 RCT [86, 102, 105] 1 controlled trial (not randomised) [103] ^c	5; 146	MUFA enriched diets may produce greater weight loss when compared to other dietary patterns [16] MUFA enriched compared with PUFA enriched diets ↓ FGL [103], glucose response to OGTT [103], HgBA1 [102] Diets with a higher alpha-linolenic acid, lower omega-6/omega-3 ratio and saturated fat content ↓ TAG, TC/HDL-C, LDL-C-/HDL-C, TAG/HDL-C, and HOMA-IR [105] High total and saturated fat meals compared with high fibre low fat meals produce prolonged ↓ in T [86]	Moran et al. 2013 [16] Yahay et al. 2021 [105] Kalgaonkar et al. 2011 [102] Kasim-Karakas et al. 2004 [103] Katcher et al. 2009 [86]
DASH	1 SR/MA (19 RCT total - 4 RCT using DASH diet) [85]	4; 228	Dietary intervention ↓ HOMA-IR, FINS, FGL, BMI, BW, WC compared with minimal intervention, and subgroup analysis showed DASH diet was more effective at improving insulin sensitivity [85]	Shang et al. 2020 [85]
Plant-based	3 RCT	3; 108	Plant-based (35% animal protein, 35% textured soy protein, 30% vegetable protein) compared to control (70% animal protein, 30% vegetable protein) ↓ BMI, FGL, FINS, TAG, HOMA-IR, T, MDA and ↑ QUICKI [67] Plant-based and control diets (calorie restriction [68] and general dietary recommendations [72]) ↓ BW [68], HOMA-IR [72], T [72], LH/FSH [72] and there was ↔ between plant-based and control diets	Turner-McGrievy et al. 2014 [68] Kazemi et al. 2020 [72] Karamali et al. 2018 [67]
Meal pattern	1 RCT	1; 40	6 meals/day compared with 3 meals/day: ↓ FINS ↑ post-OGTT insulin sensitivity	Papakonstantinou et al. 2016 [111]
Meal timing	1 RCT	1; 60	Consuming a high kilojoule breakfast compared with a high kilojoule dinner: ↓ FGL, FINS, HOMA-IR, T ↑ SHBG	Jakubowicz et al. 2013 [66]

Abbreviations: ↑ significant increase ($P \leq 0.05$), ↓ significant decrease ($P \leq 0.05$), ↔ no significant change, *BFM* Body fat mass, *BMI* Body mass index, *BW* Body weight, *CHO* Carbohydrate, *CRP* C-reactive protein, *DHEAS* Dehydroepiandrosterone-sulfate, *E* Energy, *FAI* Free androgen index, *FBM* Fat body mass, *FGL* Fasting glucose level, *FINS* Fasting insulin level, *FSH* Follicle stimulating hormone, *G* Glycaemic index, *HDL-C* High density lipoprotein cholesterol, *HOMA-B* Homeostatic Model Assessment for Beta Cells, *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance, *IR* Insulin resistance, *LDL-C* Low density lipoprotein cholesterol, *LH* Luteinizing hormone, *MDA* Malondialdehyde, *MUFA* Monounsaturated fatty acid, *OGTT* Oral glucose tolerance test, *PCOS* Polycystic ovary syndrome, *PUFA* Polyunsaturated fatty acid, *QoL* Quality of life, *QUICKI* Quantitative insulin sensitivity check index, *SHBG* Sex hormone-binding globulin, *T* Testosterone, *TAG* Triglycerides, *TC* Total cholesterol, *VLDL-C* Very low density lipoprotein cholesterol, *WC* Waist circumference, *WHR* Waist hip ratio

^a Summarises commonly used measures in PCOS research and does not report on all measured outcomes. For prospective pre-post studies significant changes from baseline are reported. For RCTs significant changes between intervention(s) and control are reported. Only experimental studies not already summarised in included systematic reviews/meta-analysis are presented

^b Shishregar et al. 2019 total study population included 62 women though only findings for the women with PCOS ($n=28$) are included

^c While habitual diet (control) was not enriched with MUFA, nutritional analysis showed that it was rich in oleic acid

Although weight loss has shown clear benefits to PCOS outcomes, including not only on reproductive function, but also glucoregulatory status, androgen status and lipid profiles [42–52], there are varying degrees of responsiveness to weight loss in terms of improvement of PCOS symptoms. One study by Pasquali et al. [53] found that when women achieved similar levels of weight loss (>5% weight) only one-third displayed a full recovery from PCOS, with the remainder showing

only partial or no recovery. Higher waist circumference (WC), waist-hip-ratio (WHR) and androstenedione at baseline were associated with a poorer chance of successful outcomes [53], suggesting that central adiposity and more severe hyperandrogenism may predict responsiveness to weight loss interventions in PCOS. Huber-Buchholz et al. [45] also reported women who achieve greater reductions in central fat and insulin sensitivity show greater symptom improvement with

weight loss. This suggests that lifestyle interventions which simultaneously reduce IR and improve body composition (namely fat distribution), may help to optimise outcomes in PCOS management independent of changes in weight status.

Diet

The 2018 PCOS guideline recognises there is insufficient evidence to suggest that any specific dietary approaches provide greater benefits on health outcomes [18]. Dietary recommendations may take on a variety of balanced dietary strategies according to the individual's lifestyle needs and preferences, as per general population recommendations [18]. This advice is based on a systematic review comparing different dietary compositions (e.g. low carbohydrate, low glycaemic index (GI) and glycaemic load (GL), high protein, monounsaturated fatty acid (MUFA) enriched and fat counting diets) to best manage PCOS, identifying minimal differences between diets on anthropometric outcomes, concluding weight loss improves the presentation of PCOS regardless of dietary composition [16, 54]. There is now an emerging body of evidence that suggests a range of dietary strategies may produce favourable effects on PCOS features that occur independent of weight loss. It is important that the emerging findings from these studies are thoroughly considered to support consumer and health professional interests. To summarise current evidence this review has grouped diets in terms of those that modify carbohydrates, protein and fat, as well as specific dietary patterns.

Carbohydrates

The use of altered carbohydrate composition remains the most researched dietary approach for PCOS management. Two systematic reviews published after guideline inception support altered carbohydrate intake to improve intermediate markers of PCOS [55, 56], finding that altering carbohydrate type, as opposed to content, is preferable to better manage PCOS [55]. RCTs [57–72] and pre-post intervention studies [73–80] demonstrate that following a low GI/GL diet for at least eight weeks significantly reduces WC [55, 73, 74] and BMI when compared to high GI/GL [56] or a regular diet [73–76], although levels of weight loss are generally comparable to other dietary compositions [59, 60, 72, 74]. These reductions are proposed to be a result of decreased hunger, which may reduce energy intake and make it easier to follow dietary recommendations in the long-term [78, 81–84]. Low GI/GL diets also improve insulin sensitivity and reproductive hormones (T, SHBG, FAI) compared to high carbohydrate [16, 55, 57, 79, 85] or control diets [56, 59, 73–76], contributing to improvements in reproductive function, specifically menstrual regularly [60, 79]. Lastly, low GI/GL diets can improve risk factors for T2DM and CVD, including glucose

[86, 87], TC [55, 56, 59, 75, 77], LDL-C [55, 59, 75, 85], TAG [55, 59, 73] and HDL-C [75], when compared to a regular or high GI/GL diet. It must be noted that beneficial effects of low GI/GL diets may also be attributed to proportional increases in protein and/or fat loads.

Protein

In women with PCOS higher protein intakes may be superior at suppressing androgen levels when compared to high carbohydrate diets. Postprandial research has shown that high protein meals can reduce insulin and dehydroepiandrosterone stimulation compared to meals rich in glucose [88]. Research in the general population has also shown that reduced appetite and energy intakes from low GI/GL diets are related to increased protein intakes [89, 90]. RCTs and pre-post intervention studies found that high protein diets (defined here as protein constituting $\geq 25\%$ energy [91]) consumed for at least four weeks reduce weight [12, 73, 74, 92–96], BMI [73, 74, 92, 95], WC [73, 74, 92, 97], WHR [73] and fat mass [74, 92, 97]. These reductions in anthropometric measures are accompanied by improved FINS [12, 74, 95, 98] and HOMA-IR [12, 73, 95, 98], blood lipids [12, 96], T [73, 92, 94] and hirsutism (Ferriman-Gallwey score) [73]. However, only three of these studies were able to show significant improvements in anthropometric measures [97], insulin sensitivity [98] and blood lipids [12] when compared to low/standard protein [12, 97] or control diets [98]. Only one study investigated effects on mental health outcomes and found that a high protein diet reduced depression and improved self-esteem [99].

Fats

Fatty acid composition is also an important consideration as metabolic disorders associated with PCOS can benefit from increased MUFA and polyunsaturated fatty acid (PUFA) intakes [63–65]. Postprandial research in PCOS reported prolonged reductions in T for high fat compared to low fat meals, which likely results from delayed nutrient absorption [86]. Two acute meal studies in lean and obese women with and without PCOS reported that proatherogenic inflammatory markers [100] and oxidative stress [101] were elevated, independent of but augmented by obesity, following saturated fat ingestion with this associated with worsened IR and androgens. Two experimental studies in PCOS investigated the effects of habitual walnut (PUFA rich diet) [102, 103] and almond (MUFA rich diet) [102] intake for at least six weeks and reported no differences in glucoregulatory status, lipids or androgens with the exception of HbA1c significantly decreasing in the walnut relative to the almond group. Kasim-Karakas et al. [103] reported increased fasting and postprandial glucose

(oral glucose tolerance test (OGTT)) for increased walnut intake compared to habitual (control), which they postulated may be related to the control diet being rich in oleic acid. Together these findings suggest minimal benefit for improving dietary PUFA compared to MUFA content. Two RCTs in women with PCOS investigated the effects of diets rich in olive [104, 105], canola [105] and sunflower [105] oil. Yahay et al. [105] reported 25g/day canola oil caused reductions in TAG, TC/HDL-C, LDL-C/HDL-C, TAG/HDL-C and HOMA, but not androgens, compared to 25 g/day olive and sunflower oils [105]. This may be related to the more favourable fatty acid composition of canola oil, with comparable MUFA content to olive oil, higher alpha-linolenic acid, lower omega-6/omega-3 ratio and saturated fat than both olive and sunflower oils. Douglas et al. [104] reported weight and the acute insulin response (OGTT) were lower following a eucaloric low carbohydrate compared to a eucaloric MUFA-enriched olive oil diet, suggesting that reduced carbohydrate intake may have greater glucoregulatory benefits than increased MUFA intake [104]. Lastly, two RCTs compared hypocaloric low-fat diets to a low carbohydrate [106] or low GI [107] diets, with reductions in weight [106], WC [106], body fat [106, 107], FINS [106] and FAI [106] in both groups but no difference between groups.

Dietary and eating patterns

In addition to diets that focus on specific macronutrient manipulations, there are a range of dietary patterns which have been explored in PCOS management. A systematic review (including 19 studies and 1,193 participants) published after guideline development (2020) found that the Dietary Approaches to Stop Hypertension (DASH) diet (rich in fruit, vegetables, wholegrains, nuts, legumes and low-fat dairy and with a predominantly low-GI carbohydrate profile) was the optimal choice for reducing IR [85]. RCTs in PCOS also report beneficial effects on weight [63, 64], BMI [62, 63], IR [62] and hormonal profile, including SHBG [64], androstenedione [64] and FAI [62] for a DASH compared to a control diet after 8–12 weeks. A vegetarian diet also reduced inflammatory markers (CRP, resistin and adiponectin) compared to a meat inclusive diet [80]. A vegan diet improved weight loss at three, but not six months [68], and a pulse-based diet led to similar reductions in weight, insulin sensitivity and reproductive hormones compared to a healthy control diet [72]. All of these dietary patterns are high in fibre and plant proteins, producing favourable effects on microbial diversity and encouraging production of short-chain fatty acids that possess potential anti-inflammatory actions [108, 109]. With mechanistic animal studies suggesting a possible pathophysiological role of gut microbiota in IR and

ovarian dysfunction, it is possible that metabolic and hormonal benefits associated with plant-based dietary patterns in PCOS are related to increased intakes of dietary prebiotics [110]. However, further mechanistic studies exploring the role of gut microbiota in PCOS and RCTs investigating effects of dietary prebiotics on PCOS outcomes are required.

Lastly, particular eating patterns, such as eating smaller more frequent meals across the day [111] and eating a larger breakfast and smaller dinner [66], have also been found to be beneficial for insulin sensitivity [66, 111] and androgen reductions [66]. This is an important finding, as women with PCOS are more likely to either skip breakfast or consume their breakfast and lunch later in the day [112].

Studies examining specific food items in relation to PCOS outcomes, including raw onions [65], concentrated pomegranate juice [69, 113–115] and flaxseed powder [70, 116] have yielded largely inconsistent results. A core limitation of these single food studies is that foods are never consumed alone within the diet, omitting the influence of the dietary matrix and the interactions that occur amongst dietary constituents within meals. These studies provide limited applicability in the context of formulating practical dietary recommendations [117]. Please see Table 1 for a summary of available evidence from reviews and experimental studies investigating the effects of different types of diets on PCOS outcomes.

Physical activity

The 2018 PCOS guideline recommends ≥150 minutes per week of moderate or ≥75 minutes per week of vigorous intensity exercise for weight gain prevention, and ≥250 minutes per week of moderate or ≥150 minutes per week of vigorous intensity exercise for weight loss and weight regain prevention [18]. Minimising sedentary time and the inclusion of strength training exercise for two days per week is also recommended [18].

To date the most comprehensive review in PCOS (including 27 papers from 18 trials up until June 2017) reported that exercise improved FINS, HOMA-IR, TC, LDL-C, TAG, body composition (body fat percentage and WC) and aerobic fitness ($\text{VO}_{2\text{max}}$) [119] compared with usual care or control groups. In regards to exercise type, subgroup analysis reported aerobic exercise improved BMI, WC, body fat percentage, FINS, HOMA-IR, TC, TAG and $\text{VO}_{2\text{max}}$. In contrast, while resistance training produced unfavourable effects on HDL-C (decrease) and BMI (increase), it improved other measures of anthropometry, including WC. Combined interventions (using both aerobic and resistance training) had no effect on any of the measured markers. Subgroup analysis also found that more outcomes improved when

Table 2 Meta-analyses investigating the effects of different types of exercise on polycystic ovary syndrome outcomes

Physical activity intervention	N reviews; N studies; N participants	Main findings ^a	References
Aerobic exercise	4; 48; 1518	↓ WC [119, 121, 124], BMI [119, 122, 124], BF% [119], HOMA-IR [119, 121, 122, 124], TC [119, 124], FINS [119, 124], TAG [119], LDL-C [119], RHR [119] ↑ VO _{2peak/max} [119, 121, 124] ↔ BMI [121], BW [119, 124], HDL-C [124], LDL-C [124], TAG [124], FGL [119, 124], BP [119], HOMA-IR [122], FAI [119, 121, 122], T [119, 122], SHBG [119], E2 [119], LH [119, 122], FSH [119, 122]	Patten et al. 2020 [121] dos Santos et al. 2020 [122] Richards et al. 2021 [124] Kite et al. 2019 [119]
Resistance training	2; 14; 505	↓ WC [119], HOMA-IR [121], FINS [119], HDL-C [119], FAI [121] ↑ BMI [119] ↔ BW [119], BF% [119], FGL [119], HOMA-IR [119], TAG [119], TC [119], LDL-C [119], VO _{2max/peak} [119], RHR [119], FAI [119], T [119], SHBG [119], E2 [119], LH [119], FSH [119]	Patten et al. 2020 [121] Kite et al. 2019 [119]
Combined aerobic and resistance training ^b	2; 3; 59	↔ BMI [119, 122], WC [119], HOMA-IR [119, 122], FINS [119], FGL [119], BP [119], TAG [119], TC [119], LDL-C [119], HDL-C [119], RHR [119], T [119, 122], E2 [119], LH [119], FSH [119]	Kite et al. 2019 [119] dos Santos et al. 2020 [122]
High intensity interval training	2; 11; 373	↓ BMI [123], WHR [123], HOMA-IR [123, 124] ↔ BF% [123], BMI [124], BW [124], WC [124], TC [123, 124], LDL-C [123, 124], TAG [124], FINS [123, 124], FGL [124], HDL-C [124], VO _{2max} [124]	Richards et al. 2021 [124] dos Santos et al. 2021 [123]

Abbreviations: ↑ significant increase ($P \leq 0.05$), ↓ significant decrease ($P \leq 0.05$), ↔ no significant change, BF% Percent body fat, BMI Body mass index, BW Body weight, BP Blood pressure, E2 Estradiol, FGL Fasting glucose level, FAI Free androgen index, FINS Fasting insulin, FSH Follicle stimulating hormone, HOMA-IR Homeostatic assessment of insulin resistance, LDL-C Low density lipoprotein cholesterol, LH Luteinizing hormone, PCOS Polycystic ovary syndrome, RHR Resting heart rate, SHBG Sex hormone-binding globulin, T Testosterone, TAG Triglycerides, TC Total cholesterol, VO_{2max} Maximal oxygen uptake, VO_{2peak} Peak oxygen uptake, WC Waist circumference, WHR Waist hip ratio

^a Significant findings from meta-analyses when comparing exercise groups to control

^b Subgroup analyses compared different types of exercise; only 1 study included for combined exercise

interventions were supervised, of a shorter duration (≤ 12 weeks) and were conducted in women who were above a healthy weight [119].

Three more recent systematic reviews have looked at the effects of specific types of exercise on PCOS outcomes [120–122]. These reviews found that vigorous aerobic exercise can improve measures of insulin responsiveness and resistance, including HOMA-IR [121] and the insulin sensitivity index [120]; body composition, including WC [121] and BMI [122]; and cardiorespiratory fitness (VO_{2max}) [121]. High intensity interval training (HIIT) alone may be effective for improving IR and BMI [123], however this has not been consistently shown [124]. Interventions involving a combination of aerobic and resistance exercise [122] or resistance training only [120] did not result in improvements in BMI [122] or weight status [120]. Exercise involving resistance training did result in other beneficial improvements to body composition (reduced body fat, WC and increased lean mass) and strength. This is important, as the degree of

central adiposity predicts responsiveness to weight loss interventions in PCOS [53], and women who achieve greater reductions in central fat show greater symptom improvement with weight loss [45]. Resistance training may also improve androgen levels, though findings are inconsistent and more research is needed to draw definite conclusions [120]. There was insufficient evidence from available data to assess the effects of exercise type on reproductive function [122]. Please see Table 2 for a summary of available evidence from meta-analyses investigating the effects of different types of exercise on PCOS outcomes.

When comparing the effects of exercise and diet combined with diet alone, a systematic review and meta-analysis (three studies) found no differences for any measured outcomes (glucose, insulin HOMA-IR, weight, BMI, WC, body fat, fat free mass, T, SHBG and FAI) [119]. In regards to exercise and diet combined compared to exercise alone, subgroup analysis (including 17 studies) from a large systematic review found that the addition of diet to exercise,

Table 3 Experimental studies investigating the effects of psychological interventions on polycystic ovary syndrome outcomes

References	Study design; study length; N participants	Intervention	Main findings
Abdollahi et al. 2019 [152]	Parallel RCT; 8 wk; 74	I = 8 weekly CBT C = minimal intervention	↑ QoL (PCOSQ) for I compared with C ↓ psychological fatigue (FIS) for I compared with C
Jiskoot et al. 2020 [162] Jiskoot et al. 2020 [154]	Parallel RCT; 1 yr; 183	I = 20 group sessions of CBT combined with nutrition advice and exercise C = usual care	↓ depression (BDI-II) and BW in I compared with C ↑ self-esteem (RSES) in I compared with C
Oberg et al. 2020 [132]	Parallel RCT; 16 wk with a follow-up at 1 yr; 68	I = behavioural modification program C = minimal intervention	↓ anxiety (PGWB) and depressed mood (PGWB) in I compared with C ↑ higher general health (PGWB) in I compared with C
Cooney et al. 2018 [153]	Parallel RCT; 16 wk; 31	I = 8 weekly CBT with lifestyle modification C = no psychological intervention with lifestyle modification	↓ BW in I compared with control ↑ QoL (PCOSQ) in I compared with control
Raja-Khan et al. 2017 [160]	Parallel RCT; 16 wk; 86	I = 8 weekly MBSR C = 8 weekly health education sessions (diet and exercise education)	↑ mindfulness (TMS) in I compared with C ↓ perceived stress (PSS-10) in I compared with C
Stefanaki et al. 2015 [156]	Parallel RCT; 8 wk; 38	I = MBSR C = minimal intervention	↓ depression (DASS21), stress (DASS21) and cortisol in I compared with control
Roessler et al. 2012 [151] ^a Roessler et al. 2013 [163] ^b	Cross-over randomised; 8 wk per arm and 16 wk total; 17	8 wk high-intensity aerobic exercise (including a ramp-up period of two weeks) and 8 wk group counselling in a cross-over design without a wash-out period	Relationships between the participants were important for changes in behaviour, especially relationships which generated helpful peer feedback and reduced social isolation ↓ BW and BMI after 16 wk only in the group who started with group counselling
Rofey et al. 2009 [158]	Single arm experimental; 8 wk; 12	8 one-on-one CBT, 3 family-based CBT and lifestyle goals (diet and exercise)	↓ BW, BMI and depression (CDI) ↑ health-related QoL (IWQoL-K)

Abbreviations: ↑ significant increase ($P \leq 0.05$), ↓ significant decrease ($P \leq 0.05$), *BDI-II* Beck Depression Inventory-II, *BW* Blood pressure, *BMI* Body mass index, *BW* Body weight, *CDI* Children's Depression Inventory, *C* Control, *CBT* Cognitive behavioural therapy, *CES-D* Centre for Epidemiologic Studies – Depression Scale, *DASS21* Depression Anxiety Stress Scales-21, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders (fourth edition), *FGL* Fasting glucose level, *FIS* Fatigue Impact Scale, *I* Intervention, *IWQoL-K* Impact of Weight on Quality of Life Questionnaire—Kids, *HP* Hip circumference, *MBSR* Mindfulness-based stress reduction, *PSS-10* Perceived Stress Scale-10, *PCOS* Polycystic ovary syndrome, *PCOSQ* Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire, *PGWB* Psychological Well-Being Index, *QoL* Quality of life, *RSES* Rosenberg Self Esteem Scale, *RCT* Randomized controlled trial, *STA* State-Trait Anxiety Inventory, *SSP* Swedish Universities Scale of Personalities, *TMS* Toronto Mindfulness Scale, *TSST* Trier Social Stress Test, *WC* Waist circumference

^a Qualitative analysis only

^b Statistical analysis compares order of intervention arms (e.g. counselling followed by exercise versus exercise followed by counselling) and doesn't compare effects of counselling versus exercise

particularly vigorous intensity aerobic exercise, resulted in greater reduction to BMI, WC, FAI and HOMA-IR than exercise only [121]. In regards to exercise (aerobic) alone versus diet alone, one intervention study found that exercise induced weight loss produced greater improvements

in menstrual frequency and ovulation rates [125], with no differences in pregnancy rates [125]. However, this study was not randomised and treatments were self-selected, which may have biased the results and precludes firm conclusions [125].

Table 4 Key observational studies that report non-clinical sleep disruption in polycystic ovary syndrome

Reference	Sample size	Sleep methodology used	Main findings
Moran et al. 2015 [182]	PCOS: n=87 Non-PCOS: n=637	Modified version of the Jenkins Sleep Questionnaire	Women with PCOS were twice as likely to experience sleep disturbance PCOS was associated with difficulty falling asleep and maintaining sleep
Mo et al 2019 [140] ^a	PCOS: n=484 Non-PCOS: n=6094	Sleep duration was self-reported on a work day and non-work day Sleep quality was self-reported through frequency questions about difficulty falling asleep, restless sleep, difficulty sleeping and severe tiredness	Women with/without PCOS had similar sleep duration Women with PCOS had higher prevalence of sleep disturbance, and this relationship maintained even after controlling for BMI, depression, income, marital status, occupation, education status and COB
Bennett et al. 2021 [183] ^a	PCOS: n=464 Non-PCOS: n=5603	Sleep duration was self-reported on a work day and non-work day Sleep quality was self-reported through frequency questions about difficulty falling asleep, restless sleep, difficulty sleeping and severe tiredness	Overall women with PCOS had greater adverse sleep symptoms and higher DGI However, subgroup analysis revealed PCOS was only associated with a higher DGI in women with adequate sleep There was no association between PCOS and DGI in women with poor sleep The higher DGI observed in women with PCOS may only be maintained in women who achieve adequate amounts of good quality sleep
Shreeve et al. 2013 [167]	PCOS: n=15 Non-PCOS: n=18	Actigraphy, PSQI and ESS	Women with PCOS had higher night time melatonin levels Women with PCOS had reduced sleep when compared to controls
Kutanaee et al. 2019 [181]	PCOS: n=201 Non-PCOS: n=199	PSQI	Women with PCOS had lower sleep quality and daytime function Women with PCOS were more likely to utilise medication to assist with sleep

Abbreviations: BMI Body mass index, COB Country of birth, DG Dietary Guidelines Index, ESS Epworth Sleepiness Scale, PCOS Polycystic ovary syndrome, PSQI Pittsburgh Sleep Quality Index

^a Mo et al. [140] and Bennett et al. [183] share the same cohort

Behavioural

The 2018 PCOS guideline promotes the use of behavioural interventions that foster self-efficacy [18]. These include the use of SMART (specific, measurement, achievable, realistic and timely) goals, self-monitoring, stimulus control, problem solving and relapse prevention [18].

Behavioural and cognitive interventions are required to improve sustainability of lifestyle changes, through considering not only the specific behaviour, but also their antecedents, consequences and cognition [126, 127]. Given that women with PCOS show higher rates of weight gain over time [9] and high attrition rates in clinical weight management research [37], there is a clear need to improve adherence to diet and physical activity interventions. However, the majority of research investigating lifestyle change in PCOS involve short-term dietary interventions with/without an exercise element, and there is a paucity of research on behavioural change strategies. As such, guideline development relied heavily on evidence taken from the general population. Only three RCTs in women with PCOS included a ‘behavioural intervention’ [128–130]. While

these studies showed enhanced weight loss [128, 130] and improved androgen and lipid profiles [129] when compared with placebo, the interventions were not well defined, with negligible context provided regarding the theoretic framework or behavioural strategies utilised.

More recently, a cross-sectional study in 501 women with PCOS [131] and two RCTs [44, 132] explored the use of self-management strategies [131] and behavioural modification interventions [44, 132] in PCOS. In the cross-sectional study, implementation of physical activity self-management strategies improved the likelihood of meeting physical activity recommendations, but had no association with BMI. Dietary self-management strategies were associated with reductions in BMI, though were not related to weight or nutritional intake [131]. In the RCTs, only the behavioural modification programme and not the control (general healthy lifestyle recommendations) produced significant weight loss after four months. A significantly greater proportion of women in the intervention group also improved menstrual regularity [44] and psychological well-being (lower anxiety and depressive

symptoms) [132] when compared to the control group. The women who achieved greater weight loss reported higher social desirability and lower embitterment scores on a personality trait assessment measure [132]. These findings are particularly novel, as they provide insight into the influence of personality traits and their contribution to success in following behavioural modifications [132].

Alcohol and smoking

In the clinical setting, smoking and alcohol consumption are often addressed alongside dietary and physical activity changes, employing the same behavioural and cognitive interventions to promote adherence. Hence, alcohol and cigarette use are considered here under traditional lifestyle strategies. The PCOS international guideline highlights the importance of assessing alcohol consumption and cigarette smoking when improving fertility and reproductive outcomes in women with PCOS [18]. Assessment of cigarette use is also recommended when evaluating CVD risk factors and thromboembolism risk associated with oral contraceptive pills [18]. These recommendations are based on existing practice guidelines used for the general population.

There is a paucity of observational research characterising alcohol consumption in women with PCOS. One Swedish study comparing women with PCOS ($n=72$) to healthy controls ($n=30$), demonstrated a lower alcohol intake in the PCOS group [133]. A larger study in Australia comparing women with ($n=409$) and without ($n=7,057$) PCOS, reported no significant difference in alcohol intake [134]. Similarly, a Spanish study ($n=22$ PCOS and $n=59$ controls) and a Chinese study ($n=2,217$ PCOS and $n=279$ controls), found no significant difference in alcohol intake between PCOS and non-PCOS groups [135, 136].

Current evidence on the impact of alcohol intake on anovulatory infertility (a common feature of PCOS) is controversial, with some studies showing adverse effects and others reporting no significant correlation [136, 137]. One prospective study including 18,555 married women from The Nurses' Health Study II, who had no history of infertility, found no clinically significant impact of alcohol intake on anovulatory infertility, after adjusting for parity and other factors [138]. Similarly, a Danish study ($n=6,120$ women aged 21 to 45 years) found no fertility effect with alcohol consumption of less than 14 standard drinks per week [137]. In contrast, a study on 3,833 women who recently gave birth and 1,050 women with infertility, reported an increased risk of anovulatory infertility and endometriosis with increasing alcohol intake [139].

Current observational evidence does not reveal any significant difference in smoking between women with and without PCOS [135, 136, 140], with the exception of one

study in pregnant women which showed a lower smoking rate in women with PCOS ($n=354$) compared to women without PCOS at 15 weeks gestation [3]. However, a significantly higher rate of smoking (including passive and active) is reported in women with PCOS and oligo-anovulation and/or reduced fertility compared to women with PCOS and normal menstruations or healthy controls [141, 142]. Smoking is also associated with PCOS risk independent of BMI and age [142]. A Mendelian randomisation study supports these findings, demonstrating a 38% higher risk of PCOS development in genetically predicted smokers (based on single-nucleotide polymorphisms associated with smoking initiation) compared with those who never smoked [143]. In PCOS, smoking is associated with increased levels of T, DHEAS, TC, LDL-C and FINS [141, 144, 145]. However, the underlying mechanisms are not fully understood and there are inconsistencies in findings from different studies. Furthermore, smoking is associated with lower conception and live birth rates and less favourable ART outcomes in women with PCOS [141, 146].

Psychological

The current guideline highlights the need for awareness, and appropriate assessment (such as stepwise screening) and management, of QoL, depression and anxiety, psychosexual dysfunction, negative body image and disordered eating [18]. The guideline emphasises the importance of clinicians and women working in partnership to address women's individual priorities; understanding that the impact of PCOS on an individual's QoL is key to delivering meaningful outcomes [147, 148]. To assist women to communicate with clinicians about what is important to them, the PCOS Question Prompt List [149] was developed and is consistent with the 2018 guideline. The 2018 guideline recommends screening for risk factors and symptoms of depression and anxiety at time of diagnosis. Women with positive screening results should be supported with further assessment and treatment by appropriately qualified clinicians. To screen for psychosexual dysfunction tools such as the Female Sexual Function Index [150] should be utilised. If negative body image, disordered eating or eating disorders are suspected, the PCOS guideline outlines a stepped approach for screening, and where appropriate promotes the use of psychological therapy offered by trained health professionals, which should be guided by regional clinical practice guidelines [18].

While the PCOS guideline provides justification and summarises evidence for mental health screening and diagnostic assessment, there is also a need for consideration of additional aspects, such as the efficacy of different types of psychological interventions and how

Table 5 Reviews and experimental studies investigating the effects of traditional, complimentary and integrative medicine on polycystic ovary syndrome outcomes

Intervention	N study design	N studies; N participants	Main findings ^a	References
Vitamins				
B-group vitamins (B1, B6, and B12)	1 RCT	1; 60	Counteracted Hcy-increasing effect of metformin ↔ HOMA-IR	Kilicdag et al. 2005 [198]
Folate (vitamin B9)	2 RCT	2; 150	↓ Hcy [199, 200], HOMA-β [199], HOMA-IR [200], FINS [200], TC:HDL-C ratio [200], CRP [199], MDA [199] ↑ TAC [199], GSH [199]	Bahmani et al. 2014 [199] Asemi et al. 2014 [200]
Inositol (vitamin B8)	1 SR/MA	9 RCT; 496	↓ HOMA-IR; ↓ FINS ↔ androstenedione, T, SHBG	Unfer et al. 2017 [191]
Vitamin D	2 SR/MA	23 RCT; 1367	↓ TC [201], LDL [201], TAG [201], HOMA-IR [203], FGL [203], FINS [203], VLDL-C [203] ↑ QUICKI [203] ↔ HDL-C [201]	Guo et al. 2020 [201] Gao et al. 2021 [203]
Vitamin E	1 RCT	1; 86	↓ FGL, HOMA-IR, SHBG, T (only when combined with coenzyme Q10)	Izadi et al. 2019 [205]
Vitamin K	1 RCT	1; 79	↓ WC, FBM, FINS, HOMA-IR, HOMA-β, TAG, FAI, DHT ↑ skeletal muscle mass, SHBG, QUICKI	Tarkesh et al. 2020 [206]
Vitamin-like supplements				
Soy isoflavones	1 pilot pre-post prospective	1; 12	↓ TC, LDL-C, LDL-C:HDL-C ratio, TAG	Romualdi et al. 2018 [208]
Carnitine (L-Carnitine)	1 RCT	1; 60	↓ MDA, MDA:TAC ratio ↑ TAC	Jamilian et al. 2017 [211]
Alpha-lipoic acid	2 pre-post prospective	2; 52	↓ BMI [214], IR [213], LDL-C [213], TAG [213], ovarian cysts [214] ↑ progesterone [214]	Masharani et al. 2010 [213] Cianci et al. 2015 [214]
Minerals				
Vitamin D and calcium	1 SR/MA	6 RCT; 480	↓ FINS, HOMA-IR, FGL, T, TAG, VLDL-C, TC, LDL-C, hirsutism ↑ QUICKI, menstrual regularity	Shojaeian et al. 2019 [219]
Zinc	1 SR	5 RCT; 285	↓ HOMA-IR, HOMA-β, FINS, MDA, CRP, T, FSH, TC, LDL-C, TAG, VLDL-C, DHEAS ↑ TAC, QUICKI	Nasiadek et al. 2020 [220]
Selenium	1 SR	5 RCT; NR	↓ IR, CRP and MDA in some RCTs ↔ (or inconsistent findings) BMI, BW, FGL, blood lipids, androgens, acne, hirsutism	Hajizadeh-Sharafabad et al. 2019 [221]
Magnesium	1 SR	3 RCT; 156	Serum magnesium concentrations were associated with IR but supplementation had inconsistent effects	Hamilton et al. 2019 [222]
Chromium Picolinate	2 SR/MA	11 RCT; 702	↓ BMI [223], FINS [223], IR [224], T [223] ↑ T [224] ↔ BMI [224], FG [223]	Fazelian et al. [223] Tang et al. [224]

Table 5 (continued)

Intervention	N study design	N studies; N participants	Main findings ^a	References
Other supplements				
Omega-3 fatty acids	1 SR/MA	9 RCT; 591	↓ HOMA-IR, TC, LDL-C and TAG. ↔ FINS, FGL, BMI, androgens	Yang et al. 2018 [225]
N-acetyl-cysteine	1 SR/MA	8 RCTS; 910	↑ rates of pregnancy and live births	Thakker et al. 2015 [226]
Coenzyme Q10	1 RCT	1; 60	↓ FGL, FINS, HOMA-IR, HOMA-β, TC, LDL-C ↑ QUICKI	Samimi et al. 2017 [227]
Probiotics	2 SR/MA	19 RCT; 1261	↓ FINS [228], TG [228], VLDL-C [228], FAI [229] ↑ QUICKI [228], SHBG [229] ↔ BW [228], FGL [228], HOMA-IR [228], TC [228], LDL-C [228], HDL-C [228], CRP [228], DHEA [228], T [229]	Liao et al. 2018 [228] Shamasbi et al. 2020 [229]
Quercetin	1 SR	3 RCT; 246	Some improvement in adiponectin-mediated IR ↔ BW, WHR	Pourteymour et al. 2020 [232]
Resveratrol	1 SR/MA	3 RCT; 131	↓ T ↑ high-quality oocytes and embryos ↔ BMI, blood lipids, FGL, pregnancy rate	Shojaei-Zarghani et al. 2021 [233]
Melatonin	1 SR/MA	2 RCT and 1 cell culture; 640	↑ pregnancy rates in assisted reproductive technology	Hu et al. 2020 [172]
Herbal medicine				
Cinnamon	1 SR/MA	5 RCT; 448	↓ HOMA-IR, TC, LDL, FGL, FINS ↑ HDL ↔ BW	Heydarpour et al. 2020 [260]
Curcumin	2 RCT	2; 118	↓ FGL [238], DHEA [238] ↔ FGL [239], FINS [238], blood lipids [239], IR [239]	Heshmati et al. 2021 [238] Sohaei et al. 2019 [239]
Sage	1 RCT	1; 70	↓ BW, BMI, WC, FGL, FINS, HOMA-IR, QUICKI ↔ WHR	Amini et al. 2020 [241]
Fennel and dry cupping	1 RCT	1; 55	↓ BMI, cycle length	Mokaberinejad et.al. 2019 [243]
Licorice	1 pre-post prospective 1 quasi-experimental	2; 41	↓ T [245] Reduce prevalence of side effects related to the diuretic activity of spironolactone [246]	Armanini et al. 2004 [245] Armanini et al. 2007 [246]
Spearmint, ginger, citrus and cinnamon	1 RCT	1; 60	↓ HOMA-IR, FINS, FGL	Ainehchi et al. 2019 [251]
Chinese herbal medicine	1 SR/MA	4 RCT; 414	↑ pregnancy rate when taken with clomiphene (versus clomiphene alone) ↔ pregnancy rate when taken alone (versus clomiphene alone) Insufficient evidence for subfertility	Zhou et al. 2016 [235]

Table 5 (continued)

Intervention	N study design	N studies; N participants	Main findings ^a	References
Other TCIM				
Acupuncture	2 SR/MA	31 RCT; 2846 ^b	↓ BMI [255], LH [254], T [254] ↑ menstrual regularity [254] ↔ FGL [255], FINS [255], live birth [254], pregnancy rate [254], ovulation [254]	Wu et al. 2020 [254] Qu et al. 2016 [255]
Yoga	2 SR [120, 257] 1 SR/MA [258] 1 RCT [259]	21; 1059 ^a	↓ WC [259], HC [259], HOMA-IR [120], FGL [258], FINS [258], T [120], LH [120], DHEA [120], androstenedione [120], adiponectin [120], clinical hyperandrogenism [259] ↑ menstrual regularity [258], menstrual frequency [257] ↓ stress and anxiety [257]	Shele et al. 2020 [120] Thakur et al. 2021 [257] Anita et al. 2021 [258] Mohseni M et al. 2021 [259]

Abbreviations: ↑ significant increase ($P \leq 0.05$), ↓ significant decrease ($P \leq 0.05$), ↔ no significant change, *BMI* Body mass index, *BW* Body weight, *DHEAS* Dehydroepiandrosterone-sulfate, *DHT* Dihydrotestosterone, *FGL* Fasting glucose level, *FINS* Fasting insulin level, *FBM* Fat body mass, *FSH* Follicle stimulating hormone, *FT* Free testosterone, *GSH* Glutathione, *HC* Hip circumference, *Hcy* Homocysteine, *HOMA-IR* Homeostatic assessment of insulin resistance, *HDL-C* High density lipoprotein cholesterol, *IR* Insulin resistance, *QUICKI* Quantitative insulin sensitivity check index, *QoL* Quality of life, *MDA* Malondialdehyde, *MA* Meta-analysis, *NR* Not reported, *OCP* Oral Contraceptive Pill, *RCT* Randomised controlled trial, *SHBG* Sex hormone binding globulin, *SR* Systematic review, *T* Testosterone, *TAC* Total antioxidant capacity, *TC* Total cholesterol, *TAG* Triglycerides, *TCIM* Traditional, complimentary and integrative medicine, *VLDL-C* Very low density lipoprotein cholesterol, *WC* Waist circumference, *WHR* Wait hip ratio

^a Summarises commonly used measures in PCOS research and does not report on all measured outcomes. For prospective pre-post studies significant changes from baseline are reported. For RCTs significant changes between intervention(s) and control are reported

^b Not all participants are included in the findings reported here (e.g. where findings from subgroup analysis are reported)

psychological interventions influence engagement with lifestyle change. This is important, as poorer mental health outcomes at baseline are positively associated with higher rates of attrition in lifestyle interventions [13]. Cognitive behavioural interventions could be considered to improve engagement and adherence to healthy lifestyle in women with PCOS. Research has shown support for a range of different psychological interventions, such as counselling [151], cognitive behavioural therapy (CBT) [152–154] and mindfulness meditation [155, 156], helping to change the way clinicians' approach and deliver optimal PCOS management.

CBT is one of the most widely-researched psychological interventions, and is well-recognised as the most effective psychological treatment for depression and anxiety [157]. One RCT showed that eight weekly group CBT sessions were effective in improving QoL ratings and reducing psychological fatigue in women with PCOS [152]. Another more recent RCT investigated the outcome of a 1 year three-component intervention focusing on CBT, diet and exercise [154] and reported improvements in self-esteem and depressive symptoms as compared to usual care [154]. Similarly, an RCT by Cooney et al. [153], comparing the effects of CBT and lifestyle modification versus lifestyle modification alone, reported the CBT/lifestyle modification group lost more than twice as much weight per week

and had greater improvements in QoL compared to lifestyle only. Depression scores decreased in the overall group and there was no difference between the two groups [153]. Lastly, a pilot intervention study of adolescents with PCOS has shown promising results for the use of CBT in the reduction of weight and improvement in depressive symptoms [158].

Mindfulness meditation programs have gained increasing popularity over the past few decades, and are being included as part of clinical trials to reduce stress and improve psychological wellbeing across a range of medical conditions [159]. Mindfulness meditation can be used to reduce the production of adrenal androgens, activated via the adrenal glands as a direct result of psychological distress [156]. Despite the proposed benefits, there are very few studies investigating the use of mindfulness meditation as a treatment for psychological symptoms associated with PCOS. One RCT ($n=86$) compared the provision of an eight week mindfulness-based stress reduction (MBSR) program, and found that when compared to the control group (health education), the MBSR group produced greater reductions in perceived stress, depressive symptoms and fasting blood glucose [160]. Similarly, another RCT investigating the impact of mindfulness meditation for eight weeks in PCOS showed reduced stress, depression and anxiety symptoms, and increased life satisfaction and QoL in the intervention

group compared to no treatment [156]. In adolescents with PCOS ($n=37$), a pilot RCT reported higher levels of nutrition and physical activity self-efficacy following a mindfulness and self-management program [161]. Mindfulness-based cognitive therapy (MBCT) combines both elements of MBSR and CBT, but as yet there are no trials investigating this intervention in PCOS.

In addition to CBT and mindfulness meditation, there is some evidence to support group counselling sessions as beneficial in conjunction with exercise programs to increase and support weight loss [151]. In one RCT ($n=17$) participants followed a high-intensity aerobic exercise program for eight weeks, followed by eight weeks of group counselling [151]. Qualitative analysis of data taken from the group counselling and physical exercise sessions revealed that development of supportive relationships was important for successful behavioural change. By fostering the exchange of narratives relating to their illness (e.g. effects of PCOS on aspects of everyday life), and generating feedback between group members, counselling sessions helped to reduce social isolation and improve adherence to the exercise intervention [151]. Please see Table 3 for a summary of experimental studies investigating effects of psychological interventions on PCOS outcomes.

Sleep

Women with PCOS have an increased risk of both clinical sleep disorders and non-clinical sleep disturbance, which is mediated by hormone derangement, in particular reduced oestrogen, progesterone and melatonin levels [164]. Oestrogen is required for the metabolism of neurotransmitters (norepinephrine and serotonin) involved in regulating sleep patterns, and plays an important role in maintaining a low body temperature at night [165]. Progesterone has sedative and anxiolytic actions that can support sleep quality, and acts as a respiratory stimulant that lessens airway resistance in obstructive sleep apnoea (OSA) [166]. Melatonin is a neuroendocrine hormone that is widely recognised as crucial in maintaining circadian rhythm regulation. However, melatonin is also involved in ovarian function, with actions including delaying ovarian senescence, promoting follicle formation and improving oocyte quality [167–173].

The current PCOS guideline recognises that OSA is 6.5–8.3 times more likely in women with PCOS [164, 174–177], and promotes routine screening to identify and treat associated symptoms, such as snoring, excessive sleepiness and the potential for fatigue to worsen mood disorders [18]. Screening should include a simple questionnaire, such as the Berlin tool [178], and where appropriate women should be referred onto a specialist for further assessment and

treatment [18]. The guidelines also highlight that treatment of OSA in PCOS should not be used to improve metabolic features. Since guideline inception evidence has emerged reporting weight, PCOS and sleep are interrelated factors that can each contribute to the worsening presentation of one another, whereby sleep disorders and disturbance may worsen the presentation of PCOS related metabolic outcomes and vice versa [179].

Hypersomnia and insomnia are also common clinical sleep disorders in PCOS [164, 177, 180], with prevalence estimated at 11% versus 1% in women with versus those without PCOS [180]. Even in the absence of clinically diagnosed sleep disorders, women with PCOS have a higher prevalence of sleep disturbances, including poor sleep quality [181], issues with sleep initiation [182], severe fatigue [140], restless sleep [140] and difficulty sleeping overnight [140]. The prevalence of sleep disturbances may be up to 20% higher in women with PCOS compared to women without PCOS [183]. Emerging research also suggests that social restrictions arising from the COVID-19 pandemic have worsened sleep disturbances in women with PCOS [177]. Findings from key studies of non-clinical sleep disturbance can be found in Table 4.

In the general population short and disturbed sleep is consistently associated with excess weight [184], IR [185], T2DM [185] and CVD [186]. Similar relationships are observed in PCOS, where OSA and sleep disordered breathing exacerbates risk of IR and metabolic consequences of abnormal glucose tolerance [187, 188]. A cross-sectional study in adolescents with PCOS ($n=103$) reported those with sleep disordered breathing had significantly higher BMI Z-scores, and a higher prevalence of metabolic syndrome (METS) [188]. Similar metabolic consequences are seen in women with PCOS who suffer from non-clinical sleep disturbance [164]. Underlying mechanisms linking sleep disorders and disturbance with worsened metabolic outcomes include amplified sympathetic tone and oxidative stress [164], reduced adipose tissue lipolysis, and an increase in energy intake stemming from heightened hedonic and endocrine appetite signals [189].

Unfavourable effects on energy metabolism and appetite regulation, may explain why women with PCOS who display sleep disturbance have a reduced capacity to maintain dietary interventions [183]. Moreover, depression and anxiety share a bidirectional relationship with disrupted and reduced sleep [190], and as stated previously, interventions that improve mental health can help to increase engagement with dietary and physical activity recommendations [131]. Optimising sleep may therefore be an important consideration when promoting healthy lifestyle change in women with PCOS [183].

Table 6 Current recommendations for clinical practice and research gaps identified by this review

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Effectiveness of lifestyle interventions		
Healthy lifestyle behaviours encompassing healthy eating and regular physical activity should be recommended in all those with PCOS to achieve and/or maintain healthy weight and to optimise hormonal outcomes, general health, and QoL across the life course.	CCR	<ul style="list-style-type: none"> • Improves sustainability of weight loss interventions. • Identifies subgroups who respond to weight loss with clinically relevant metabolic and reproductive improvements (this requires the inclusion of more clinical reproductive outcomes in RCTs). • Defines weight loss thresholds for improvements in different PCOS features (metabolic, reproductive and psychological). • Characterises the degree of metabolic and reproductive improvements related to different lifestyle factors (diet, physical activity and behavioural) independent of weight changes. • Considers effects of weight gain prevention on limiting the progression/worsening of PCOS features. • Investigates how different dietary, physical activity and behavioural interventions affect engagement, adherence and sustainability of lifestyle change. • Investigates efficacy and effectiveness of healthy lifestyle changes independent of weight change.

Table 6 (continued)

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Dietary interventions		
A variety of balanced dietary approaches could be recommended to reduce dietary energy intake and induce weight loss in women with PCOS and overweight and obesity, as per general population recommendations.	CCR	<ul style="list-style-type: none"> Low GI/GL diets may provide benefits in reducing weight and IR in women with PCOS. Further research needs to assess additional risk factors including reproductive function and CVD risk. Identify and define the optimal diet for PCOS management by comparing a range of different dietary approaches (e.g. DASH, Mediterranean or low GI/GL).
General healthy eating principles should be followed for all women with PCOS across the life course, as per general population recommendations.	CCR	
To achieve weight loss in those with excess weight, an energy deficit of 30% or 500 - 750 kcal/day (1,200 to 1,500 kcal/day) could be prescribed for women, also considering individual energy requirements, body weight and physical activity levels.	CPP	
In women with PCOS, there is no or limited evidence that any specific energy equivalent diet type is better than another, or that there is any differential response to weight management intervention, compared to women without PCOS.	CPP	
Tailoring of dietary changes to food preferences, allowing for a flexible and individual approach to reducing energy intake and avoiding unduly restrictive and nutritionally unbalanced diets, are important, as per general population recommendations.	CPP	
Physical activity interventions		
Health professionals should encourage and advise the following for prevention of weight gain and maintenance of health:	CCR	While evidence supports the provision of supervised vigorous aerobic exercise, which may provide greater benefits on PCOS symptoms than other types of exercise (e.g. resistance training), additional larger and longer-term studies are required to: <ul style="list-style-type: none"> Characterise optimal exercise prescription for PCOS management. Identify factors that improve adherence to exercise interventions. Identify subgroups who respond to exercise with clinical improvements.
• in adults from 18 – 64 years; a minimum of 150 min/week of moderate intensity physical activity or 75 min/week of vigorous intensities or an equivalent combination of both, including muscle strengthening activities on 2 non-consecutive days/week;		
• in adolescents, at least 60 minutes of moderate to vigorous intensity physical activity/day, including those that strengthen muscle and bone at least 3 times weekly;		
• activity be performed in at least 10-minute bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days.		
Health professionals should encourage and advise the following for modest weight-loss, prevention of weight-regain and greater health benefits:	CCR	
• a minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensity or an equivalent combination of both, and muscle strengthening activities involving major muscle groups on 2 non-consecutive days/week;		
• minimised sedentary, screen or sitting time.		
Physical activity includes leisure time physical activity, transportation such as walking or cycling, occupational work, household chores, games, sports or planned exercise, in the context of daily, family and community activities.	CPP	
Daily, 10000 steps is ideal, including activities of daily living and 30 minutes of structured physical activity or around 3000 steps.		
Structuring of recommended activities need to consider women's and family routines as well as cultural preferences.		

Table 6 (continued)

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Behavioural interventions		
Lifestyle interventions could include behavioural strategies such as goal-setting, self-monitoring, stimulus control, problem solving, assertiveness training, slower eating, reinforcing changes and relapse prevention, to optimise weight management healthy lifestyle and emotional wellbeing in women with PCOS.	CCR	<ul style="list-style-type: none"> To identify behavioural and cognitive strategies that should be targeted in women with PCOS, more observational research that characterises women's use of self-management strategies is needed. To aid replication and interpretation of findings, RCTs must clearly define the theoretical frameworks and behavioural components used in intervention design.
Comprehensive health behavioural or cognitive behavioural interventions could be considered to increase support, engagement, retention, adherence and maintenance of healthy lifestyle and improve health outcomes in women with PCOS.	CPP	
Assessment and treatment of infertility (as it relates to alcohol and smoking use)		
Cardiovascular disease risk (as it relates to alcohol and smoking use)	CPP	<ul style="list-style-type: none"> Determine whether women with PCOS are at a higher risk of alcohol and smoking-related infertility complications (with a focus on anovulatory infertility) when compared to women without PCOS. Determine whether women with PCOS are at a higher risk of smoking-related CVD complications when compared to women without PCOS.
Factors such as blood glucose, weight, blood pressure, smoking, alcohol, diet, exercise, sleep and mental, emotional and sexual health need to be optimised in women with PCOS, to improve reproductive and obstetric outcomes, aligned with recommendations in the general population.	CCR	
If screening reveals CVD risk factors including obesity, cigarette smoking, dyslipidaemia, hypertension, impaired glucose tolerance and lack of physical activity, women with PCOS should be considered at increased risk of CVD.	CCR	
Quality of life		
Health professionals and women should be aware of the adverse impact of PCOS on quality of life.	CCR	<ul style="list-style-type: none"> Validate QoL tools longitudinally to identify clinically meaningful differences in QoL scores.
Health professionals should capture and consider perceptions of symptoms, impact on quality of life and personal priorities for care to improve patient outcomes.	CCR	
The PCOS quality of life tool (PCOSQ), or the modified PCOSQ, may be useful clinically to highlight PCOS features causing greatest distress, and to evaluate treatment outcomes on women's subjective PCOS health concerns.	CPP	

Table 6 (continued)

Recommendation(s) from current guidelines ^a	Category of recommendation ^b	Research gaps
Depression and anxiety symptoms, screening and treatment		
Psychosexual function		
Body image		
Eating disorders and disordered eating		
Health professionals should be aware that in PCOS, there is a high prevalence of moderate to severe anxiety and depressive symptoms in adults; and a likely increased prevalence in adolescents.	CCR	<ul style="list-style-type: none"> To determine accurate prevalence of psychological conditions in PCOS, more adequately powered cross-sectional studies using structured diagnostic interviews administered by appropriately qualified professionals are required. Future research should consider the efficacy of different types of psychological interventions in PCOS, with a focus on how changes to mental health symptoms influence engagement with lifestyle change. In particular, the development of a PCOS specific CBT program, tailored to meet the specific mental health needs of women with PCOS is warrant.
Anxiety and depressive symptoms should be routinely screened in all adolescents and women with PCOS at diagnosis. If the screen for these symptoms and/or other aspects of emotional wellbeing is positive, further assessment and/or referral for assessment and treatment should be completed by suitably qualified health professionals, informed by regional guidelines.	CCR	
If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered in PCOS, informed by regional clinical practice guidelines.	CCR	
Factors including obesity, infertility, hirsutism need consideration along with use of hormonal medications in PCOS, as they may independently exacerbate depressive and anxiety symptoms and other aspects of emotional wellbeing.	CPP	
All health professionals should be aware of the increased prevalence of psychosexual dysfunction and should consider exploring how features of psychohirsutism and body image, impact on sex life and relationships in PCOS.	CCR	
If psychosexual dysfunction is suspected, tools such as the Female Sexual Function Index can be considered.	CCR	
Health professionals and women should be aware that features of PCOS can impact on body image.	CCR	
All health professionals and women should be aware of the increased prevalence of eating disorders and disordered eating associated with PCOS.	CCR	
If eating disorders and disordered eating are suspected, further assessment, referral and treatment, including psychological therapy, could be offered by appropriately trained health professionals, informed by regional clinical practice guidelines.	CCR	

Table 6 (continued)

Recommendation(s) from current guidelines^a

Category of recommendation ^b	Research gaps
Obstructive sleep apnoea (OSA)	<ul style="list-style-type: none"> To determine accurate prevalence of subclinical sleep disturbances in PCOS, more adequately powdered cross-sectional studies using validated subjective and objective sleep measures are required. While emerging evidence suggests that disturbed sleep may exacerbate IR via decreasing energy expenditure and increasing adipose tissue deposition, more research in women with PCOS is needed to confirm this hypothesis. Investigate effects of CBT interventions in women with PCOS who have disturbed sleep (outcomes of interest include food intake, metabolic rate, appetite hormones, weight, adherence to lifestyle changes and PCOS features).
Screening should only be considered for OSA in PCOS to identify and alleviate related symptoms, such as snoring, waking unrefreshed from sleep, daytime sleepiness, and the potential for fatigue to contribute to mood disorders. Screening should not be considered with the intention of improving cardiometabolic risk, with inadequate evidence for metabolic benefits of OSA treatment in PCOS and in general populations.	CCR
A simple screening questionnaire, preferably the Berlin tool [178], could be applied and if positive, referral to a specialist is considered.	CPP
A positive screen raises the likelihood of OSA, however it does not quantify symptom burden and alone does not justify treatment. If women with PCOS have OSA symptoms and a positive screen, consideration can be given to be referral to a specialist centre for further evaluation.	
Inositol	<ul style="list-style-type: none"> EBR Women taking inositol and other complementary therapies are encouraged to advise their health professional.
Inositol (in any form) should currently be considered an experimental therapy in PCOS, with emerging evidence on efficacy highlighting the need for further research.	CPP

Abbreviations: BMI Body mass index, CBT Cognitive behavioural therapy, CV/D Cardiovascular disease, DASH Dietary approaches to stop hypertension, GI Glycaemic index, GL Glycaemic load, IR Insulin resistance, NAC N-acetyl-cysteine, PCOS Polycystic ovary syndrome, RCT Randomised controlled trial, QoL Quality of life

^a Recommendations are taken directly from the 2018 International Evidence-Based Guideline for the Assessment and Management of PCOS [18]. Does not include all recommendations, only those relevant to the findings of this review are presented

^b EBR Evidence based recommendations: Evidence sufficient to inform a recommendation made by the guideline development group. CCR Clinical Consensus Recommendations: In the absence of evidence, a clinical consensus recommendation has been made by the guideline development group. CPP Clinical Practice Points: Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or clinical consensus recommendations

Traditional, complementary and integrative medicine

The 2018 PCOS guideline includes recommendations on inositol supplementation, though do not include evidence regarding the use of other supplements, herbal medicine or other TCIM approaches, including acupuncture and yoga [18].

Vitamins, vitamin-like supplements, minerals and other supplements

The 2018 guideline highlights that inositol (including myo-inositol (MI) and di-chiro inositol) is a nutritional supplement that may be involved in insulin signalling transduction [191]. MI in particular is a key endocrine regulator that displays impaired metabolism in PCOS [191]. MI supplementation has been explored in a meta-analysis of nine RCTs ($n=496$), which showed improved metabolic profiles and reduced hyperandrogenism [191]. These findings are supported by two earlier meta-analyses, reporting improved ovulation, menstrual cyclicity, and hormonal profiles following MI supplementation [192, 193]. The 2018 PCOS guideline recommends that inositol (in any form) should be considered as an experimental therapy in PCOS management. The guideline also recognises that women participating in any form of TCIM should be encouraged to advise their health professional. However, it does not consider emerging evidence for the use of other types of TCIM in PCOS treatment as this was outside of the scope of the 2018 guideline.

Vitamins

B-group vitamins (B₁, B₆ and B₁₂), folic acid (B₉) and vitamins D, E, and K are critical for several biological processes that can affect metabolic and reproductive features of PCOS. B-group vitamins work alongside folic acid (the synthetic form of folate) to regulate homocysteine (Hcy) via re-methylation of Hcy to methionine [194]. Hcy is an amino acid that confers an increased risk of CVD at high levels, and which is often deranged in women with PCOS [195], likely related to a higher prevalence of folate deficiency [196–198]. One RCT explored the use of B-group vitamins combined with folic acid in 60 women with PCOS, and reported a reduction in the Hcy increasing effect of metformin [198]. Folic acid alone has also been examined in two RCTs of women with PCOS ($n=69$ [199] and $n=81$ [200]), improving FINS, HOMA-IR, C-reactive protein, total antioxidant capacity (TAC) and glutathione with doses ≥ 5 mg/day when compared with placebo [199, 200]. Regarding vitamin D supplementation, three large-scale meta-analyses reported improvements in measures of IR (HOMA-IR [201, 202], FINS [201]), fasting glucose [201]), lipid profiles (LDL-C [201–203], TC [203] and TAG [203]) and androgens (T) [202], when compared

with placebo. While vitamin E (or tocopherol) has various reported benefits on fertility outcomes in other populations [204], and has improved androgen profiles when co-supplemented with coenzyme Q10 (CoQ10) in women with PCOS [205], to date no RCTs have examined the use of vitamin E supplements alone in PCOS. Vitamin K also has limited available literature in PCOS, with only one RCT ($n=84$) demonstrating improvements in anthropometry, insulin and androgen profiles following supplementation (90 µg/day Menaquinone-7 for eight weeks), compared with placebo [206].

Vitamin-like supplements

Vitamin-like supplements including bioflavonoids, carnitine and alpha-lipoic acid (α-LA) have well-recognised antioxidant properties and play a role in fatty acid and glucose metabolism, providing possible metabolic benefits in PCOS [207]. Bioflavonoids consist of plant-derived polyphenolic compounds, some of which have been inversely associated with METS in women with PCOS [207]. In a pilot prospective study of 12 women with PCOS, 36 mg/day of the soy isoflavone genistein for six months improved lipid profiles but not anthropometry, IR, hormonal profiles or menstrual cyclicity [208]. Carnitine, particularly the active form L-carnitine, is reported to be lower in women with PCOS and linked with hyperandrogenism, hyperinsulinaemia and reduced oocyte quality [209, 210]. One RCT explored L-carnitine use in PCOS and found beneficial effects on mental health parameters and markers of oxidative stress [211], although the integrity of these have come under scrutiny and hence should be interpreted with caution [122212]. Regarding α-LA, a small pre-post study ($n=6$) administered 1200 mg/day for 16 weeks, and reported improved IR, LDL-C and TAG, though no effects on TAC or plasma oxidation metabolites [213]. Another RCT reported improved anthropometric (BMI), metabolic (FINS and HDL-C) and reproductive (menstrual cyclicity) features in 46 women with PCOS receiving α-LA supplementation (600 mg/day for 180 days) compared with controls [214]. However, as these women were co-supplemented with 1000 mg/day D-chiro-inostiol, findings are not isolated to the effects of α-LA alone [214].

Minerals

Minerals such as calcium, zinc, selenium, magnesium and chromium picolinate (CrP) have been explored in PCOS due to their reported insulin sensitising, antioxidant and anti-inflammatory properties [215–217]. A small number of studies have also reported women with PCOS are at higher risk of being deficient in calcium [218], zinc [215, 217] and selenium [195]. A recent systematic

review (six RCTs) reported that vitamin D and calcium co-supplementation in women with PCOS improved lipid and androgen profiles, follicular health and menstrual cyclicity [219]. While these findings are promising, it is difficult to attribute benefits to calcium alone, given calcium is often co-supplemented with vitamin D due to their complementary mechanisms of action. One systematic review (five RCTs) in PCOS reported zinc (often co-supplemented with other nutrients such as calcium, vitamin D and magnesium), improved HOMA-IR, lipids, T, FSH and DHEAS [220] compared to placebo. Another systematic review (five RCTs) examining selenium supplementation reported reduced IR, oxidative stress and inflammation, while results for anthropometry, lipids, androgens and hirsutism were inconsistent [221]. Regarding magnesium (an intracellular cation involved in insulin metabolism), while supplementation in PCOS has been associated with reduced IR in observational research [222], these findings are not supported by data from RCTs, with considerable inconsistencies between studies [222]. Two meta-analyses examined CrP in women with PCOS [223, 224]. While one reported that CrP supplementation reduced BMI, FINS and free testosterone [223], the other reported decreased IR, but not BMI, and increased levels of T [224].

Other supplements

Other supplements purported to provide a range of antioxidant and anti-inflammatory benefits, including omega-3 fatty acids, N-acetyl-cysteine (NAC), CoQ10, probiotics, quercetin, resveratrol and melatonin have been explored in PCOS. A meta-analysis (nine RCTs) of women with PCOS ($n=591$) receiving omega-3 supplementation reported reductions in HOMA-IR, TC, TAG and LDL-C, though showed no effect on other metabolic parameters or T [225]. In a meta-analysis of eight RCTs ($n=910$) examining NAC supplementation (the acylated form of L-cysteine), researchers reported improved glucose regulation and a greater likelihood of conception and livebirths in women with PCOS compared with placebo [226]. In a single RCT ($n=60$) CoQ10 supplementation (100 mg/day for 12 weeks) improved fasting glucose and insulin, HOMA-IR, insulin sensitivity index and TC, compared with the placebo group [227]. Two meta-analyses reported probiotics improved FAI, SHBG, IR and blood lipids, with no differences in weight or hirsutism between intervention and placebo groups [228, 229]. These findings may be linked to lower microbial diversity and increased intestinal permeability in women with PCOS [230, 231]. In regards to quercetin and resveratrol, which are both food derived polyphenols with a strong antioxidant capacity, one systematic review (three experimental studies, $n=246$ women with PCOS) reported

quercetin supplementation improved measures of IR and testosterone levels, but not anthropometry compared with placebo [232]. Similarly, one RCT in women with PCOS ($n=61$) reported resveratrol (800–1500 mg/day for four days) improved androgen and metabolic profiles and oocyte and embryo quality compared with placebo [233]. Finally, a systematic review (two RCTs and one cell-culture study) investigating the effects of melatonin supplementation in women with PCOS using assisted reproductive technologies reported melatonin significantly increased clinical pregnancy rates but not live birth rates [172]. A more recent RCT ($n=56$) reported improved levels of T, hirsutism, inflammatory and oxidative stress profiles in women receiving 10 g melatonin/day for 12 weeks, compared with placebo [234].

Herbal medicine

To date the most recent and comprehensive review (Cochrane review including five RCTs and $n=414$ women with PCOS) investigating the effects of herbal medicine on reproductive outcomes, reported no difference between the use of Chinese herbal medicine (CHM) and clomiphene for pregnancy rates, and limited evidence of increased pregnancy rate for CHM with clomiphene compared with clomiphene alone [235]. This review concluded that there was inadequate evidence to promote the use of CHM for the treatment of subfertility in women with PCOS [235]. Similarly, a smaller systematic review (five studies) investigating the effects of four herbal medicines (green tea, cinnamon, spearmint and black cohosh) on menstrual regularity in PCOS, found limited high-quality evidence from RCTs to support their clinical use and concluded that evidence for safety was lacking [236].

More recently, a number of small RCTs investigating metabolic and reproductive effects of a range of herbal medicines have been published. Curcumin, an active compound in turmeric (*Curcuma longa*), may exert hypoglycemic effects via a number of mechanisms, including attenuation of circulating levels of tumor necrosis factor- α [237]. One RCT ($n=67$) reported decreased levels of fasting glucose following supplementation compared with placebo [238], while another ($n=51$) which used a lower dose (1000 mg/day versus 1500 mg/day) and shorter duration (six weeks versus 12 weeks), reported no between group differences for fasting glucose, HOMA-IR or lipids [239]. *Salvia officinalis* or sage contains multiple active compounds that display antioxidant effects and therefore effects on glucose metabolism and insulin sensitivity [240]. One RCT ($n=72$) reported consuming sage extract for eight weeks improved IR and reduced BMI, with no effects on WHR or blood pressure [241]. *Foeniculum vulgare*

or fennel may provide protective effects on hormonal abnormalities in PCOS via its actions as a phytoestrogen [242]. One RCT ($n=55$) reported that six months of fennel tea and dry cupping was as effective as metformin for reducing BMI and menstrual cycle length [243]. *Glycyrrhiza glabra* or licorice contains active phytochemicals including isoflavane and glabridin, which have been shown to have antiandrogenic effects [244]. Two experimental studies in healthy women ($n=9$) [245] and women with PCOS ($n=32$) [246] reported that 3.5 g/day of licorice extract decreased T [245] and reduced side effects of spironolactone [246]. *Mentha spicata* (spearmint), *Zingiber officinale Roscoe* (ginger), *Cinnamomum cassia* (cinnamon) and *Citrus sinensis* (citrus) have been shown to exert anti-inflammatory and hypoglycemic effects [247–250]. One RCT in infertile women with PCOS ($n=60$) comparing the effects of a herbal mixture (citrus, ginger, cinnamon and spearmint) with clomiphene citrate (CC), herbal mixture alone, or CC alone reported that the herbal mixture, with or without CC, improved circulating antioxidant levels, IR and fasting blood glucose, but not menstrual regularity when compared to CC alone [251]. While observations from emerging research are promising, to support the safe translation of findings into the clinical setting there is a clear need for larger clinical trials investigating the efficacy and safety of herbal medicine use in PCOS.

Other traditional, complimentary and integrative medicine approaches

Acupuncture may provide beneficial impacts on sympathetic function [252] and ovarian blood flow [253] in women with PCOS. A recent meta-analysis of 22 RCTs ($n=2315$ women with PCOS) reported recovery of the menstrual period in the acupuncture group when compared with placebo, but no evidence for differences between groups in terms of live birth, pregnancy and ovulation [254]. While an earlier meta-analysis reported a significant reduction in BMI following acupuncture use, this was mainly due to one RCT ($n=80$) which compared acupuncture and the oral contraceptive pill to the oral contraceptive pill alone [255]. When this study was removed, the pooled analysis was no longer significant [255].

Yoga gymnastics have been recommended as an example of moderate physical activity in the 2018 evidence-based PCOS guideline [18]. However, as yoga is considered a mind-body therapy that incorporates aspects of meditation, it may provide additional benefits beyond those gained through other forms of exercise [256]. While one systematic review (16 observational and experimental studies, $n=365$ women with

PCOS) reported yoga may provide a range of psychological, reproductive and metabolic benefits, no meta-analysis was performed and a limited summary of included studies made it difficult to confirm findings [257]. A more recent systematic review (11 experimental studies) included a meta-analysis of two RCTs and found that yoga significantly decreased clinical hyperandrogenism, menstrual irregularity and fasting glucose and insulin [258]. Lastly, findings from a recent RCT ($n=67$ women with PCOS) suggests that 90 minutes of yoga per day for six weeks can significantly reduce hirsutism, waist and hip circumference when compared to controls [259]. Please see Table 5 for a summary of available evidence from meta-analyses and experimental studies investigating the effects of TCIM on PCOS outcomes.

Summary of findings and research gaps

The 2018 International Evidence-Based Guideline for the Assessment and Management of PCOS highlights lifestyle (diet, physical activity and/or behavioural) management as the primary initial treatment strategy [18]. It is important to consider that the definition of lifestyle management may warrant expansion consistent with the whole person model of healthcare provision, which may include care addressing psychological and sleep interventions, as well as a range of TCIM approaches [20]. In line with patient interest [31–35], and to assist women and healthcare providers in understanding the evidence to aid safe implementation of adjunct therapies, rigorous assessment of the evidence for these alternative lifestyle strategies in PCOS management is warranted. Using a holistic definition of patient care, this review has summarised evidence to date on the traditional components of lifestyle change (diet, physical activity and behavioural change), psychological interventions and non-pharmacological strategies (sleep, supplements, herbal medicine and other TCIM approaches). Table 6 provides a overview of current guideline recommendations alongside the key findings from this review, summarising the identified research gaps that need to be addressed before evidence-based recommendations for clinical practice can be updated.

With regards to traditional lifestyle treatment, the majority of studies focussed on weight loss as a primary treatment goal. This indicates more research is warranted to understand the role of diet and exercise in lean women and/or in weight gain prevention. RCTs using lifestyle interventions under isocaloric conditions that investigate effects on IR, body composition and androgens independent of weight loss are needed. Given the high risk of failure with long-term weight management [9, 37, 40, 261] and high attrition in weight loss trials in

PCOS [13], exploring interventions that focus on weight neural messaging around dietary quality and physical activity may also aid in optimising engagement, adherence and sustainability of lifestyle interventions. Future research should also identify subgroups who respond more favourably to weight loss [45, 53], to aid provision of a more targeted and personalised treatment approach.

With regards to diet strategies, there is a need for more research understanding the impact of low GI/GL diets on androgen status, as well as the biological mechanisms by which low GI/GL diets may impact reproductive and cardiometabolic outcomes associated with PCOS. With regards to physical activity, additional longer-term studies are required to guide exercise prescription in PCOS, although promising evidence supports the provision of vigorous aerobic exercise performed under supervised conditions (i.e. through referral to an exercise physiologist). While behavioural interventions are essential for long term sustainability of dietary and physical activity change, research in PCOS is scarce and interventions are not well defined. Future research should incorporate appropriate theoretical frameworks and clearly outline behavioural components utilised. This will aid intervention duplication and tailoring of active elements to ensure relevance in women with PCOS.

There is currently a lack of research investigating whether women with PCOS are at a higher risk of alcohol and smoking-related complications. This is particularly relevant given the well-established relationship between higher alcohol and cigarette use and rates of depression and anxiety in the general population [262–265]. There is also a need to better understand the relationship between alcohol intake and reproductive outcomes (particularly anovulatory infertility) [139], as safe alcohol limits in PCOS is currently unknown [139].

With regards to psychological interventions, the current evidence base for prevalence of mental health concerns in PCOS relies heavily on symptom prevalence. More adequately powered, gold standard prevalence studies using structured diagnostic interviews administered by appropriately qualified professionals are needed. While QoL has recently been highlighted as a core outcome in PCOS research [266], the application of QoL tools in clinical care is still unclear, with research yet to validate QoL tools longitudinally or identify clinically meaningful differences in QoL scores. The emerging evidence showing support for the use of CBT in PCOS [152–154] highlights an opportunity for tailoring of this psychological intervention to meet the specific mental health needs of women with PCOS, with a focus on how management of mental health symptoms affect lifestyle modifications. CBT that incorporates elements of

mindfulness-based stress reduction also warrants further investigation.

Future research in PCOS and sleep disorders should include more high-quality research in subclinical disorders using objective sleep measures (polysomnography and actigraphy). Future work should also consider emerging evidence showing that disturbed sleep can detrimentally effect energy expenditure, which may increase adipose tissue deposition and exacerbate IR [164, 184, 186, 267–271], thereby worsening the presentation of PCOS. Further, a consideration of how sleep disturbance can reduce engagement with positive lifestyle changes, for example through the disruption of appetite regulation [272, 273] or via contributing to poor mental health outcomes [190, 274], is warranted. CBT interventions including elements of stimulus control and psychoeducation are effective non-pharmacological treatments for both clinical sleep disorders and sleep disturbances in the general population [275–277]. RCTs in women with PCOS that investigate effects of CBT on dietary intake, energy metabolism, appetite regulation, anthropometry, adherence to lifestyle changes and PCOS features are required.

With regards to TCIM, there is a vast array of literature suggesting some beneficial effects of vitamins (B-group vitamins, folate, vitamins D, E and K), vitamin-like nutrients (bioflavonoids, carnitine and α-LA), minerals (calcium, zinc, selenium, and CrP) and other formulations (such as melatonin, omega-3 fatty acids, probiotics, NAC and cinnamon) in PCOS [278]. However, the quality of evidence across studies ranges from meta-analyses of RCTs (vitamin D, omega-3 fatty acids and NAC) to single retrospective observational studies (vitamin K and carnitine). In addition, heterogeneity in results related to factors including variable PCOS presentation and study methodology make it difficult to draw definite conclusions. Future research should focus on specific populations within PCOS, for example age, BMI or phenotype (factors which substantially affect nutrient sufficiency), and outline more consistent approaches to supplement formulation, dosage, intervention duration and type of comparator used. Mechanistic studies are also needed to investigate herb- or nutrient-drug interactions (with common pharmacological treatments used in PCOS) and other possible interactions with the biological processes underpinning PCOS. In regards to acupuncture and yoga, more sufficiently powered RCTs are needed to determine clinical relevance and integration into PCOS management is not yet warranted.

While current research is not sufficiently robust to support integration of TCIM into routine clinical practice, healthcare providers should broaden their knowledge pertaining to how these therapies can be safely and

appropriately utilised as adjuncts to conventional medical management [279–281]. TCIM is frequently used by women, with uptake of TCIM approaches increasing steadily over the past 10 years [31–35]. In women with PCOS, one cross-sectional study ($n=493$) found that 70% reported use of TCIM, namely nutritional and herbal supplements [282]. The most common reasons for use were to treat PCOS symptoms, improve general wellbeing and reduce depression. Of the women using TCIM, 77% had consulted with a complementary practitioner (acupuncturists, chiropractors, naturopaths and massage therapists) [282]. While the study did not report participants engagement with medical physicians, research in the general population has shown that patients are resistant to discuss TCIM use with their consulting physician [283–288]. Qualified health-care providers should be involved in TCIM discussions to help ensure appropriate use, maximise possible benefits and minimize potential harm [289]. For example, to sustain patient engagement in women who express the desire to experiment with supplementation, health-care providers could consider inositol supplementation, using a nuanced and case-specific approach that encapsulates the variety of pathologies in PCOS.

When considering all of the research summarised here, across traditional lifestyle, psychological, sleep and TCIM interventions, there is a clear need for more real-world PCOS research. This involves the translation of findings from clinical trials (where highly selected populations, intensive treatment protocols and expert multidisciplinary teams provide an ideal research setting), into the heterogeneous situations that face clinicians [290–292]. Health professionals provide care to women from diverse social contexts, are often restrained by finite resources and are required to juggle many competing demands for their time [290–292]. While some barriers to implementation, including time, resource and access issues are considered in the current PCOS guideline, they were generated by the guideline development groups and research is needed to validate and clarify their proposed concerns. Real-world research is required to: a) fully understand whether lifestyle recommendations can be practically integrated into current healthcare settings; b) tailor interventions to meet the unique needs of women with PCOS; and c) generate evidence on clinical outcomes that are of great relevance to patients and clinicians, such as live birth, miscarriage and menstrual regularity, which can be collected through routine care.

It is also important to highlight that while lifestyle management is a first-line treatment for PCOS, the addition of pharmacological therapies to further improve clinical features of hyperandrogenism, menstrual irregularity and infertility are often indicated [293]. In these instances,

prescribing physicians should consider how medical management and lifestyle change can be used in adjunct to optimise treatment. For example, the use of combined oral contraceptive pills may have detrimental effects on weight gain [294] and mental health [295], which can be mitigated by appropriate lifestyle intervention. Further, the combination of lifestyle modification and metformin has been shown to lower BMI, subcutaneous adipose tissue and improve menstruation compared with lifestyle modification alone, and hence may have an additive effect on improving cardio-metabolic outcomes in high risk groups [296].

Conclusion

Using the whole person or holistic definition of health, this review has highlighted emerging areas of research that could be considered for integration into future classifications of lifestyle management in PCOS. When developing lifestyle recommendations for PCOS management, interpreting and communicating evidence not only for diet, physical activity and behavioural interventions, but also psychological, sleep and TCIM approaches, will aid clinicians to deliver patient-centred care by affording women more choice and therefore autonomy over their treatment options. This sentiment aligns with the core objectives underpinning the 2018 PCOS guideline, which sought to understand the unmet needs of women with PCOS through continuing to engage consumers in co-design of guideline development, implementation, translation and dissemination.

Abbreviations

α -LA	Alpha-lipoic acid
BMI	Body mass index
CVD	Cardiovascular disease
CHM	Chinese herbal medicine
CrP	Chromium picolinate
CoQ10	Coenzyme Q10
CBT	Cognitive behavioural therapy
DASH	Dietary Approaches to Stop Hypertension
FINS	Fasting insulin level
FSH	Follicle stimulating hormone
FAI	Free androgen index
GI	Glycaemic index
GL	Glycaemic load
HDL-C	High density lipoprotein cholesterol
Hcy	Homocysteine
IR	Insulin resistance
LDL-C	Low density lipoprotein cholesterol
LH	Luteinizing hormone
$VO_{2\max}$	Maximal rate of oxygen
METS	Metabolic syndrome
MUFA	Monounsaturated fatty acid
MI	Myo-inositol
NAC	N-acetyl-cysteine
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovary syndrome
PUFA	Polyunsaturated fatty acid
RCT	Randomised controlled trial
SHBG	Sex hormone-binding globulin
TAC	Total antioxidant capacity

TC	Total cholesterol
T	Testosterone
TCIM	Traditional, complementary and integrative medicine
TAG	Triglycerides
T2DM	Type 2 diabetes
WC	Waist circumference
WHR	Waist-hip-ratio

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SC, SL, CA, SP, RT, MG, RB, NN, CB, CE, VR, AM, SA and LM reviewed the literature and wrote the first draft of the manuscript. SC, SL, CA, SP, RT, MG, RB, NN, CB, CE, VR, AM, SA and LM revised and edited the manuscript. SC and LM conceptualised and determined the scope of the manuscript and had primary responsibility for the final content. LM supervised the review process. All authors meet ICMJE criteria for authorship and approved the final version for publication.

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Management of Polycystic Ovary Syndrome in India

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrinopathy affecting women.^[1] It has an unknown etiology and is recognized as a heterogeneous disorder that results in overproduction of androgens, primarily from the ovary, and is associated with insulin resistance (IR).^[1] The Rotterdam 2003 criteria defines PCOS as incidence of any two of the three key criteria, namely, oligoovulation and/or anovulation, excess androgen activity and polycystic ovaries(PCO).^[1,2] However, the terminology used in the context of PCOS needs to be revisited to reflect the actual clinical nature of PCOS.

Studies of PCOS in India carried out in convenience samples reported a prevalence of 3.7% to 22.5%,^[3,4] with 9.13% to 36% prevalence in adolescents only.^[5,6] The wide variation in prevalence might be due to heterogeneous presentation of symptoms, diagnostic criteria practiced, limitations in diagnosis, age groups, and ethnic populations studied. Therefore, it is essential to consider these factors before diagnosis and/or management is initiated. Further studies are needed to understand the dynamics in prevalence rates of PCOS across India. Although there is a paucity of data from large scale surveillance studies, the higher incidence of PCOS risk factors (high body mass index

(BMI), IR) in India, suggests that the real extent of the problem might be currently underestimated.^[7]

The most common symptoms of PCOS can range from menstrual disorders, infertility, hyperandrogenemia to metabolic syndrome (MS).^[8] Elevated insulin levels due to IR may lead to development of PCOS by contributing to the underlying abnormalities seen in the hypothalamic-pituitary-ovarian axis. The resulting complex of physiological dysfunction produced by interrelated metabolic and hormonal factors, predisposes patients with PCOS to different complications like endometrial hyperplasia and cancer, cardiovascular disease (CVD), miscarriage, and acanthosis nigricans (AN).^[8] The complications add to the burden faced by patients, besides effecting social and emotional wellbeing, especially in adolescents, who are under the impression of being afflicted by a 'disease'.

Efficient management of PCOS provides a prospective window of opportunity to avoid the risk of associated complications. Treatment is broadly aimed at tackling (IR), effects of hyperandrogenism, irregular menstruation, and infertility. However, given the complex nature of PCOS, tailoring treatment options to the needs of individual patients can be a difficult clinical exercise. Long-term risks of PCOS must be balanced against current acute needs of the patients like the desire for continued fertility and the need to ameliorate the cosmetic challenges associated with PCOS. Due to its heterogeneous nature, effective management of PCOS needs a sustained, multi-pronged strategy with inter-disciplinary expertise, based on strong evidentiary framework to guide the standardization of care. However, in contemporary clinical practice in India, successful interdisciplinary cross-linking of efforts is stymied by the lack of awareness about PCOS and guidelines addressing its management. Further, in view of the higher risk of PCOS in Indian women, and the relative lack of medical infrastructure to deal with the chronic outcomes of PCOS, effective, evidence-based treatment guidelines for India are an immediate necessity. The current good clinical practice recommendations (GCPs) are an effort to provide a comprehensive framework for addressing

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issues relating to the management of PCOS in India. It is aimed at providing scientific evidence and well-balanced information on multi-disciplinary approach for the management of PCOS to health care providers in India.

METHODOLOGY

Systematic review of literature was conducted to provide the best possible evidence base for the GCPR. Existing guidelines, meta-analyses, systematic reviews, key cited articles relating to PCOS were reviewed by a group of doctors and recommendations relevant to Indian scenario were framed. The recommendations were discussed by an expert panel of gynecologists, physicians, ultrasonologists, endocrinologists, dermatologists, and pediatricians in a series of meetings. GCPR for each section of the guidelines were discussed and where there was little or no evidence, the panel relied on experience, judgment and consensus to make their recommendations. The current consensus GCPR are developed in accordance to the American Association of Clinical Endocrinologists (AACE) protocol for standardized production of clinical practice guidelines. Recommendations are based on clinical importance (graded as A: strongly recommended, B: suggested, and C: unresolved) coupled by four intuitive levels of evidence (1 = 'at least one randomized controlled trial (RCT) or meta-analysis of RCTs', 2 = 'at least one non-randomized or non-controlled, prospective epidemiological study', 3 = 'cross-sectional or observational or surveillance or pilot study' and 4 = 'existing guideline or consensus expert opinion on extensive patient experience or review').^[9]

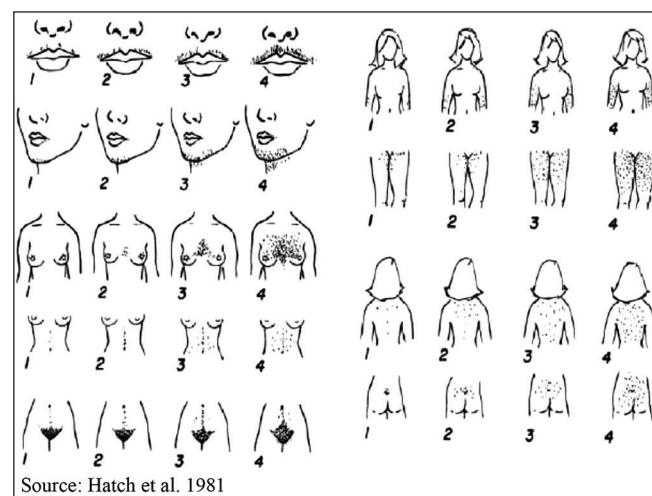
RISK FACTORS FOR THE ASSESSMENT OF PCOS

Current Evidence:

Several risk factors are associated with the incidence of PCOS, but not all are causative or predisposing factors for PCOS. However, their presentation is indicative of the incidence of PCOS. Thus the risk factors included in the current section indicate the risk for PCOS diagnosis but not the etiological likelihood of disease development. A preliminary understanding of the clinical characteristics and medical history of the patients is an invaluable resource for assessing the risk of PCOS incidence.

Biochemical risk factors

BMI is a key risk factor associated with the incidence of PCOS (mean BMI: 29.3 ± 7.5 vs. $25.6 \pm 5.8 \text{ kg/m}^2$, $p < 0.001$ in women with and without PCOS);^[10,11] higher BMI has been implicated as an important indicative marker of PCOS status. In women with PCOS, changes in BMI during adolescence are positively associated with changes in waist circumference ($p < 0.0001$), low density lipoprotein-cholesterol (LDL-C) ($p = 0.01$), triglycerides (TG) ($p = 0.008$), and systolic blood pressure (SBP) ($p = 0.002$).^[12] In adults, a BMI $\geq 23 \text{ kg/m}^2$ is considered overweight /obese,^[13] whereas in adolescents BMI $> 97.5^{\text{th}}$ percentile for age and gender are regarded as overweight/obese.^[14,15] In addition, development of clinical features of PCOS is often preceded by a history of weight gain,^[16,17] and factors independently associated with BMI: higher energy intake and glycaemic index, low physical activity, smoking, alcohol intake.^[18,19]



Source: Hatch et al. 1981

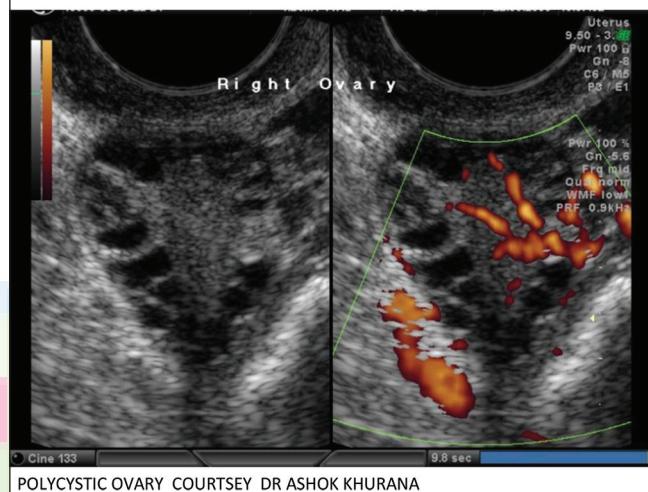


Figure 1: Modified Ferriman-Gallwey hirsutism scoring system

Development of IR and dysregulation of lipid metabolism are seen even in the early stages of PCOS.^[19] Significantly higher IR (fasting serum insulin) is observed in patients with PCOS with apparently normal oral glucose tolerance test (OGTT).^[20] Similarly, early signs of lipid metabolic dysregulation (elevated serum total cholesterol, TG and LDL-C levels and carotid intima-media thickness) were observed in age-matched patients with PCOS between 18-35 years.^[19] Presence of family history of PCOS or diabetes or an inadequate lifestyle have also been shown to be important risk factors for incidence of PCOS [Figure 1].^[21,22]

Clinical risk factors

Patients with normal menstrual cycle compared to patients with oligo/amenorrhea show significantly better metabolic parameters (BMI, fasting insulin, and Homeostasis Model Assessment-insulin resistance (HOMA-IR)).^[23] Due consideration to the patient's demographic profile is important in determining the PCOS status of a patient, since the risk and presentation varies in different patient groups. In adolescent patients, the diagnostic criteria of PCOS based on the signs and symptoms often overlap with the characteristics of normal puberty. In adolescents and younger women with PCOS, primary risk factors include disturbances in periodicity/timing of menstrual cycle and chronic anovulation while, in older women obesity, IR, and metabolic disturbances are

predominant.^[24] An association between younger age at menarche and development of PCOS was observed in adolescents (odds ratio: 0.63 [95% CI: 0.47; 0.85] p = 0.003).^[25] Thus, careful consideration must be given to the age of puberty and presentation of PCOS; deviations in terms of early or late puberty may be a risk factor for development of PCOS. Cutaneous manifestations like early acne or hirsutism, persistent acne and hirsutism for > two years, persistent severe acne; frequent relapse in acne; acne in facial V area are also known to be associated with PCOS [Figure 1].^[26,27]

Compared to women with PCOS of Caucasian ethnicity, Indian women with PCOS have a higher degree of hirsutism, infertility, and acne; and experience lower live birth rates following in vitro fertilization.^[28] Similarly, South Asians with PCOS have a higher prevalence of IR and MS compared to BMI matched PCOS patients from other ethnic groups (Definition: Appendix I).^[28] A rapid increase in the prevalence of PCOS associated morbid conditions such as IR, excess body fat, adverse body fat patterning, hypertriglyceridemia, and obesity-related disease (diabetes and CVD) in Asian Indians has been noted in a recent review of literature on PCOS.^[7] Thus, in patients of South Asian and specifically Indian ethnicity, regular PCOS surveillance is warranted.

Existing Guidelines:

Currently, no strategy for stratifying the risk of PCOS in the general population has been suggested by any major guidelines. The clinical practice guidelines from Endocrine society, USA,^[29] PCOS Australian alliance, Australia,^[30] The Royal College of Obstetricians and Gynecologists (RCOG), UK,^[31] and Society of Obstetricians and Gynecologists of Canada (SOGC), Canada^[32] have not proposed a system of risk classification in general population. However, in Indian clinical practice a preliminary assessment of risk in general population is likely to help in further referrals to higher medical centers for appropriate diagnosis and management. Such a risk classification is only to help in a preliminary assessment and not to posit an alternative scheme of diagnosis; in primary care settings such a risk classification is likely to help in proper channeling of patients to specialized centers for systematic diagnosis.

Recommendations on risk factors for assessment of PCOS

- It is recommended that Indian women showing at least one biochemical characteristic in conjunction with one clinical

symptom should be considered for further evaluation for the likelihood of PCOS (Grade A, EL 3).

- Biochemical characteristics: high BMI for overweight/obesity > 23 kg/m² for adults and > 97.5th percentile for age in adolescents, insulin resistance (acanthosis nigricans as clinical marker of insulin resistance), family history of diabetes or PCOS, obesity and inadequate lifestyle, any marker of lipid metabolic dysregulation (elevated serum total cholesterol, triglyceride and LDL-C levels),
- Clinical symptoms: pubertal deviations (early or late), disturbances in periodicity/timing of menstrual cycle, presence of PCO and clinical signs of hyperandrogenism such as early acne or hirsutism, persistent severe acne, frequent relapse in acne, acne in facial 'V' area, persistent acne and hirsutism for more than two years
- In women suspected to have PCOS, it is recommended to screen and appropriately document all clinical and biochemical risk factors in the case history (Grade A, EL 4).
- It is recommended that patients who currently show either a clinical symptom or fit into a biochemical characteristic may be referred for further diagnosis when feasible or should be regularly monitored for appearance of other presentations of PCOS (Grade A, EL 4)
- It is recommended that individual patients with two or more clinical risk factors be subjectively assessed by the gynecologist and referred to an appropriate healthcare provider for further diagnosis of PCOS (Grade B, EL 4).

DIAGNOSTIC CRITERIA FOR ADULTS AND ADOLESCENTS WITH PCOS

The three main criteria for diagnosis of PCOS are androgen excess (AE), chronic anovulation, and presence of (PCO) [Table 1].^[2,29,33,34] Initially, hyperandrogenism (clinical or biochemical) and anovulation along with recommendations for exclusion of other mimicking etiologies were common diagnostic criteria.^[2,33,34] The European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) sponsored Rotterdam group on PCOS introduced an extension to incorporate ovarian morphology (based on an ultrasoundogram).^[2] The Rotterdam criteria proposed that a positive observation of two of the three criteria (AE, ovulatory dysfunction, or PCO) constituted a diagnosis for PCOS. A recent National Institute of Health (NIH)-sponsored workshop on PCOS endorsed the Rotterdam criteria for diagnosis of PCOS.^[35]

Table 1. Diagnostic criteria for PCOS

Category	Specific abnormality	Recommended diagnosis	NIH	Rotterdam	AE-PCOS
Androgen status	Clinical hyperandrogenism Biochemical hyperandrogenism	Hirsutism, acne, and central alopecia Increased total, bioavailable, or free serum testosterone levels	XX XX	X X	XX XX
Menstrual history	Oligo- or anovulation	Anovulation: frequent (< 21 d) or infrequent (> 35 d) bleeding intervals			
Mid-luteal progesterone test: for anovulatory bleeding in women with regular ovulation	XX	X		XX	
Ovarian appearance	Ovarian size/morphology on ultrasound	PCO morphology: presence of ^a 12 follicles of 2-9 mm diameter and/or ovarian volume > 10 mL without a cyst or dominant follicle > 10mm		X	X

PCOS: polycystic ovary syndrome; NIH: National Institute of Health; AE-PCOS: Androgen excess-polycystic ovary syndrome; PCO: Polycystic ovary, Source: Adapted from Legro *et al.* 2013

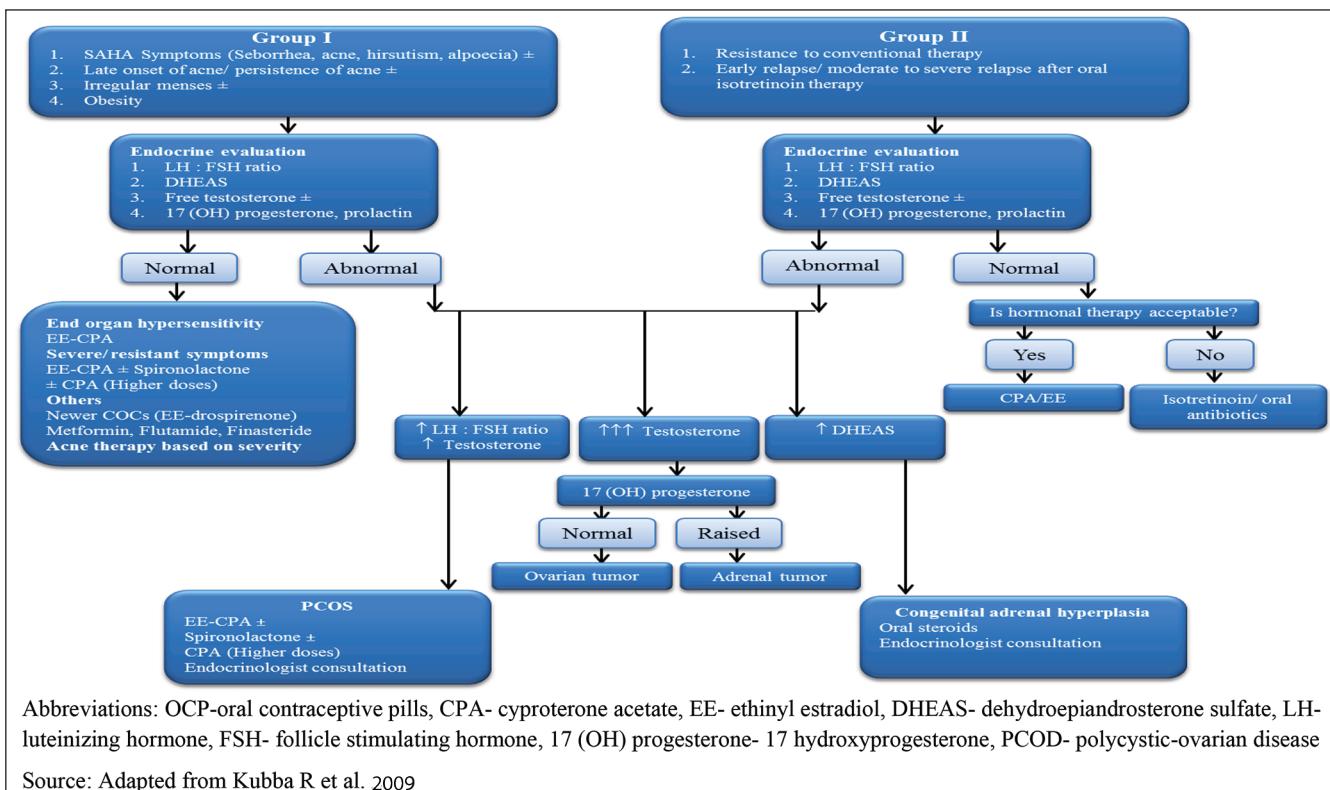


Figure 2: Treatment algorithm for acne, based on endocrine evaluation-Recommendation of Indian Acne Association

The diagnostic criteria proposed for diagnosis of PCOS are established in adults, and requires objective evaluation for diagnosis in adolescents.

Current evidence

Androgen excess

It is established using either clinical or biochemical determination of hyperandrogenism.^[2]

Biochemical hyperandrogenism

Biochemical hyperandrogenism is a measure of androgen levels, determined by total, bioavailable, or free serum testosterone (T) levels.^[36] In addition, the free androgen index (FAI = 100 x [total testosterone/ Sex hormone-binding globulin]) is also widely used.^[30] However, total serum T levels are considered more reliable and suitable for diagnosing androgens status.^[3,37] Given the methodological challenges, variability in T levels during pubertal development,^[38] and uncertainty in clinical practice^[39] defining absolute values using local assays that are diagnostic of PCOS and/or to exclude other causes of hyperandrogenism is preferable. Further, since the physiological T levels alter with pharmacological agents used for induction of periods, diagnosis of AE should not be carried in these subjects.

Clinical hyperandrogenism

Clinical hyperandrogenism includes hirsutism, acne, and androgenic/ central alopecia.^[30]

A. Hirsutism: Hirsutism is the excessive growth of thick, dark terminal hair in women where hair growth is normally absent.

^[40] The modified Ferriman-Gallwey (mFG) score is used to grade hirsutism,^[41] which is also used in India.^[37,42-44] A score of 0

Appendix Table 1: Grading of acne severity: Recommendation of Indian Acne Association

Mild acne (Grade I)	Comedones < 30
Predominance of comedones	Papules < 10 No scarring
Moderate acne (Grade II)	Comedones any number Predominance of papules
Severe acne (Grade III)	Papules > 10 Nodules < 3 With or without scarring
Many nodules	Comedones any number Papules any number Nodules/cysts > 3 With scarring

Source: Kubba R et al. 2009

Appendix Table 2: Acne distribution by age groups: Recommendation of Indian Acne Association

Age group	Location of lesions	Type of lesions	Sex
Neonates	Cheeks, chin, eyelids, forehead	Papules and pustules, no comedones	Both
Infants	Full face	Comedones, papules, nodules, scars	Male
Preadolescent	Forehead, upper cheeks, nose	Predominantly comedonal, occasional papule	Both
Adolescent	Full face, seborrheic areas of torso	All types of lesions	Both
Adults	Chin, upper lip, jaws	Papules, excoriated papules	Female

Source: Kubba R et al. 2009 (Consensus recommendations of Indian Acne Association)

(none) to 4 (severe) in nine areas of the body is assigned with a maximum possible score of 36. Scores < 4 indicate mild hirsutism, 4–7 indicate moderate hirsutism, ≥ 8 indicate severe hirsutism.^[40,41] In addition, presentation of AN with or without obesity is suggested an additional diagnostic criteria in adults and adolescents [Figure 2].

B. Acne: Acne can be graded as mild, moderate, and severe forms of acne, based on the number and types of inflammatory lesions [Appendix Table 1]. The prevalence of acne varies in relation to age and ethnicity. In girls, acne starts between 12–14 years of age, and in boys between 14–16 years of age.^[45] A description of the location and type of acne lesions according to the age group, as described by the Indian Acne Association (IAA) is presented in Appendix Table 2.

Among the different variants of acne, the SAHA syndrome (seborrhea, acne, hirsutism, alopecia) denotes acne specific to endocrine abnormality of a subject. When diagnosing PCOS in adolescents, acne, a common and transient feature^[46] should not be interpreted in isolation, as is the case with androgenic alopecia.^[47]

C. Alopecia: Androgenic/central alopecia may also be presented as female pattern hair loss in some patients with PCOS. Ludwig score is used to grade androgenic alopecia.^[48]

Ovulatory dysfunction

Ovulatory dysfunction is assessed by menstrual history of oligo/anovulation with bleeding intervals outside the normal interval (25–35 days), happening frequently at ≤ 21 days and/or infrequently at ≥ 35 days. In adults with regular cycles and anovulation, the Rotterdam criteria suggest determining anovulation with mid-luteal progesterone test to help diagnose PCOS.^[11] The presence of oligomenorrhea during normal reproductive maturation in adolescents must not be confused with PCOS.

In adolescents, anovulatory cycles comprise 85%, 59% and 25% during the first, third and sixth years, respectively of normal puberty after menarche. Therefore, determining anovulation with mid-luteal progesterone test might help diagnose PCOS in adolescents, and is a matter of clinical debate. The high serum androgen and leutinizing hormone (LH) levels, occurring naturally during anovulatory cycles of adolescence, might not be sufficient to diagnose PCOS in them.^[49] A persistent observation of oligo-/amenorrhea beyond two years of menarche in children/adolescents can be evaluated as an early clinical sign of PCOS.^[50,51]

Table 2: Diagnostic tests for exclusion of PCOS

Test	Disorder	Abnormal values
Serum thyroid stimulating hormone	Thyroid disease	Hypothyroidism: If TSH > upper limit (0.5 mU/L) Hyperthyroidism: If TSH < lower limit (< 0.1 mIU/L)
Serum prolactin	Prolactin excess	> Upper limit of normal (2–29 ng/mL)
Serum 17-hydroxyprogesterone*	Non-classical congenital adrenal hyperplasia	Early follicular phase of normal cycle: 200–400 ng/dL

PCOS: Polycystic ovary syndrome, TSH: Thyroid stimulating hormone,

*To be done before 8 a.m.

Polycystic ovary

Polycystic ovary morphology as defined by ESHRE/ASRM consensus criteria is as at least one ovary with ≥ 12 follicles of 2–9 mm (between day 2–5 of cycle) or ovarian volume > 10 mL in the absence of a cyst or dominant follicle > 10 mm,^[52] established with ultrasound examination of ovaries. It is also endorsed by the Rotterdam criteria^[2] and NIH.^[35] It is important to distinguish PCO from multi-follicular ovaries to make an appropriate diagnosis of PCO morphology.^[2,29] Multi-follicular ovaries contain larger (up to 10 mm diameter) and fewer (up to 6 each ovary) cysts, without hypertrophic echogenic stroma.^[53] A study comparing sonographic ovarian morphology in Indian women with and without PCOS found that a combination of two-three sonographic criteria is required to improve the sensitivity of PCO diagnosis.^[54]

In normal adolescent physiology, presence of multi-follicular/PCO is a common feature that decreases with cycle regularity^[55] and requires strict interpretation of ultrasonography findings of PCO morphology.^[56] Since no well-defined cut-off values for determining the levels of anti-mullerian hormone (non-invasive test) exist, ultrasound examination of ovaries is recommended for the diagnosis of PCO morphology in adolescents also.^[51] In adolescent girls with PCOS, obesity is common; magnetic resonance imaging (MRI) scanning is a more accurate modality^[57] to evaluate PCO in these adolescents.^[58]

On the other hand, ovarian volume and follicle number decrease from peak reproductive years to age > 40 years in normal as well as PCOS women.^[59] Therefore, diagnostic criteria with a combination of age, log ovarian volume, follicle number, and testosterone can be used to distinguish PCO morphology in women at menopausal stage.^[58]

Exclusion criteria for diagnosis of PCOS

PCOS is considered a diagnosis of exclusion. During the diagnosis of PCOS, it is important to screen all women to exclude other disorders like thyroid disease, prolactin excess and non-classical congenital adrenal hyperplasia, which mimic the symptoms of PCOS [Table 2].^[60–62] Mild prolactinemia and subclinical hyperthyroidism are common features in patients with PCOS. Therefore a referral to specialist is required if excess values are reported for prolactin and thyroid stimulating hormone (TSH) T4 levels.

Minimal diagnosis of PCOS in adolescents

Since the three diagnostic criteria for PCOS defined by the guidelines were derived for adults, to establish the diagnosis of PCOS in adolescents, other biochemical and clinical estimations can be ordered by the consulting physician or gynecologist. However, it is essential to order use minimal tests possible to diagnose PCOS in adolescent subjects to avoid burden of tests [Figure 2].

Existing guidelines

The clinical practice guidelines from Endocrine society, USA,^[29] PCOS Australian alliance, Australia,^[30] The RCOG, UK,^[31] and SOGC, Canada^[32] endorse the Rotterdam criteria for the diagnosis of PCOS. However, all guidelines advocate that specific phenotypes leading to diagnosis of PCOS be documented in all research studies and clinical care.

Recommendations for the diagnosis of PCOS in adults and adolescents

- In women with PCOS, for the objective assessment of cutaneous manifestations such as hirsutism, acne and androgenic alopecia, Indian specific grading should be performed with appropriate scales and possibility of other etiologies should be excluded (Grade B, EL 3)

Adults

- In adult women, it is recommended that diagnosis of PCOS be made using the Rotterdam criteria, meeting two of the following three conditions: (Grade A, EL 4)
 - Androgen excess
 - biochemical: serum total testosterone
 - clinical: persistent acne, hirsutism, female pattern hair loss
 - Ovulatory dysfunction
 - Polycystic ovary
- Presentation of acanthosis nigricans with or without obesity is an additional diagnostic criterion for PCOS in adults and adolescents* (Grade B, EL 4).
- Mild prolactinemia and subclinical hypothyroidism are common in PCOS; referral to specialist should be made when indicated by prolactin or TSH, T4 levels (Grade B, EL 4).
- Determination of anti-mullerian hormone levels for diagnosis of PCO is not recommended in adult and adolescent women (Grade A, EL 4).
- In peri-menopausal and menopausal women with a clinical history of prolonged periods of androgen excess and oligomenorrhea during the reproductive years, additional evidence of PCO morphology, low ovarian volume, follicle number, and testosterone should be considered as a diagnosis of PCOS (Grade B, EL 3).

Adolescents

- In adolescents, presence of oligomenorrhea or amenorrhea beyond two years of menarche should be considered an early clinical sign of PCOS, followed by Rotterdam criteria (of adults) for diagnosis of PCOS (Grade B, EL 4).
 - Androgen excess
 - biochemical: serum total testosterone
 - clinical: acne, hirsutism, female pattern hair loss
 - Ovulatory dysfunction
 - PCO with strict interpretation of ultrasonography findings
- Minimal diagnosis of PCOS in adolescents should include 5 tests (Grade A, EL 4):
 - Serum total testosterone (cut off 60 ng/dL)
 - OGTT (at zero and two hours after 75 g glucose load)
 - Serum 17-hydroxy progesterone (assessed at 8 am)
 - Serum TSH
 - Serum prolactin levels
- For the diagnosis of PCOS in adolescents, serum LH, follicle stimulating hormone (FSH) and cortisol should be assessed as indicated (Grade B, EL 4).

*Healthcare provider should assess other signs of IR and MS

MANAGEMENT OF PATIENTS WITH PCOS

Management of PCOS stretches beyond the realm of symptomatic treatment and encompasses management of long-term consequences that have clinical and psychological effects on women with PCOS. Both non-pharmacological and pharmacological management

strategies are crucial in overall management of PCOS. Because the three main characteristics of PCOS (hyperandrogenism, oligoovulation and IR) drive most of its long-term consequences, management approaches targeted at them may potentially provide improvement in all aspects of the syndrome.

Non-pharmacological interventions for management of obesity and body weight in patients with PCOS

Management of IR and obesity should be considered the first-line of treatment of PCOS. A meta-analysis reported improved levels of FSH, sex-hormone binding globulin, total T, androstenedione, FAI, and mFG score in women with PCOS as a result of lifestyle interventions (diet and physical activity); similar improvements in metabolic indicators were also reported.^[63-65]

Exercise

Current Evidence

Studies on PCOS from India reported a prevalence rate of 37.5%^[66] to 62.5%^[37] for obesity in patients with PCOS. A family history of obesity is also associated with PCOS phenotype.^[67] Obese women with PCOS have a higher incidence of characteristics of MS (hypertension, impaired glucose tolerance (IGT) and type 2 diabetes Mellitus (T2DM) as well as higher odds of irregular menstrual cycles and clinical hyperandrogenism than lean women with PCOS.^[66] Despite lack of large RCTs, the benefits of physical activity (at least 150 minutes of per week) in improving metabolic status and reducing the incidence of diabetes in high risk groups of general population have been demonstrated in small controlled studies.^[68,69]

In Indian adolescents with PCOS, compared to controlled (C) treatment with physical exercise, holistic yoga (Y) was found to significantly reduce the T levels ($Y = -6.01$, $C = +2.61$, $p = 0.014$), mFG score for hirsutism ($Y = -1.14$, $C = +0.06$, $p = 0.002$), and improved menstrual frequency ($Y = 0.89$, $C = 0.49$, $p = 0.049$).^[70] Another RCT on adolescents with PCOS from India found significantly improved fasting insulin and glucose levels, HOMA-IR, and lipid values, independent of their anthropometric changes, with yoga practice compared to conventional physical exercise.^[71]

Existing guidelines

Clinical practice guidelines from Endocrine society^[29] and RCOG^[31] suggest exercise therapy in the management of weight and obesity in PCOS.

Recommendations on non-pharmacological management of PCOS- physical activity

- In adults and adolescents with PCOS, daily strict physical activity sessions for at least 30min/day or 150min/ week are recommended (Grade A, EL 4).

Diet

Current evidence

While the benefits of diet control on obesity and IR in PCOS have been widely reported, data from RCTs, especially in Indian women is limited. Women with PCOS have been reported to have higher prevalence of central obesity.^[72] In women with PCOS and obesity, weight loss through diet control has been shown to improve pregnancy rates, normalize hyperandrogenemia,^[64,73,74] improve

insulin sensitivity, menstrual functions, and hirsutism.^[73,75]

However, no PCOS-specific diet has been reported. Therefore, it is essential to consult dietician for optimal weight management in women with PCOS. In patients with weight loss response after lifestyle modification + calorie-restricted diet as first-line therapy, weight neutral, insulin sensitizer drugs such as metformin can be used as second-line therapy.

Existing guidelines

The clinical practice guidelines from Endocrine society,^[29] RCOG^[31] and PCOS Australia alliance,^[30] suggest using low calorie diet as first-line therapy for the management of obesity in PCOS.

Recommendations on non-pharmacological management of PCOS- dietary

- For the management of obesity in adults (BMI > 23 kg/m²) and adolescents (BMI > 97.5th percentile for age) with PCOS, it is recommended to follow lifestyle modifications in combination with healthy, balanced diet consisting of regular, calorie-restricted meals (Grade B, EL 4).
- In adult and adolescent women with PCOS, it is recommended to routinely screen for BMI and waist circumference as an index for increasing adiposity and development of hyperandrogenism (Grade A, EL 3).
- It is recommended to follow calorie restricted diet (low carbohydrate and fat, high protein) in consultation with dietician and lifestyle modification as first-line therapy for at least 6 months, then add metformin as second-line therapy (Grade B, EL 4).

PHARMACOLOGICAL INTERVENTIONS FOR MANAGEMENT OF PATIENTS WITH PCOS

As discussed above, the choice of treatment in women with PCOS can be broadly categorized to treat the symptoms of menstrual irregularities (MI) and hyperandrogenism.

Menstrual irregularity

Current evidence

In women with (MI), proliferation of endometrium can be inhibited using either cyclic progestin or combined oral contraceptives (COCs: estrogen + progestin). Low-dose COCs (< 50 mcg of estrogen in combination with a progestin) have been the mainstay of treatment for MI in patients with PCOS not willing to conceive. In order to reduce the risk of endometrial proliferative disorders, progesterone withdrawal bleeds are generally accepted as first-line therapy to ameliorate cycle regularity in women with PCOS. Three issues have to be considered while choosing a COC: type of progestin compound used, type of estrogen compound used (usually 30 mcg ethinyl estradiol [EE]), and dosage of progestin and estrogen compounds in combination.^[76]

Current evidences from India in the management of MI in women with PCOS are available on COCs with two progestin components- drospirenone and desogestrel. The effects of two COCs 3 mg drospirenone vs. 0.15 mg desogestrel (in combination with 30 mcg EE) on MI in women with PCOS were compared for 6 month treatment period and 6 months

post-treatment.^[42] Although patients from both groups achieved menstrual regularity during the treatment, higher proportion of patients from drospirenone group continued to have regular cycles (44.8%) than desogestrel group (17.2%) at 6 months post-treatment ($p < 0.01$). In another study, drospirenone group was effective in reducing the hirsutism score in patients with both MI and.^[42] Overall, drospirenone containing COCs are more efficient compared to desogestrel containing COCs because of its anti-androgenic effects on menstrual cycle regularity, lipid profile, Blood Pressure(BP), and hormonal profile.^[42] Besides drospirenone and desogestrel, other progestins commonly used in India for clinical practice, either as cyclic progestin or COCs, for the management of MI in women with PCOS include natural micronized progesterone, dienogest, nor-ethisterone and the levonorgestrel- intrauterine system (LNG-IUS).

Since there is limited evidence of use of COCs in adolescents with MI, physician discretion is needed to judge the long-term effects of estrogen component during normal pubertal development. With clinical experience on patients with PCOS pan-India, the expert panel has suggested use of only low-dose COCs for short-periods (up to 7 days) to attain MI in 12-16 year old patients. In this age group, MI was defined as achievement of at least 4 cycles/ year. Similarly, in adolescents above 16 years of age, use of low-dose COCs is permissible for the management of MI.

The AE in women with PCOS is also linked to IR and consequent hyperinsulinemia,^[77] driving the use of insulin sensitizers such as metformin^[78] and thiazolidinediones^[79] in the management of PCOS. The effects of metformin on glucose homeostasis and improved cycle pattern are mainly attributed to increased insulin sensitivity.^[80] Metformin in combination with a low-dose anti-androgen (spironolactone) was more beneficial than either drug alone in improving MI in adult women with PCOS, presenting with oligo-/amenorrhea, hyperandrogenism and PCO morphology.^[81,82]

However, metformin monotherapy for six months resulted in regular menses within 4 months of treatment, but a consistent reversal towards pre-treatment conditions was observed within 3 months of metformin withdrawal.^[83] Adverse events such as vomiting, nausea, diarrhea, and hyperadrenergic symptoms were reported in patients taking metformin including drug withdrawal in subjects.^[81] Therefore the expert panel recommends against the use of metformin as first-line therapy for MI, but as second-line therapy with or without low-dose COCs, if COCs are not successful or tolerated.

The duration of metformin treatment for treatment of ovulatory dysfunctions in adolescents is not established due to very limited evidence from long-term studies and conflicting evidences from short-term studies. Therefore an extrapolation of evidence from studies conducted in adults may be required to recommend the use of metformin in adolescents. Use of spironolactone alone for the management of MI seems clinically inappropriate, since MI have been reported in 18% patients with low-dose spironolactone (50-100 mg daily) and in 70% patients with high-dose (200 mg daily).^[84,85] In an Indian study, polyuria (> 5%), abdominal pain, MI (> 10%), and dryness of mouth were reported in patients with PCOS taking spironolactone, and caused drug withdrawal in four subjects.^[81]

Existing guidelines

The ACOG recommends low-dose COCs as primary treatment option for improved MI and other menstrual disorders in women with PCOS.^[86] The clinical practice guidelines from Endocrine society,^[29] RCOG^[31] and PCOS Australia alliance,^[30] also recommend use of hormonal contraceptives as first-line therapy for menstrual abnormalities of PCOS. The guidelines from Endocrine society^[29] further recommend screening contraindications to COC use via established criteria set by 'Centers for disease control and prevention (CDC)- US medical eligibility criteria for contraceptive use'.

Recommendations on management of menstrual irregularity in PCOS [Figure 2]

Adults

- In adults with PCOS showing menstrual irregularity, it is recommended to include progesterone withdrawal bleeds as first-line therapy till menopause to avoid the risk of endometrial proliferative disorders (Grade A, EL 4)
- In adults with PCOS who do not intend to conceive, it is recommended to use COCs (drospirenone and desogestrel as progestin component) for the management of menstrual irregularity (Grade A, EL 1). Drospirenone has been shown to be more beneficial than desogestrel in Indian conditions.
- In women with PCOS, metformin is not recommended as first-line therapy for the management of menstrual irregularity (Grade A, EL 4).
- In women with PCOS, spironolactone is not recommended for menstrual irregularity (Grade B, EL 4)
- In adults and adolescents with PCOS, if there is no improvement of menstrual irregularity with COCs or COCs are not tolerated, it is recommended to use insulin sensitizers such as metformin (with or without progestins), but not thiazolidinediones for the management of menstrual irregularity (Grade A, EL 2).

Adolescents

- In adolescents with PCOS, it is suggested to use low-dose COCs (with or without anti-androgenic progestins- drospirenone and desogestrel) for the management of MI (Grade A, EL 4).
- Between 12-16 years of age, low-dose COCs only to be used, for short period (up to 7 days)
- After 16 years, low-dose COCs to be used
- Menstrual regularity: 4 cycles/year in adolescents of 12-16 years
- In adults and adolescents with PCOS with menstrual irregularity and hirsutism, low-dose COCs are suggested (Grade A, EL 2).

Hyperandrogenism

Current evidence

Hirsutism, acne and androgenic alopecia are the clinical symptoms of hyperandrogenism observed in women with PCOS. The AE in women with PCOS is manifested as excessive terminal hair growth and acne.^[87] A prevalence of 44.16% for hirsutism and AN and 20% for acne were observed in PCOS women from India.^[37] Features of clinical hyperandrogenism-hirsutism (33.6% vs. 28%) as well as acne and oily skin (40.6% vs. 22.6%) were found to be significantly higher in obese women with PCOS than lean PCOS women.^[66]

Management of hirsutism

Management of hyperandrogenism requires long-term and multi-dimensional treatment. This involves a combination of lifestyle modification, mechanical hair removal methods and pharmacological therapy for androgenic suppression.

Lifestyle modifications

A recent review comparing minimal or no treatment with lifestyle modifications (diet, exercise, behavioral or combined treatments) in patients with PCOS, reported improved body composition, hyperandrogenism and IR in women with PCOS.^[18] Further, metformin + weight reduction therapy are reported to reduce IR and T levels in women with PCOS.^[88]

Pharmacological therapy

As with menstrual cycles, COCs are first-line agents for pharmacologic treatment of hirsutism in women not willing to conceive.^[76] COCs with anti-androgenic progestins such as cyproterone acetate (CPA), drospirenone, desogestrel are generally used for the management of hirsutism in women with PCOS. Parallel administration of direct (mechanical) hair removal methods ameliorates the condition and reduces the time required.

Treatment with two mg CPA was shown to significantly reduce mean FG scores from (14.3 to 5.7) after 12 weeks of therapy in women with PCOS.^[89] In another study, two mg CPA + 35 mcg EE (for 48 consecutive cycles) demonstrated significant reduction of mFG score (mean FG score 10.4) in 73% subjects.^[90] No significant side effects or patient withdrawal were reported during 48 cycles of therapy, probably due to considerable effects on hirsutism, complete remission of acne, excellent cycle regularity and endometrial control observed with EE/CPA.^[90] Evidence from India comparing COCs: CPA, desogestrel (deso), and drospirenone (dros) in women with PCOS reporting MI + hirsutism, found that CPA showed the strongest anti-androgen activities with significant decrease in mFG score (treatment difference: CPA -5.29, dros -2.12, deso -1.69) after 12 months of treatment.^[91] In this study, very few patients reported adverse events: desogestrel group- bloatedness and sensation of weight gain, nausea and headache, rise of BP; CPA group- breast tenderness and absence of withdrawal bleeding in the pill-free week; drospirenone group- one patient with nausea, vomiting, and vertigo, another with altered liver function test. Studies on drospirenone (3 mg + 30 mcg EE)^[92] and desogestrel (150 mcg + 30 mcg EE)^[91] also demonstrated significant improvement in mFG score (4.6 vs. 6.4) compared to baseline.

In another evidence from India, compared to metformin, spironolactone demonstrated better improvement in hirsutism score (12.5 ± 4.9 and 12.9 ± 3.2 at baseline to 10.0 ± 3.3 and 8.7 ± 1.9 , respectively) after 6 months therapy in women with PCOS reporting MI, hirsutism.^[93] Whereas finasteride (5 mg/day), a 5 α -reductase inhibitor, in comparison with CPA (25 mg/day on days 5-14) + EE (20 mcg/day on days 5-25) was equally effective in reducing mFG scores after 9 months of treatment.^[94] However, due to the risk of teratogenicity (feminization of male infant) with their use,^[95,96] the expert panel has recommended to cease the use at least 6 months before planned pregnancy. Therefore, spironolactone and finasteride can be used as second-line treatment for the management of hirsutism in patients with PCOS.

Insulin sensitizers

In addition to hormonal therapy, administration of insulin sensitizers can improve the hyperinsulinemic as well as hyperandrogenic state in women with PCOS. However, due to limited evidence on use of metformin in adolescents without established glucose intolerance, the expert panel recommends against its use in adolescents with PCOS. Further, lifestyle modification is better than metformin in improving hyperandrogenism, obesity and signs of IR. Therefore the expert panel recommends lifestyle modification as first-line therapy followed by metformin in adolescents and children. Metformin should be initiated in children only after a wait-period of two years post-menarche.

By virtue of the nature of hyperandrogenism, the source of androgen cannot be eliminated permanently, and evidence suggests that hyperandrogenism requires long-term therapy. Therefore, ideal time to stop the hormonal therapy for hyperandrogenism cannot be established.

Risk of venous thromboembolism

Use of different COCs with varying risks of venous thromboembolism (VTE) is reported in general population.^[97] However evidence in women with PCOS is inconsistent. A recent meta-analysis of trials using either COCs with anti-androgens, or metformin in women with PCOS found that thromboembolic episodes were not reported in any study.^[98] A cross-sectional analysis on a database (2003-2008, US women) observed that PCOS women were more likely to have thromboembolism than those without and reported a protective association (OR 0.8; 95% CI: 0.73-0.98) with use of COCs.^[99] Since there is lack of consistent data on diagnosis and management of VTE specific to PCOS, the expert panel has suggested ways to minimize the risks and maximize the benefits of COC use. It is essential to regularly monitor the risk and provide three months of pause after one year of COC regimen. Investigations used to monitor VTE risk in general population (such as using duplex ultrasonography for deep vein thrombosis and chest X-ray/ventilation-perfusion scan/CT pulmonary angiography for pulmonary embolism) can also be adopted in women with PCOS.^[100]

Mechanical hair removal methods

Apart from the pharmacological approaches to deal with hirsutism, temporary and permanent methods of hair removal/reduction should also be used as first-line therapy for management of hirsutism in women with PCOS. Permanent methods of hair reduction therapy include electrolysis and photo epilation devices such as laser and intense pulsed light. In patients seeking permanent hair reduction therapy, it is essential to initiate pharmacologic therapy to minimize hair regrowth. Temporary hair removal methods such as depilation, epilation, and bleaching are effective in reducing facial hair growth in women with PCOS. In addition, topical treatment with eflornithine, an ornithine decarboxylase inhibitor approved by United States of food and drug administration (US-FDA), is also effective.^[76,86,101]

Management of acne

Management of acne needs careful selection of anti-acne agents according to clinical presentation and individual patient needs. Adjunctive therapies of topical applications along with hormone

therapy should be used as first-line therapy for synergistic effects. Physical treatment methods (lesion removal, phototherapy) are also suggested for acne management.^[102]

Topical applications

Based on the clinical presentation of acne in individual patient, specific topical medication for mild and moderate acne, and maintenance therapy should be prescribed in consultation with dermatologist. Benzoyl peroxide, topical retinoids, and topical antibiotics are used as first-line treatment for acne management.

Hormone therapy

Hormone therapy is suggested as first-line therapy for androgenic acne in women with PCOS, SAHA syndrome, HAIRAN syndrome (hyperandrogenism, IR, AN), or cutaneous hyperandrogenism. The IAA consensus guideline further justifies hormonal therapy in refractory/difficult acne and in nodulocystic acne where isotretinoin is either contraindicated or inadequate.^[45] However, due to the multiple causes of acne vulgaris, evaluation of hormonal status is a prerequisite before initiating hormone therapy.^[45]

Treatment with two mg CPA (+ 35 mcg EE) for 12 cycles significantly reduced acne score in all 41% cases (at baseline), with improved facial acne by the end of third cycle and improved thorax and back acne by end of 6th cycle.^[89] Treatment with CPA/EE combination for 48 cycles demonstrated a complete recovery of various types of acne lesions (moderate 67%, severe 33% cases at baseline) in all subjects (100%) within 24 cycles of treatment.^[90] In a study conducted in Indian women with PCOS, CPA demonstrated numerically higher reduction in acne score (CPA -1.52, drospirenone -1.42, desogestrel -1.41) compared to other pills.^[91] CPA has been well studied as an androgen receptor blocking agent, effective in acne management in females.^[103,104] Higher doses of CPA have been reported to be more effective than lower dose to treat acne.^[102]

In another study, drospirenone (3 mg + 30 mcg EE) containing COC showed significant improvement in acne at six cycles (54.9% vs. 31.4%, p < 0.05) compared to baseline.^[43] Although EE/drospirenone^[43] was administered only for 6 months, the beneficial effects in reducing hyperandrogenic features of hirsutism and acne were maintained up to 12 months after treatment. No adverse effects were reported. Similarly, desogestrel (150 mcg) + EE 30 mcg also showed significant improvement in the incidence of acne (54.1% vs. 23.4%) in women with PCOS from India after 6 cycles of treatment.^[44] No adverse effects were reported up to one year with EE/desogestrel also.^[44]

The guidelines issued by IAA recommend hormonal therapy in patients presenting acne with symptoms of SAHA syndrome (with or without irregular cycles) or resistance to conventional therapy/ relapse after isotretinoin therapy along with altered endocrine function. Based on the consensus developed by IAA, hormone therapy with low-dose EE/CPA or high-dose CPA or spironolactone are specifically suggested.^[45]

In adolescents with PCOS, improvement in acne was observed with the use of oral contraceptives with anti-androgen activity. In a latest randomized cross-over trial, therapy with

Appendix Table 3. Summary of studies from India conducted with anti-androgen progestins for the management of hyperandrogenism

Study author	Study details	Study end point summary
Cyproterone acetate Bhattacharya, et al. 2012 ¹¹	<ul style="list-style-type: none"> Double-blind randomized clinical trial Effects of OCPs containing DSG 30/150 µg (<i>n</i>=58), CPA 35/2000 µg (<i>n</i>=56) and DRSP 30/3000 µg (<i>n</i>=57) in PCOS, after 6 and 12 months of therapy 	<p>Change in baseline at 6 months and 12 months</p> <ul style="list-style-type: none"> mFG score: -2.09±3.29 and -5.29±5.88 Acne: -0.48±1.18% and -1.42±1.27% FAI: -6.09±7.51 and -10.57±7.93 T levels: -0.04±0.24 ng/mL and -0.03±0.42 ng/mL SHBG levels: 93.75±85.71 nmol/L and 142.91±60.71 nmol/L
Drospirenone Bhattacharya, et al. 2011 ¹²	<ul style="list-style-type: none"> Open label, single arm study Combination of DRSP 3mg vs EE 30mcg cyclically in the traditional (21±7) regimen <i>n</i>=51 (15-32 years) Evaluation at baseline and after six and twelve cycles of treatment 	<p>Baseline at 6 months and end point at 12 months</p> <ul style="list-style-type: none"> FG score: 6.7±5.2 at 0 month, 4.8±3.1%, at 6 months, 4.6±2.9 at 12 months, (<i>P</i><0.05) Acne: At 6 cycles 54.9% vs. 31.4%, (<i>P</i><0.05) and at 12 cycles 54.9% vs 29.4%, (<i>P</i><0.05) T levels: 0.51±0.3 ng/mL at baseline, 0.30±0.1 ng/mL at 6 months, 0.28±0.16 ng/mL at 12 months SHBG levels: 31.4±15.9 nmol/L at baseline, 155.1±67.0 nmol/L at 6 months, 157.6±68.7 nmol/L at 12 months FAI: 6.4±4.2 at baseline, 0.94±1.2 at 6th month, 0.81±0.89 at 12th month DRSP regular cycles 44.8% compared to DSG group 17.2% at 6 months post-treatment (<i>P</i><0.01) Study group, FG score at baseline 12.6± 4.5 to 8± 4.3 end of 6 months of treatment (<i>P</i>=0.04) at 8.4± 3.8 at 6 months post-treatment Out of 10 patients with acne, 50% in study group vs. 30% in the control group responded by 6 months treatment (<i>P</i>=.87) SHBG: Study- 20±12.0 nmol/L at base line; 62.3±50.3 nmol/L for 6 months (<i>P</i>=.5) Control- 22.5±17.2 nmol/L at baseline; 60±41.0 nmol/L for 6 months FAI: Study-8.9±7.9 at baseline; 2.8±4.9 for 6 months Control- 8.3±6.9 at baseline; 3.9±1.9 for 6 months(<i>P</i>=.12)
Kriplani, et al. 2010 ¹³	<ul style="list-style-type: none"> Randomized trial EE + DRSP vs DSG containing COCs <i>n</i>=60 (16-40 years) Study group-DRSP 3 mg + EE 30 mcg Control group-DSG 150 mcg + EE 30mcg, for 6 months and evaluation at 1,3 and 6 months during and post treatment 	<p>Change in baseline at 6 months and 12 months</p> <ul style="list-style-type: none"> mFG score: -1.53±3.98 and -2.12±6.58 Acne: -0.63±1.17% and -1.52±1.25% FAI: -5.27±9.22 and -7.89±9.13 T levels: -0.04±0.28 ng/mL and -0.06±0.32 ng/mL SHBG levels: 97.52±94.55 nmol/L and 131.52±72.89 nmol/L
Bhattacharya, et al. 2012 ¹¹	<ul style="list-style-type: none"> Double-blind randomized controlled trial Effects of OCPs containing DSG 30/150 µg (<i>n</i>=58), CPA 35/2000 µg (<i>n</i>=56) and DRSP 30/3000 µg (<i>n</i>=57) in PCOS, after 6 and 12 months of therapy 	<p>Change in baseline at 6 months and 12 months</p> <ul style="list-style-type: none"> mFG score: -1.53±3.98 and -2.12±6.58 Acne: -0.63±1.17% and -1.52±1.25% FAI: -5.27±9.22 and -7.89±9.13 T levels: -0.04±0.28 ng/mL and -0.06±0.32 ng/mL SHBG levels: 97.52±94.55 nmol/L and 131.52±72.89 nmol/L
Desogestrel Bhattacharya, et al. 2012 ¹¹	<ul style="list-style-type: none"> Double-blind randomized controlled trial Effects of OCPs containing DSG 30/150 µg (<i>n</i>=58), CPA35/2000 µg (<i>n</i>=56) and DRSP 30/3000 µg (<i>n</i>=57) in PCOS, after 6 and 12 months of therapy 	<p>Change in baseline at 6 months and 12 months</p> <ul style="list-style-type: none"> mFG score: -1.57±1.97 and -1.69±5.69 Acne:-0.95±1.21% and -1.41±1.32% FAI:-5.13±8.72 and -5.58± 9.15 T levels: -0.09±0.22 ng/mL and -0.10±0.39 ng/mL SHBG levels: 76.05±79.41 nmol/L and 99.53±67.52 nmol/L
Bhattacharya, et al. 2012 ¹¹	<ul style="list-style-type: none"> Open label, single-arm study, <i>n</i>=42 Therapeutic effects DCG (150 mg) and EE (30 mg) combination pill for 12 months 	<p>Change from baseline and 12 months</p> <ul style="list-style-type: none"> FG score: 6.4±5.0 at baseline 4.6 ±3.6 at 6th month 3.7±3.4 at 12thmonth Acne reduced from 21% and 6%, (<i>P</i><0.0001) FAI: 8.4±9.7 at base line 1.1±1.1 at 6th month and 1.61±2.0 at 12th month SHBG levels: 31.03 ±22.2 nmol/L at base line 141.9 ±78.72 nmol/L at 6th month and 143.4 ±75.3 nmol/L at 12th month (<i>P</i><0.0001) T levels: 0.94±0.2 ng/mL at base line, 0.34±0.2 ng/mL at 6th month and 0.37±0.2 ng/mL at 12th month
Spironolactone Ganie, et al. 2013 ¹⁴	<ul style="list-style-type: none"> Open-label, randomized study for 6 months Efficacy of combination of low-dose spironolactone and metformin vs either drug alone, <i>n</i>=169 Metformin <i>n</i>=56, spironolactone <i>n</i>=51, combination <i>n</i>=62 Dose- metformin (1000 mg/d), spironolactone (50 mg/d) 	<ul style="list-style-type: none"> Menstrual cycles/y baseline 6.13-2.54 cycles/y to 9.30-3.08 (<i>P</i>=.004) at 3 months and to 11.86 -3.20 (<i>P</i>=.01) at 6 months FG score: 13.11± 3.05 at baseline, 10.05 ±2.9 at 3 months and 0.09 ± 2.29 at 6 months (<i>P</i>=.05) T levels: 3.10±1.55 ng/mL at baseline, 2.19±1.17 ng/mL at 3 months, 1.58±0.74 ng/mL at 6 months

Appendix Table 3: Continued

Study author	Study details	Study end point summary
Ganie et al. 2004 ¹⁵	<ul style="list-style-type: none"> Open labelled and randomized controlled study Efficacy of spironolactone (50 mg/d) vs metformin (1000 mg/d) n=82 Metformin n=35 Spironolactone n=34 	<ul style="list-style-type: none"> The number of menstrual cycles in spironolactone from 6.6±2.1 at baseline, 9.0±1.9 at 3rd month and 10.2±1.9 at 6th month, (P=0.001) Metformin: 5.7±2.3/year at baseline, 7.4±2.6/year at 3rd month, 9.1±2.0/year at 6th month, (P=0.001) FG score spironolactone: 12.9±3.2 at baseline to 10.1±3.1, at 3rd month and 8.7±1.9 at 6th month, (P=0.034) Metformin: 12.5±4.9 at baseline, 11.4±4.1 at 3rd month and 10.0±3.3 at 6th month T values metformin: 83.9±45 ng/mL at baseline, 872.9 ±54 ng/mL at 3 months and 849.9±24.8 ng/mL at 6 months, (P=0.001) Spironolactone: 102.9±9.8 ng/mL at baseline, 55.9±28.8 ng/mL at 3 months and 55.9±28.8 ng/mL at 6 months, (P=0.001) Spironolactone: 73.3% in 11 acne patients Cimetidine: 42.8% in 6 acne patients The response of acne vulgaris to spironolactone was superior to that of cimetidine and this difference was significant (P<.05) Significant reduction in both the 0 and 2 h glucose with spironolactone also in those with AGT Significant reduction in the 1 and 2 h glucose and insulin levels with metformin therapy in those with AGT
Vaswani N et al. 1990 ¹⁶	<ul style="list-style-type: none"> Randomized trial Relative efficacy of spironolactone vs cimetidine n=15 spironolactone (100 mg daily), n=14 cimetidine (1400 mg daily) cyclically for 12 weeks 	<ul style="list-style-type: none"> The response of acne vulgaris to spironolactone was superior to that of cimetidine and this difference was significant (P<.05) Significant reduction in both the 0 and 2 h glucose with spironolactone also in those with AGT Significant reduction in the 1 and 2 h glucose and insulin levels with metformin therapy in those with AGT
Kulshreshtha et al. 2012 ¹⁷	<ul style="list-style-type: none"> Effect of 6 months of therapy with metformin (an insulin sensitizer) and spironolactone on glucose tolerance, n=88 n=42-metformin 1g daily n=46-spironolactone 50–75 mg daily 	<ul style="list-style-type: none"> Significant reduction in both the 0 and 2 h glucose with spironolactone also in those with AGT Significant reduction in the 1 and 2 h glucose and insulin levels with metformin therapy in those with AGT

CPA: Cyproterone acetate, COC: Combined oral contraceptives, OCP: Oral contraceptive pills, FG: Ferriman-gallwey, FAI: Free androgen index, mFG: Modified ferriman-gallwey, DSG: Desogestrel, EE: Ethynodiol dihydrogen, DRSP: Drospirenone, AGT: Abnormal glucose tolerance, T-levels: Testosterone levels, DCG: Dynamic electro cardiogram

medroxyprogesterone acetate and CPA for four months each,^[105] CPA significantly improved acne score and LH/FSH ratio.^[105] Due to the limited evidence on long-term use of COCs for hyperandrogenic features in adolescents, the expert panel suggested using COCs in adolescents based on the clinical presentation of acne, in consultation with a dermatologist.

A summary of studies conducted in India with COCs containing anti-androgen in progestins (cyproterone acetate, drospirenone, and desogestrel) for the management of hyperandrogenism features is presented in Appendix Table 3.

Management of alopecia

Although there is limited evidence on the management of alopecia, COCs and androgen blockers can be used to reduce alopecia. It is essential to determine and exclude etiologies that mimic alopecia. In a study on alopecia in general population, CPA+EE demonstrated a marked improvement in alopecia (success rate: 55%).^[106] In another study, CPA (for 6–9 months) demonstrated a marked reduction in hair loss, hair thinning, and seborrhea in androgenic feminine alopecia.^[107]

Existing guidelines

The clinical practice guidelines from Endocrine society,^[29] recommend use of hormonal contraceptives as first-line therapy for management of clinical features of hyperandrogenism such as hirsutism/acne in women with PCOS. The consensus guideline from IAA recommends the use of hormone therapy with low-dose EE/CPA or higher doses of CPA or spironolactone.^[45]

Recommendations for management of Hyperandrogenism in PCOS

Hirsutism

- Following options can be used alone or in combination to suit individual patient needs and clinical requirements for the management of hirsutism:
 - In adult women with PCOS who do not intend to conceive, it is recommended to use low-dose COCs with anti-androgen progestin (cyproterone acetate, drospirenone, or desogestrel) for the management of hirsutism (Grade A, EL 1). Cyproterone acetate has been shown to be more beneficial than other progestins in Indian conditions.
 - Use of direct hair removal methods are recommended along with COCs as fist-line therapy (Grade A, EL 1).
 - If there is no improvement with COCs or COCs are not tolerated, it is recommended to use spironolactone or finasteride (Grade A, EL 2); spironolactone or finasteride are suggested but recommended to stop 6 months before planned pregnancy.
- In women with PCOS, if menstrual irregularity and hirsutism are diagnosed, low-dose COCs with anti-androgenic activity (CPA, drospirenone, desogestrel) are suggested (Grade A, EL 2). The ideal time to stop hormonal therapy for hyperandrogenism cannot be established with existing evidence (Grade A, EL 4).
- Risk of thromboembolism with use of COCs can be managed by identifying susceptible patients and/or pausing treatment for 3 months after one year of treatment (Grade A, EL 4).
- In adolescents/children with hyperandrogenism, obesity and signs of insulin resistance, lifestyle modification is first-line

therapy; metformin is second-line therapy with a wait period of 2 years post-menarche in children (Grade A, EL 4).

- In adolescents with hyperandrogenism, if glucose intolerance is not established by OGTT, metformin should not be started (Grade B, EL 4).
- Due to insufficient evidence, alternative (acupuncture) and complementary therapeutic options (e.g. myoinositol, omega-3 fatty acids) are not recommended for the management of hyperandrogenism (Grade B, EL 4).

Acne

- In adults and adolescents with PCOS and acne, it is suggested to use topical medication along with pharmacological interventions based on the clinical presentation of acne as early as possible, in consultation with dermatologist (Grade A, EL 4).
- In adults with PCOS, it is suggested to use oral contraceptives (cyproterone acetate, drospirenone, or desogestrel as progestin component) as first-line therapy for management of all types of acne lesions (Grade A, EL 1). Cyproterone acetate has been shown to be more beneficial than other progestins in Indian conditions.
- In adolescents with PCOS and acne, it is suggested to use oral contraceptives (cyproterone acetate, drospirenone, or desogestrel as progestin component) based on the clinical presentation of acne, in consultation with dermatologist (Grade A, EL 2).

Alopecia

- In women with PCOS presenting with alopecia, COCs and androgen blockers are recommended as first line therapy (Grade B, EL 3).

EVALUATION AND MANAGEMENT OF ASSOCIATED MORBID CONDITIONS

A number of short- and long-term health problems are associated with PCOS. These include short-term psychosocial problems and long-term problems such as T2DM,^[108] obesity, CVD, sleep-disordered breathing^[109] and increased risk of endometrial cancer (EC) as well as short-term problems such as impaired fertility, complications during pregnancy.^[110]

PSYCHOSOCIAL MANAGEMENT

PCOS is strongly associated with reproductive and metabolic

implications affecting patients' psychological functioning and satisfaction with life.^[8] Psychological implications entail challenges in depression, physical appearance/feminine identity, eating habits and psychosexual dysfunction with significant impact on quality of life (QoL).^[111]

Depression

Current evidence

Increased rate of depressive symptoms compared to non-BMI matched controls^[112,113] with prevalence ranging from 28 to 64% (for depression) and 34 to 57% (for anxiety) have been reported in women with PCOS.^[114,115] Also, a lower health related QoL^[116] and increased risk of mental depression are reported in women with PCOS.^[113] In Indian women a 54% prevalence of depression (GHQ28 score ≥ 8) was reported, of whom 72% were obese, 70% had hirsutism, 61% had acne and 56% were infertile indicating a considerable effect on QoL of these women.^[117] The Patient Health Questionnaire 9 (PHQ-9) can be used to measure the severity of depression [Appendix Table 4],^[118] whereas the generic Short Form-36 (SF-36)^[119] and disease-specific polycystic ovary syndrome questionnaire (PCOSQ)^[120] are used to assess the health related QoL in women with PCOS [Appendix Table 5].

Existing guidelines

The clinical practice guidelines from Endocrine society^[29] and PCOS Australian alliance, Australia^[30] suggest screening all women with PCOS for depression and anxiety by history and, if identified, provide appropriate referral and/or treatment.

Recommendations on management of depression in PCOS

- In adults and adolescents with PCOS, it is recommended to routinely screen for depression and anxiety with appropriate psychological instruments (Grade B, EL 3).
- In patients with PCOS evaluated with depression and/or anxiety, psychological counseling by an appropriate professional is suggested, based on severity of disease (Grade B, EL 4).

Other psychosocial dysfunctions

Current evidence

In patients with PCOS, negative self-image coupled with lower self-esteem owing to their physical appearance that significantly

Appendix Table 4. Patient health questionnaire 9-scale for severity of depression

Name:

Date:

Over the last 2 weeks, how often you have been bothered by any of the following problems	Not at all	Several days	More than half the day	Nearly every day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Trouble falling or staying asleep, or sleeping too much	0	1	2	3
Feeling tired or having little energy	0	1	2	3
Poor appetite or overeating	0	1	2	3
Feeling bad about yourself- or that you are a failure or have let yourself or your family down	0	1	2	3
Trouble concentrating on things such as reading the newspaper or watching television	0	1	2	3
Moving or speaking slowly that other people could have noticed?				
Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
Thoughts that you would be better off dead or hurting yourself in some way	0	1	2	3
Total				

Source: Kroenke et al. 2001

Appendix Table 5. Polycystic ovary syndrome questionnaire

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
	A Severe Problem	A Major Problem	A Moderate Problem	Some Problem	A Little Problem	Hardly Any Problem	No Problem
Weight							
Concerned about being overweight?*							
Had trouble dealing with weight?*							
Felt frustration trying to lose weight?*							
Feel like you are not sexy because of being overweight?*							
Have difficulties staying at your ideal weight?*							
Infertility problems							
Concerned with infertility problems?*							
Felt afraid of not having children?*							
Feel a lack of control over the situation with PCOS?*							
Feel sad because of infertility problems?*							
Emotions							
Depressed having PCOS?*							
Easily tired?*							
Moody as a result of having PCOS?*							
Had low self-esteem having PCOS?*							
Felt frightened of getting cancer?*							
Worried about having PCOS?*							
Self-conscious as a result of having PCOS?*							
Late menstrual period?**							
Body Hair							
Growth of visible hair on chin?*							
Growth of visible hair on upper lip?*							
Growth of visible hair on your face?**							
Embarrassment about excessive body hair?**							
Growth of visible body hair?*							
Menstrual problems							
Headaches?*							
Irregular menstrual periods?*							
Abdominal bloating?*							
Menstrual cramps?*							

*During the past two weeks, how much of the time have you felt? **In relation to your last menstruation, how much the following issues were a problem for you? Source: Cronin *et al.* 1998

Appendix Table 6. Risk factors for cardiovascular disease and lipid target values^a in women with polycystic ovary syndrome

PCOS	At risk	At high risk
Risk factors	Obesity, cigarette smoking, hypertension, dyslipidemia, subclinical vascular disease, IGT, family history of premature CVD (55 years of age in male relative, 65 years of age in female relative)	Metabolic syndrome, T2DM, overt vascular or renal disease, cardiovascular diseases
Waist circumference, cm	88 *; ≥80 **	
BMI, kg/m ²	>30 ***	
BP, mmHg	Systolic=120; Diastolic=80	
Triglycerides, mg/dL	<150	
LDL target, mg/dL	≤130	70-100
Non-HDL target, mg/dL	≤160	100-130

^a Values are based on at least 12-h fasting lipid determinations. Predictive utility for CVD events based on non-fasting lipoprotein lipid values has not yet been clearly validated. *For Caucasian/African-American women, **For Hispanic, Native American, Asian (East and South), and European women, ***A 2-h post 75-g oral glucose challenge be performed in PCOS women, or alternatively in lean PCOS women with advanced age (>40 year), personal history of gestational diabetes, or family history of T2DM. PCOS: Polycystic ovary syndrome, IGT: Impaired glucose tolerance, CVD: Cardiovascular disease, T2DM: Type 2 diabetes mellitus, BMI: Body mass index, BP: Blood pressure, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, Source: Adapted from Wild *et al.* 2010

impacts the mood and QoL^[121] are observed. Similarly, significantly more patients with PCOS compared to community controls reported eating disorders (12% vs. 4%) and/or social phobia (27% vs. 2%)^[122], which may cause medical, psychological, social and occupational difficulties.^[123,124] Physical manifestations of PCOS such as hirsutism, obesity, MI and infertility can have a negative effect on the patients' sexual life.^[125]

Existing guidelines

The clinical practice guidelines from PCOS Australian alliance,

Australia^[30] suggest the screening and assessment of patient's psychosocial dysfunctions and if identified, offer appropriate treatment.

6.1.2 Recommendations on management of other psychosocial dysfunctions in PCOS

- If a woman with PCOS is positive on screening for any psychosocial dysfunction, the practitioner should perform a more detailed clinical interview (Grade B EL 4).

- In those evaluated with any psychosocial dysfunction, appropriate treatment for improvement of quality of life is suggested (Grade B, EL 4).

Type 2 diabetes mellitus

Current evidence

Diagnosis of PCOS confers a 5- to 10-fold increased risk of developing T2DM.^[126-128] IR, resulting in hyperinsulinemia also plays a role in the pathogenesis of reproductive disorders in women with PCOS.^[126,129] The prevalence of glucose intolerance in Indian women with PCOS^[93] was reported as 16.3% (adults 19.1%, adolescents 9.7%).^[67]

Due to the risk of IGT, T2DM, and IR in PCOS, evaluation of abnormalities in glucose intolerance at periodic intervals is essential.^[9,31,82] (A 75-gm (OGTT with 75 g- oral glucose load) has been recommended over measuring glycated hemoglobin (HbA1c) for the detection of T2DM^[130] and fasting glucose^[67] for assessment of IGT.^[2] An observational study from India reported '2-hour post-glucose insulin levels' as a better indicator of IR in women with PCOS than other techniques.^[131]

Lifestyle modification with exercise and diet are the first-line treatment for weight management and impaired IGT in women with PCOS. Due to the inherent IR in this condition, oral anti-diabetics (OADs) particularly insulin sensitizers such as metformin are the most promising pharmacological option.^[132] However, an early referral to specialist diabetological care is recommended for timely management of diabetes and its complications. Metformin alone or in combination with low-dose spironolactone/clomiphene has demonstrated significant alleviation of not only the MI but also glucose tolerance and insulin sensitivity in patients with PCOS.^[81,133]

Hyperthyroidism

Evidence from India reported high prevalence of thyroid disorders (higher mean TSH level 4.547 ± 2.66 vs. 2.67 ± 3.11 , $p < 0.05$) in women with PCOS than those without.^[134] Metformin can lower TSH levels in women with PCOS and hypothyroidism. Metformin (1500 mg/day) was shown to significantly decrease (mean \pm SD) TSH levels (7.78 ± 1.74 at baseline to 6.14 ± 2.47 , $p < 0.001$) over placebo in overweight women with PCOS and hypothyroidism after 6 months of treatment, with no significant change in free T3 and free T4 levels throughout the study.^[135]

Existing guidelines

The clinical practice guidelines from Endocrine society, USA recommend screening women with PCOS for IGT test and T2DM using OGTT or HbA1c and suggest rescreening based on development of clinical factors and/or symptoms of diabetes.^[29] The RCOG suggests fasting blood glucose test or an OGTT for screening of diabetes in women with PCOS. The clinical practice guidelines from Endocrine society recommend use of metformin in women with PCOS with T2DM or IGT and fail lifestyle modification and suggest the same in adolescent stage if the goal is to treat IGT/MS.^[29]

Recommendations for the management of diabetes in PCOS

- In women with PCOS who develop symptoms and/or a risk

factor of diabetes, screening at a clinically feasible periodicity is suggested (Grade B, EL 4).

- It is recommended to screen adult and adolescent women with PCOS for impaired glucose tolerance and T2DM using a 75 gm oral glucose tolerance test; an HbA1c test should be used only when an OGTT is not feasible (Grade A, EL 2).
- In women with PCOS who have impaired glucose tolerance or T2DM, it is recommended to use metformin alone, or in combination with oral contraceptives (Grade A, EL 1).
- Early referral to specialist diabetological care is recommended for timely management of diabetes and its complications (Grade A, EL 4)

Cardiovascular risk

Women with PCOS often have cardiovascular disease risk factors. The AE-PCOS society recommends all women with PCOS to be assessed for CVD risk; to test for BMI, waist circumference and blood pressure at each clinical visit.^[136,137] In women diagnosed with PCOS, a complete fasting lipid profile as well as OGTT (if $BMI > 30 \text{ kg/m}^2$, age > 40 years, personal history of GDM, or family history of T2DM) are recommended.^[136] A stratification of risk factors for CVD in women with PCOS given by AE-PCOS society is presented in Appendix Table 6.

In India a 37.5% prevalence of obesity ($BMI > 27.5 \text{ kg/m}^2$),^[66] high levels of BP ($SBP/DBP > 120/80 \text{ mm of Hg}$) inform prospective^[138] and cross sectional^[139] studies were reported in women with PCOS. Further, increased LDL-C, CVD risk factors, markers of dyslipidemia were noted^[131,139,140] markers of and atherosclerosis, flow-mediated dilatation of brachial artery ($12.18 \pm 2.3\%$ in PCOS vs. $8.3 \pm 2.23\%$ in control) and carotid intima media thickness (0.68 ± 0.11 in PCOS vs 0.52 ± 0.02 in control, $p = 0.01$) were reported in women with PCOS compared to control subjects.^[139] Epidemiological data from USA reported a relative risk of 1.53 (95% CI: 1.24; 1.90) for CVD (after adjustment for BMI and potential confounders) in women with very irregular cycles.^[141] Therefore, in women with PCOS showing CV risk factors, specialist CV monitoring and care is recommended, irrespective of the severity of their symptoms.

Existing guidelines

The clinical practice guidelines from Endocrine society, USA,^[29] PCOS Australia alliance, Australia,^[30] RCOG,^[31] and AE-PCOS society^[136] recommend screening women with PCOS for CV risk factors. The clinical practice guidelines from Endocrine society^[29] suggest lifestyle modifications as first-line therapy for CVD and metformin as second line therapy in patients failing to achieve weight reduction with lifestyle modification.^[29] The RCOG guidelines^[31] suggest hypertension should be treated, but recommended against the use of routine lipid-lowering treatment in women with PCOS and risk of CVD. Consultation with specialists has been recommended by other guidelines for prescribing lipid lowering agents.

Recommendations for the management of cardiovascular risk in PCOS

- It is recommended to screen for CV disease in adult women with PCOS by assessing risk factors: obesity (especially abdominal obesity), smoking, hypertension, dyslipidemia

- (increased LDL-C), vascular disease, IGT, high-sensitivity C-reactive protein, homocysteine, and family history of premature CVD (Grade A, EL 1).
- It is recommended to screen for CV disease in adult women with PCOS by assessing high risk factors: metabolic syndrome, T2DM, overt vascular or renal disease (Grade A, EL 1).
 - It is suggested to assess obesity (by BMI and WC), lipid profile, oral glucose tolerance test, and BP in adult women at baseline, and repeat lipid profile and OGTT at 6 months for borderline risk and one year for normal profiles (Grade B, EL 4).
 - Specialist CV monitoring and care is recommended in all patients showing CV risk factors, irrespective of the severity of their symptoms (Grade A, EL 4).

Pregnancy complications

Current evidence

A population based cohort study among women with PCOS from Sweden observed that PCOS was strongly associated with pre-eclampsia (adjusted OR 1.45, 95% CI: 1.24-1.69), preterm birth (2.21, 1.69 to 2.90), more than double risk of GDM (2.32, 1.88 to 2.88), and birth of large for gestational age infants (1.39, 1.19 to 1.62).^[142] The results are further confirmed in an independent meta-analysis by Kjerulff.^[143] Recurrent pregnancy loss (RPL) in women with PCOS is commonly associated with IR,^[144] hyperhomocystinemia (HHcy)^[145] and obesity.^[146] In a retrospective study on RPL, a significantly higher incidence of HHcy (70.63% vs. 57.26%, p < 0.04) and IR (56.34% vs. 6.83%, p < 0.0001) was observed in women with PCOS compared to controls. Further analysis revealed HHcy as a strong plausible factor for diagnosis of RPL than IR (probability percentage: HHcy = 43.32%, IR = 37.29%). Findings on association of PCOS and GDM are conflicting with respect to BMI. Recent systematic review and meta-analysis in women with PCOS observed a significantly higher risk for development of GDM in PCOS women than those without (OR: 2.89, 95% CI: 1.68-4.98), albeit with significant statistical heterogeneity due to sensitivity analysis (I² = 59.3%).^[147] An RCT in women with PCOS treated with metformin found no difference in the prevalence of pre-eclampsia (p = 0.18), preterm delivery (p = 0.12), or prevalence of GDM (p = 0.87) compared to controls during pregnancy.^[148]

A latest meta-analysis of RCTs (n=5) comparing the effects of metformin with insulin on glycaemic control, maternal and neonatal outcomes in GDM concluded that metformin is comparable with insulin and might be more suitable for women with mild GDM.^[149] An observational study from India reported significantly higher benefits of using metformin over insulin in the management of GDM and T2DM.^[150] Although metformin is reported to be comparable with or superior to insulin in terms of glycaemic control and neonatal outcomes, lack of strong evidence on use of metformin in Indian subjects restricts its clinical use.

Existing guidelines

The clinical practice guidelines from Endocrine society, USA^[29] recommend pre-conceptual assessment of BMI, BP and OGTT whereas RCOG guidelines recommend screening for GDM before 20 weeks of gestation, in PCOS women requiring ovulation.^[31] The clinical practice guidelines from Endocrine society^[29] and

RCOG guidelines^[31] suggest against the use of metformin as first-line treatment for pregnancy complications in women with PCOS.

Recommendations for the management of pregnancy complications in PCOS

- In women with PCOS planning to have children, it is recommended to screen for markers of obesity, hypertension and IR to reduce the risk of pregnancy related complications (Grade A, EL 3).
- In women with PCOS who have experienced a miscarriage, it is suggested to assess serum homocysteine levels for identification and treatment of hyperhomocystenemia mediated repeated pregnancy losses (Grade B, EL 3).
- In women with PCOS, it is recommended not to use metformin therapy only during pregnancy until specific evidence on beneficial effects is demonstrated (Grade B, EL 3).

Endometrial cancer

Current evidence

Long-term studies and meta-analyses have observed an increased risk of development of EC in women with PCOS.^[151-153] The symptoms, oligo-/amenorrhea, hirsutism, and infertility, as well as risk factors of PCOS, obesity and T2DM, are common to EC.^[154,155] Evidence for the applicability of transvaginal sonography (TVS) for predicting endometrial hyperplasia has been inconsistent in literature.^[156-158]

Indian studies on the measurement of endometrial thickness in women with PCOS have routinely used TVS at a cut-off of 4 mm.^[159-161] In the context of increased risk of EC in PCOS patients with prolonged amenorrhea, abnormal uterine bleeding, obesity and/or diabetes, it is essential to assess endometrial thickness and raise awareness about EC in these women. It has been established that inducing a withdrawal bleed every 3 to 4 months with progestogens can reduce the risk of EC in women with PCOS.^[156] However, since hyperinsulinemia is the primary cause of endometrial hyperplasia, use of insulin sensitizers can reduce the hyperplasia in these women. Overall, for timely detection and management of EC, it is appropriate to screen for development of cancer at regular intervals with reference to oncological specialist.

Existing guidelines

The clinical practice guidelines from Endocrine society^[29] suggest against routine screening for endometrial thickness in women with PCOS. The RCOG guidelines suggest investigating oligomenorrheic women and absence of normal withdrawal bleeds using local protocols such as ultrasound scan, endometrial sampling and/or hysteroscopy^[31] and recommend treatment with progestogens to induce a withdrawal bleed at least every 3-4 months.

Recommendations for assessment and management of endometrial cancer in PCOS

- In women with PCOS without abnormal bleeding, routine screening using TVS is not recommended (Grade B, EL 1)
- In women with PCOS with unexpected bleeding and spotting, it is suggested to assess endometrial thickness using TVS and report the same to the physicians (Grade B, EL 4).

- In women with PCOS and risk of endometrial carcinoma, it is suggested to use progestogens every 3-4 months (Grade B, EL 3).
- Regular oncological referrals, for screening at a clinically feasible periodicity, are recommended for timely detection of endometrial cancer (Grade A, EL 4).

Obstructive sleep apnea

Current evidence

Studies have identified a higher incidence of obstructive sleep apnea (OSA) in women with PCOS compared to controls, even after controlling for BMI.^[162,163] Fasting plasma insulin levels and glucose-to-insulin ratios were strongest predictors for OSA. Therefore factors other than obesity may be involved in the high prevalence of OSA in women with PCOS. Interestingly, a decreased likelihood of OSA was reported in adult and post-menopausal women taking hormonal contraceptives.^[163,164] There is a lack of quality evidence on OSA in women with PCOS from India.

Existing guidelines

The clinical practice guidelines from Endocrine society^[29] suggest screening all overweight/ obese women with PCOS for symptoms suggestive of OSA and, if identified, diagnosed using polysomnography and referred for appropriate therapy. The RCOG guidelines suggest an enquiry of snoring and daytime fatigue/somnolence in all women with PCOS, and educate about the possible risks of OSA, and, if identified, offer diagnosis and appropriate therapy.^[31]

6.6 Recommendations for of obstructive sleep apnea in PCOS

In adult and adolescent women with PCOS, it is suggested to routinely screen for OSA and insomnolence, if symptoms are suggestive of OSA, investigate using polysomnography and refer to appropriate institution for further therapy (Grade B, EL 4).

Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis

Current evidence

Ethnicity, increasing age and characteristics of MS (obesity, hypertension, dyslipidemia and diabetes) are risk factors of non-alcoholic fatty liver disease/ non-alcoholic steatohepatitis (NAFLD/NASH).^[165] A 15-60% prevalence of NAFLD is reported in women with PCOS.^[166-168] A cross-sectional, hospital-based study of women with PCOS from India reported a 67%, 31% and 35% prevalence of NASH, NAFLD and MS, respectively.^[169]

In the absence of other specific factors, serum markers for liver dysfunction (such as alanine amino transferase) may be used to screen PCOS women with co-existent IR and metabolic risk factors. However, because of low specificity and sensitivity of elevated levels of serum alanine amino transferase, diagnosing NAFLD in these women (PCOS with IR and/or MS) may require non-invasive quantification of fibrosis (ultrasound) and liver biopsy.^[170] In view of the potential complications of NAFLD and NASH in women with PCOS having IR and/or MS, early identification and management of NAFLD and MS is essential for overall reduction of effects of MS in PCOS women.

In non-diabetic non-cirrhotic NASH patients^[171] and pediatric

NASH patients,^[172] treatment with vitamin E (800IU/day) for 96 weeks demonstrated significant improvement in serum aminotransferase levels, hepatic steatosis, and lobular inflammation (early stage features) but not portal inflammation and hepatic fibrosis (more advanced histologic features). However, based on a meta-analysis^[173] that showed that RCTs with vitamin E and other antioxidants were heterogeneous (with respect to type and dose of drug, treatment duration and follow-up, population [pediatric versus adult], and implementation of lifestyle intervention) a recent review noted a firm conclusion on the effect of vitamin E on NAFLD cannot be made.^[174]

Existing guidelines

The clinical practice guidelines from Endocrine society^[29] suggest against routine screening of NAFLD and NASH but provide awareness of their possibility in women with PCOS.

Recommendations for NAFLD and NASH in PCOS

- In adult and adolescent women with PCOS, it is suggested to provide sufficient awareness on symptoms and complications of NAFLD and NASH and carry out appropriate screening in those diagnosed with insulin resistance and/or metabolic syndrome (Grade B, EL 4).
- In patients with PCOS and NASH, treatment with vitamin E is preferred and metformin is not suggested for reduction of metabolic syndrome with specialist inputs from a multidisciplinary team (Grade B, EL 1).

SUMMARY

PCOS is an important emergent public health problem in India that represents a unique trans-generational risk of transmission of a variety of systemic chronic diseases. It has not been possible in contemporary Indian clinical practice to formulate a comprehensive response which is commensurate with the scale of problem that PCOS poses. This has been mainly due to a lack of strong public and academic discourse centered on the proper management of this gargantuan, yet ill-recognized problem. A strong evidentiary foundation is the cornerstone on which the academic discourse on PCOS must be based. In addressing a key driver that feeds the inertia surrounding PCOS, the current GCPR seek to fundamentally redefine the paradigms of PCOS care in India. The approach of current recommendations is to provide a strong rationale for harnessing the mutual synergies in a modern multidisciplinary clinical setting to deliver quality PCOS care while providing an evidence-based structure to standardize the approach to PCOS management across treatment settings. It is hoped that the current GCPR will fulfil a key role in helping current clinical practices to transition to a comprehensive PCOS care paradigm in India.

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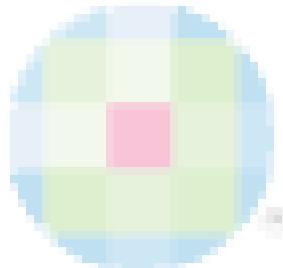
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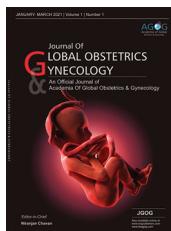
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Review Article



Adolescent Polycystic Ovary Syndrome

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ABSTRACT

Adolescence is a crucial stage of development defined by the World Health Organization as spanning from 10 to 19 years of age. It is marked by significant physical, cognitive, emotional, and social changes, including puberty, which is a key aspect of this phase. Diagnosing polycystic ovary syndrome (PCOS) in adolescents can be challenging because symptoms such as irregular periods, acne, and weight changes can overlap with normal hormonal changes during puberty. Irregularities in menstrual cycle and hyperandrogenism are considered for the diagnosis of adolescent PCOS. Polycystic ovarian morphology on ultrasound should not consider for the diagnosis of adolescent PCOS. Emotional well-being is a crucial but often overlooked aspect in adolescent girls with PCOS. A holistic approach is essential in managing PCOS. While pharmacotherapy plays a role, it should be integrated with education, counseling, lifestyle interventions, and other options such as cosmetic therapy. This comprehensive approach addresses the physical, emotional, and psychological aspects of PCOS.

Key words: Adolescence, Combined oral contraceptive pill, Pharmacotherapy, Polycystic ovary syndrome, Ultrasound

INTRODUCTION

Polycystic ovary syndrome (PCOS) is indeed one of the most common endocrine disorders among women of reproductive age.^[1] It affects 6–18% of adolescent girls.^[2,3] Adolescence is a crucial stage of development defined by the World Health Organization as spanning from 10 to 19 years of age. It is marked by significant physical, cognitive, emotional, and social changes, including puberty, which is a key aspect of this phase. Diagnosing PCOS in adolescents can be challenging because symptoms such as irregular periods, acne, and weight changes can overlap with normal hormonal changes during puberty (irregular menstrual cycles, acne, and polycystic ovarian morphology on pelvic ultrasound) with adult PCOS diagnostic criteria.^[4,5] These challenges highlight the complexity surrounding the diagnosis and management of PCOS. Under-diagnosis, delayed diagnosis, and over-diagnosis can all impact the quality of care women receive. In addition, inconsistent and non-evidence-based approaches among health-care professionals further complicate matters. The lack of robust evidence exacerbates these challenges, emphasizing the need for standardized protocols and continued research to improve the understanding and treatment of PCOS.^[6,7]

CRITERIA REQUIRED FOR DIAGNOSIS

Irregular menstrual cycles and ovulatory dysfunction

When irregular menstrual cycles are present, a diagnosis of PCOS should be considered. During adolescence, variations in menstrual cycle intervals are common, especially in the early years after menarche. Anovulation is also typical during this time. The maturation of the hypothalamic-pituitary-ovarian axis progresses gradually during adolescence, leading to differences in ovulation and menstrual cycles compared to women of reproductive age. This underscores the importance of understanding the unique hormonal dynamics during adolescence when diagnosing conditions like PCOS.^[8-10] Ovarian dysfunction can occur in adolescents or women with apparently regular menstrual cycles. Measuring serum progesterone levels can indeed help confirm anovulation, which is a key aspect of PCOS diagnosis, even in those with seemingly normal menstrual cycles.

Definition of irregular menstrual cycles in adolescents according to time post-menarche

Time post-menarche	Definition of irregular menstrual cycles
<1-year post-menarche	Irregular menstrual cycles are normal pubertal transition
>1-<3-year post-menarche	<21 or >45 days
>3-year post-menarche	<21 or >35 days or <8 cycles per year

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Time post-menarche	Definition of irregular menstrual cycles
More than 1-year post-menarche	>90 days for any one cycle

Hyperandrogenism

Biochemical

Assessing biochemical hyperandrogenism is an important aspect of diagnosing PCOS. Tests such as calculated free testosterone, free androgen index, or bioavailable testosterone can provide valuable information about androgen levels in the body.

Use of high-quality assays for assessing testosterone levels in PCOS, and how markers such as androstenedione and DHEAS can provide additional information. Androstenedione can help exclude other causes of hyperandrogenism, while DHEAS can reflect adrenal androgen activity, potentially indicating adrenal dysfunction or tumors. Careful interpretation of androgen levels is vital in diagnosing conditions like PCOS. Considering the reference ranges from the laboratory used and normal values based on well-phenotyped populations, while also factoring in age and pubertal-specific stages, ensures accurate assessment and diagnosis.

In cases where clinical hyperandrogenism is not evident, assessing biochemical hyperandrogenism using appropriate high-quality assays becomes even more important for an accurate diagnosis of conditions like PCOS.

Clinical

A comprehensive history and physical examination are essential for identifying symptoms and signs of clinical hyperandrogenism, particularly in adolescents, where manifestations such as severe acne and hirsutism are common indicators. The recommendation to prioritize this assessment was made due to the lack of evidence-based guidance and the understanding that certain presentations, like moderate-to-severe acne during early puberty or perimenarcheal years, are less common and more likely to be associated with clinical hyperandrogenism. Visual scales like the modified Ferriman-Gallwey score are preferred for assessing hirsutism in nine primarily androgen-dependent areas. Each area is visually scored from zero (no terminal hair visible) to four (terminal hair consistent with a well developed (male) with a level of $\geq 4-6$ indicating hirsutism, adjusted for ethnicity. It is worth noting that self-treatment practices are prevalent and can affect the clinical assessment.^[11]

INVESTIGATIONS NOT RECOMMENDED

Pelvic ultrasound for PCOS diagnosis

Since younger individuals may naturally have multi-follicular ovaries, using pelvic ultrasound alone may not provide an accurate diagnosis of PCOS in those with a gynecological age of <8 years.

Using adult polycystic ovarian morphology criteria for ultrasound diagnosis during adolescence may lead to inaccuracies and increase the risk of over-diagnosis of PCOS. It is crucial to

consider the natural variations in follicle numbers per ovary in adolescents and the potential impact on diagnostic criteria.

Anti-Müllerian hormone (AMH)

AMH has been increasingly used in the diagnosis of PCOS, particularly when pelvic ultrasound is not feasible. Since AMH is secreted by granulosa cells of the preantral and small antral ovarian follicles, it provides valuable information about ovarian reserve and follicular activity, aiding in the diagnosis of PCOS.

The significant overlap in serum AMH levels between individuals with polycystic ovarian morphology, PCOS, and those without these features underscores the complexity of using AMH as a standalone diagnostic marker. Factors such as variations in assays, life stages, and phenotypes of the populations studied, as well as different PCOS criteria, contribute to this heterogeneity. Thus, while AMH can provide valuable insights, its interpretation must be contextualized within the broader clinical picture.^[12,13]

EXCLUSION OF OTHER CONDITIONS

The diagnosis of PCOS relies on excluding other potential causes of menstrual irregularities and hyperandrogenism. This approach is crucial even though certain causes may be less common in adolescents. It ensures accurate diagnosis and appropriate management tailored to the individual's specific condition. The most important cause of amenorrhea in a sexually active adolescent is pregnancy.

Menstrual irregularities due to functional hypothalamic amenorrhea or secondary deficiency due to any systemic cause could be present.

Furthermore, hypothyroidism, hyperprolactinemia, glucocorticoid excess due to Cushing's disease, glucocorticoid resistance, and androgen-secreting ovarian or adrenal tumors can cause menstrual irregularity and/or hyperandrogenism.^[14]

A thorough history and physical examination are mandatory for the evaluation of the appropriate condition.

TREATMENT

Lifestyle modification

Lifestyle interventions are essential, particularly for individuals with PCOS and excess weight. Multi-component approaches, including dietary changes, increased physical activity, reduction in sedentary behavior, and behavioral strategies, can effectively target weight reduction, central adiposity, and insulin resistance. These interventions not only address the symptoms but also promote overall health and well-being in individuals with PCOS.

Pharmacological principles of treatment in PCOS

The combined oral contraceptive pill (COCP) and/or metformin are recommended pharmacological treatments for adolescents with PCOS. These medications can help manage symptoms

effectively in those with a clear diagnosis or in adolescents deemed “at risk” of PCOS. COCPs can regulate menstrual cycles and reduce androgen levels, while metformin can improve insulin sensitivity and help with weight management in adolescents with PCOS.

These practice points underscore the importance of personalized care when considering pharmacotherapy for adolescents with PCOS:

1. Individual characteristics, preferences, and values should be taken into account when recommending pharmacotherapy, ensuring a patient-centered approach
2. Both the benefits and potential adverse effects of medications, both in PCOS and in general populations, should be carefully considered
3. It is important to discuss with adolescents and their families that medications such as COCPs, metformin, and other pharmacological treatments are generally “off-label” for PCOS treatment. This discussion should include evidence and potential side effects to make informed decisions together.

A comprehensive approach is crucial in managing PCOS. Integrating pharmacotherapy with education, counseling, lifestyle adjustments, and even cosmetic therapy can significantly improve outcomes for individuals with PCOS.

ANTIANDROGENS

When COCPs are contraindicated or not well tolerated, and effective contraception is ensured, antiandrogens can be considered for treating conditions like hirsutism or androgen-related alopecia.

EMOTIONAL WELL-BEING

Healthcare providers should be vigilant about the increased risk of anxiety and depressive symptoms in individuals with PCOS. Implementing appropriate screening measures and offering management strategies can significantly improve the overall well-being and quality of life for those affected by PCOS. Early detection and intervention are key in addressing these mental health concerns effectively.

Emotional well-being is a crucial but often overlooked aspect in adolescent girls with PCOS. More research is necessary to understand the pathophysiology of emotional symptoms, their onset in adolescence, and the most effective treatment strategies. In addition, investigating how these symptoms might affect engagement with management strategies is essential for providing comprehensive care to adolescents with PCOS. By addressing emotional well-being alongside physical health, health-care providers can better support adolescents in managing their condition and improving their overall quality of life.

CONCLUSION

Diagnosis of PCOS during adolescence is both controversial and challenging due to the overlap of normal pubertal physiological changes.

Polycystic ovarian morphology on ultrasound should not consider for the diagnosis of adolescent PCOS.

Emotional well-being is a crucial but often overlooked aspect in adolescent girls with PCOS. A holistic approach is essential in managing PCOS. While pharmacotherapy plays a role, it should be integrated with education, counseling, lifestyle interventions, and other options such as cosmetic therapy. This comprehensive approach addresses the physical, emotional, and psychological aspects of PCOS.

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