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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 underpinnings[4] 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

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 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]

Table 2. Diagnostic criteria for the insulin resistance syndrome in women.

Any three or more of the following:
Waist circumference >88 cm
Triglycerides ≥ 150 mg/dL[a]
HDL-cholesterol <50 mg/dL[b]
Blood pressure ≥130/85
Fasting glucose ≥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.

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]
Cushingís 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 μg/dL (21.7 μmol/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 adrenocorticotropic hormone (ACTH)-stimulation with an intravenous 250 μg dose and a 30 minute value (stimulated values ≥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 (LS/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 (>5.5cm^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 may[37] 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 $\geq$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/m^2) 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/m^2) 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/m^2) 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/m^2), 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/m^2).[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 all[82] *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 thickness[102] and an almost 6-fold increased prevalence of coronary artery calcification[103] 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.

		Hirsutism		
Intervention	**Decreased T**	**Response rate**	**Degree of improvement**	**Rate of improved menses/ovulation**
Weight loss (≥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 hyperandrogenism[107] 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] Palmert 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 IR[13] (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] hyperandogenism,[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 Hoeger[118] 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 obesity[125] 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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