Chapter

Causes of Polycystic Ovarian Syndrome

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Abstract

PCOS is a multifactorial syndromic disorder—the exact etiology is not known. Genetic, epigenetic, and environmental factors may be the causative factors. It is the most common cause of an-ovulatory infertility, and in adolescents, the young girl may present with irregular periods. Most of the women with PCOS are either overweight or obese. Another variety of PCOS women is lean. Sleep apnea, metabolic syndrome, and endometrial carcinoma are the late consequences of women with PCOS. As new research shows that gut microbiome is one of the attributing factors of PCOS, it will lead to a new horizon in the management of PCOS. Fecal implantation or probiotics may be helpful in PCOS management. Physical and emotional stress is one of the contributing factors to PCOS. Neuroendocrine factors are also an attributive factor for the development of PCOS. Most of the research about neuroendocrine factors is very preliminary and limited to the mice model. The incidence of PCOS varies from region to region as dietary and environmental factors differ. More human research is required to have more knowledge about the etiology of PCOS, which will guide the management of PCOS.

Keywords: PCOS, FSH, LH, EDC, SFA, ROS, Genomic variants, hyperandrogenism, NEFAs, SHBG, gut microbiome

1. Introduction

PCOS is a reproductive dysfunction resulting from an interaction between endocrine and metabolic disorders. Hyperandrogenism and insulin resistance complement one another in the development of PCOS. Primarily, it is affected by alteration of the hypothalamus-pituitary-ovarian axis. The cyclic pattern of hormone concentrations, which is the characteristic determinant of normal ovulatory menstrual cycles, is lost in women with PCOS. In these women, there is chronic anovulation resulting in a "steady low state" of gonadotropin and sex steroid concentrations. Daily production of both androgens and oestrogens is increased. Chronic hyperandrogenemia and insulin resistance (usually, though not always, associated with obesity) also result in ovarian dysfunction of PCOS. PCOS women suffer from oligomenorrhoea, infertility, metabolic syndrome, acne and oily skin, hirsutism, and endometrial carcinoma at a later age. The pathophysiology of PCOS is most likely multifactorial, involving endocrine, metabolic, genetic, epigenetic, and environmental factors. Increased

serum luteinising hormone (LH) concentrations, low-normal follicle-stimulating hormone (FSH) levels and increased LH-to-FSH ratios is a feature of women with PCOS. Insulin resistance is usually seen in obese PCOS women and, to a lesser extent, in women with lean PCOS. In general, the prevalence varies from 50 and 75% [1]. About 35% of women with polycystic ovary syndrome exhibit impaired glucose tolerance, and up to 10% meet the criteria for type 2 diabetes mellitus. Insulin and LH act synergistically, resulting hyperandrogenism. Insulin resistance and hyperinsulinemia are the cause, not the result, of hyperandrogenism in PCOS. Women with PCOS have increased visceral fat than subcutaneous fat. Women with lean PCOS have an increased percentage of body fat, a higher waist–hip ratio, and greater intra-abdominal, peritoneal, and visceral fat compared to normal women matched for body mass index (BMI) [2]. Women with PCOS suffer from different psychological disorder. The diagnosis of PCOS is based on the 2003 Rotterdam criteria, where the incidence of two out of the three criteria hyperandrogenism (clinical and/or biochemical), irregular cycles, and polycystic ovary morphology. Evidence-based medicine suggests that the anti-Mullerian hormone in serum can be used as a substitute for the follicular count, and it is thereby emerging as an official polycystic ovarian morphology/PCOS marker. The limitation of this criteria is mainly in the diagnosis of adolescents as the features of PCOS overlap with the normal physiological change in puberty. Therefore, PCOM should not be considered a criterion in the first 8 years of menarche, and the essential criteria are irregular menstrual cycles and clinical and/or biochemical hyperandrogenism.

2. Genetic association

Familial aggregation studies identify PCOS as an inherited disorder. Higher frequency of genetic polymorphism at 2p16.3 (rs13405728), 2p21 (rs13429458), and 9q33.3 (rs2479106) are noted in women with PCOS. In one group of patients, X-linked inheritance was seen. Siblings and parents of patients suffering from PCOS have a high prevalence of hyperinsulinemia and hypertriglyceridemia, PCOS in females, and premature balding in males. Monozygotic twin sisters have twice the risk of developing PCOS. About 50% of sisters of patients with PCOS have increased levels of total or bioavailable testosterone concentrations, and 35% of their mothers also suffer from PCOS [3]. First-degree relatives of women with PCOS have features of metabolic syndrome. PCOS is described as a polygenic disorder that includes the interplay of various genomic variants (**Table 1**).

In pregnancy in PCOS mothers, there is placental dysfunction due to hyperinsulinemia leading to hyperandrogenic foetal micro-environment. The theory of hyperinsulinemia suggests that there are two factors involved: maternal insulin resistance and decreased placental aromatase, which work together to maintain balance in the system. Epigenetic reprogramming can occur with or without alterations or deletions to the existing DNA, potentially affecting chromatin. Methylation of DNA inhibits gene expression, while hydroxymethylation enhances gene expression. The first type of reprogramming involves cytosine at its fifth carbon in the pyrimidine ring, known as CpG islands. This can include methylation, hydroxymethylation, formylation, or carboxylation. The second method is histone modification, which can involve acetylation, methylation, phosphorylation, ubiquitination, or sumoylation. This reprogramming, which occurs in germ cells, has the ability to pass these changes on to

S. no.	Gene	Cytogenic location	Anomalies
1	*AR*	Xq12	X inactivation
2	*FSHR*	2p16.3	Gene variation
3	*FTO*	16q12.2	SNP rs9939609
4	*CAPN10*	2q37.3	Polymorphism
5	*CYPA1A*	15q24.1	T6235C
6	*CYP11A1*	15q24.1	SNP rs4077582
7	*CYP17A1*	10q24.32	T>C
8	*CYP1A1*	15q24.1	Ile/Val
9	*CYP21A2*	6p21.33	Heterozygous mutation
10	*CYP3A7*	7q22.1	Variant allele
11	*CYP19A1*	15q21.2	Arg264Cys

Table 1.
Genomic varients related to pcos.

offspring. Next-generation sequencing (NGS) is used to identify this genetic reprogramming. The various physiological processes related to follicular development, steroidogenesis, glucose metabolism, insulin regulation, and inflammatory mediation are associated with luteinising hormone/choriogonadotropin receptor (LHCGR), FST, LMNA, PPARGC1, and EPHX1 genes. In PCOS, there is decreased methylation and over-expression of LHCGR and PPAR-gamma genes. Obesity also plays an epigenetic modifier in the development of PCOS. These two epigenetic modifications complement each other, resulting in changes in DNA. Two hit theories include the first hit in intrauterine life, and the second one is a provocative factor after delivery in her lifetime. A genome-wide association study identifies a gene that regulates gonadotropin secretion, action, and ovarian function. These genes are FSHB (follicle-stimulating hormone B polypeptide), LHCGR (luteinising hormone/choriogonadotropin receptor), FSHR (follicle-stimulating hormone receptor), anti-Mullerian hormone (AMH), and DENND1A (DENN domain-containing 1A) and genes associated with metabolism, such as THADA (thyroid-adenoma-associated gene) and INSR (insulin receptor).

3. Environmental factors

Endocrine-disrupting chemicals (EDC) are present in whatever we use in our day-to-day life. These are phenols or halogens like chlorine and bromine [4]. They mimic steroid hormone action. Longer and uninterrupted exposure to EDCs from prenatal to adolescence is a causative factor of PCOS [5]. Bisphenol A (BPA), which is used for packaging food and drink and many other purposes, interferes with oogenesis [4, 6]. BPA acts on granulosa cells and reduces the expression of aromatase enzyme and the production of oestrogen, thereby interfering with oocyte development and maturation. BPA is also a potent ligand for sex hormone-binding globulin (SHBG) and replaces testosterone thereby increasing free testosterone concentration. High androgen deactivates the uridine diphosphate-glucuronosyl transferase enzyme and

decreases BPA clearance in the liver. Thereby, it increases the concentration of free BPA in blood, leading to further negative effects on the ovaries [4, 6–8]. BPA upregulates adipogenesis-related genes and activates glucocorticoid receptors, thus acting as an obesogenic. BPA also gives rise to the release of interleukin 6 (IL6) and tumour necrosis factor α (TNF-α), which prompts adiposity and insulin resistance. BPA also affects glucose homeostasis by directly influencing pancreatic cells. Advanced glycation end products (AGEs), also called glycotoxins, are pro-inflammatory molecules affecting women's health. They interact with the surface receptor called RAGE (receptor for AGE) and stimulate proinflammatory pathways and oxidative stress [9, 10]. It prompts adiposeness. Increased body mass index decreases the clearance of glycotoxin and is responsible for its deposition in ovaries. This worsens the inflammatory process and metabolic syndrome of PCOS [9].

4. Physical and emotional stress

Chronic stress causes hypertrophy and hyperplasia of adipocytes, stimulating adipocrine secretion attraction and activation of stromal fat immune cells [11]. Chronic stress also causes increased levels of inflammatory cytokines, like IL-6 and TNF-α, and affects oxidant-antioxidant balance. It has a role in increased insulin resistance. Stress induces hypothalamic-pituitary axis to release cortisol. Cortisol leads to IR by stimulating visceral fat accumulation, gluconeogenesis, lipolysis, and increased glucose production in liver [12]. Stress effect on PCOS may refer to intervention with anti-Mullerian hormone (AMH) and changing sex hormone levels [12, 13]. Recent research studies on animals have shown that AMH stimulates LH release and increases the gonadotropin-releasing hormone, thereby linking AMH to endocrine instability.

Diet with saturated fatty acids (SFAs): it produces an inflammatory status [14] and lowers insulin sensitivity [15]. Vitamin D deficiency aggravates comorbidities associated with PCOS [15, 16]. Vitamin D deficiency increases insulin resistance by causing chronic inflammation [15, 17]. Vitamin D supplementation may have a beneficial effect on AMH and antral follicle count (AFC) in women with PCOS [18].

There is a decreased response of cells to insulin in women with PCOS. It is seen both in lean and obese PCOS women. Insufficient response to insulin is tissue-specific. Insulin response in ovarian tissue and adrenal is not affected [19, 20]. Insulin promotes growth of ovarian follicle and steroidogenesis. Insulin like growth factor coacts with LH. Hyperinsulinemia increases androgen production from ovary [21]. IR independently augment CYP17A1 activity, the secretory enzyme in androstenedione and testosterone production [22]. Hyperinsulinemia decreases hepatic SHBG and elevates free testosterone levels in blood. It also increases IGF-1 production in liver, which increases androgen production by stimulating theca cells. Hyperinsulinemia also stimulates LH receptors in pituitary and increases both frequency and amplitude of LH secretion. Insulin has been found to be associated with enhanced pituitary gonadotropin sensitivity to GnRH. Thus, hyperinsulinemia promotes GnRH neuron activity. It stimulates adiposeness and lipogenesis and inhibits lipolysis. Insulin resistance causes a decrease in omentin level that is independent of the patient's body mass index (BMI). Insulin's indirect effect on PCOS is enhanced by pituitary gonadotropin sensitivity to GnRH, and hyperinsulinemia promotes GnRH neuron activity [23]. Hyperglycaemia causes inflammation by secreting TNF-α from mononuclear cells (MNCs) [24].

5. Hyperandrogenism

It reduces sex hormone-binding globulin and increases serum-free testosterone. In women with PCOS, higher testosterone is converted to estrone in adipose tissue. Estrone is converted to estradiol, which affects follicular growth and alters LH and FSH ratio, which affects ovulation [10]. Hyperandrogenism upregulates AMH level, which inhibits follicular growth and ovulation. IGF-II level, which is positively related to follicular diameter, decreased in follicular fluid caused by increased androgen level. Hyperandrogenism increases LH level. Hyperandrogenism adds to PCOS-related inflammatory factors, insulin resistance, and oxidative stress. PCOS women have adipose tissue similar to men because of hyperandrogenism. Increased levels of white blood cell, C-reactive protein (CRP), and other inflammatory biomarkers in peripheral blood are associated with PCOS [25]. Inflammation induces hyperandrogenism. TNF-αexacerbates insulin resistance. IL-1 affects the FSH and LH receptors, which interfere with follicular development and ovulation.

6. Oxidative stress

It denotes an imbalance between pro-oxidants and antioxidants. Oxidative stress molecules include reactive oxygen species (ROS) (e.g., O^{2-}, H_2O_2, and OH^-) and reactive nitrogen species (RNS). Excess production of oxidative chemicals causes various damage to vital molecules such as lipids, proteins, and DNA. Oxidative stress inhibits the insulin signalling pathway and adds to IR. Oxidative stress leads to obesity [26].

7. Obesity

Obesity can lead to insulin resistance, hyperinsulinemia, and hyperandrogenism. Visceral obesity can cause an increase in non-esterified fatty acids (NEFAs) in the bloodstream. Skeletal muscles utilise NEFAs as an energy source instead of glucose. This can cause hyperglycaemia, triggering a rapid response in the pancreas and resulting in hyperinsulinemia. Visceral fat adipocytes undergo necrosis in response to catecholamines. This leads to release of cytokines like TNF and IL6, which are further responsible for adrenal steroidogenesis and hyperandrogenemia. This obesity-induced inflammatory process is also responsible for impairing insulin clearance, hence also contributing to hyperinsulinemia. Adipocytes produce high levels of leptin, which inhibits the expression of aromatase mRNA in granulosa cells and prevents the conversion of androgens to oestrogen and thus hampers ovarian folliculogenesis. Adiponectin, secreted by adipocytes, is insulin-sensitising, anti-diabetic, and has anti-inflammatory properties. Visceral fat secretes lower levels of adiponectin compared to subcutaneous fat. Omentin-1, a chemical secreted by adipose tissue, enhances IGF-1-induced progesterone and estradiol secretion, stimulates the expression of steroidogenic acute regulatory protein and CYP450 aromatase, and improves IGF-1 receptor signalling in adipose tissue. The accumulation of lipids in non-adipose tissues, known as lipotoxicity, can lead to oxidative/endoplasmic reticulum stress associated with inflammation and insulin resistance. Excessive fatty acids in muscles and liver can induce insulin resistance through serine phosphorylation of the insulin receptor by diacylglycerol.

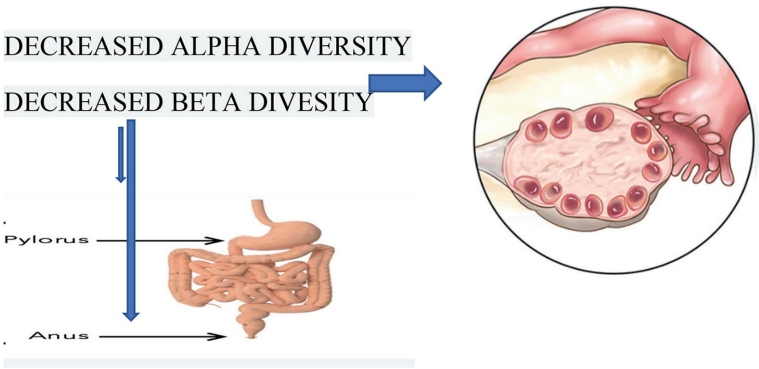

Figure 1.
Gut microbiome and PCOS.

8. Gut microbiome

The clinical manifestations of PCOS women are also associated with the brain-gut axis [27]. The release of endotoxin by the gut microbiome as a response to gut inflammation is found to be a contributing factor in PCOS. Various gut microbiota play a role in maintaining physiological balance and preserving structural integrity and histological homeostasis. Additionally, the gut microbiome is involved in the production of vitamins, short-chain free fatty acids, and conjugated linoleic acid. It also plays a role in the biotransformation of bile acids, ammonia synthesis, and detoxification. Short-chain fatty acids such as acetate, butyrate, and propionate are produced by the gut microbiome and have anti-inflammatory, anticarcinogenic, and immunomodulatory effects [28]. The metabolism of butyrate and propionate is important for energy metabolism, as it regulates the gluconeogenesis process and cholesterol metabolism. Furthermore, the gut microbiome modulates the immune system [29]. The diversity of the microbiome is crucial for restoring the host's health. Obese individuals with PCOS have lower alpha and beta diversity compared to those without PCOS [30]. The main species of firmicutes in the human gut are *Lactobacillus*, *Clostridium*, and *Ruminococcus*. Among these, *Lactobacillus* has a direct association with PCOS and its impact on human health [31]. Liu et al. observed a decrease in Ruminococcaceae and *Clostridium* in obese individuals with PCOS [32]. The presence of the Proteobacteria phylum, specifically *Salmonella*, is associated with PCOS. Bacteroidetes, on the other hand, were significantly lower in the stools of PCOS patients and were associated with reproductive hormones such as thyroid-stimulating hormone (TSH) and luteinising hormone (LH) [33]. There is an immune neurological network formed by the central nervous system, intestinal neural network, and pituitary adrenal axis. Correlation between gut microbiome and PCOS will lead to a newer management option for women suffering from PCOS (**Figure 1**).

9. Neuroendocrine correlation

Polycystic ovary syndrome is symbolised by excess androgen and ovulatory dysfunction. There is a rapid pulse frequency of gonadotrophin-releasing hormone due to the decreased sensitivity to the progesterone and oestrogen feedback inhibition at the level of hypothalamus [34]. The pulsatile release of GnRH is from the median

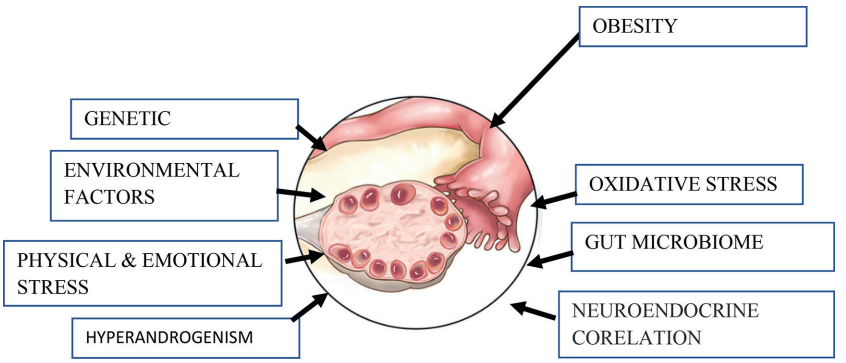

Figure 2.
Causes of PCOS.

eminence, which controls the pulsatile LH secretion from the anterior pituitary. This hormonal imbalance leads to increased LH and FSH ratio which accounts for excess androgen secretion from ovary and arrest of follicular growth and oligo ovulation [35]. The various neuronal modulators associated with PCOS are KDNy neurons, kisspeptin released from hypothalamus, γ-aminobutyric acid (GABA), AMH, and others. There is an increased level of kisspeptin in women with PCOS. Thus, the blending effect of kisspeptin and LH is lost in PCOS women, resulting in dysregulated gonadotrophin-releasing hormone pulsatility. γ-Aminobutyric acid (GABA) and anti-Mullerian hormone also stimulate gonadotrophin-releasing hormone neurons directly. GABA has an excitatory effect on gonadotrophin-releasing hormone neurons. Thus, an increased level of γ-aminobutyric acid (GABA) is found in cerebrospinal fluid in women with PCOS. Direct action of hyperandrogenism in brain might have a role in the development of PCOS traits [36]. Many clinical studies have found a positive correlation between PCOS and psychiatric disorders. A higher incidence of PCOS in bipolar disorder might be due to neurotransmitter imbalance on the neuroendocrine axis executing reproductive dysfunction [37]. Women suffering from depression have a 35% of occurrence of PCOS [38]. Studies show there is also an increased incidence of PCOS in women with epilepsy. Women using valproate have an increased incidence of PCOS due to increased GABA levels. A clinical trial has shown a favourable result by targeting KDNy neuron with Ank3 receptor antagonist in women with PCOS to decrease LH pulsatility [39]. Early response of antral follicle to dysregulated LH reaches the incipient end-stage resulting in ovarian morphology in women with PCOS (**Figure 2**).

10. Conclusion

The exact aetiology of PCOS is not known, and it may be multifactorial in origin. Genetic factors, metabolic factors, and environmental factors interplay in the pathophysiology of PCOS. Genomic studies have identified the various genes involved in gonadotropin secretion, gonadotropin action, ovarian follicular development, and insulin sensitivity. This genetic association, with their epigenetic regulators, are still under constant research, which will further improve the understanding of disease, thereby improving its diagnosis and treatment modalities. Newer research on neuroendocrine factors and gut microbiome will facilitate innovative approach for the

management of PCOS and its consequences. Neuroendocrine and gut microbiome topics of research for the aetiology of PCOS are in early stage and mostly based on the mice model. Further research, specifically on humans, is required to establish these factors as the causative factors of PCOS, and that will open the innovative window for the management of this endocrine and metabolic disorder.

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