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(REVIEW ARTICLE)

A review on PCOS: Its causes, symptoms, pathogenesis and management

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Abstract

The aim of this review is to provide an overview on the Polycystic Ovarian Syndrome (PCOS) including its causes, symptoms and management. The most prevalent endocrine and metabolic conditions affecting women in their reproductive years is PCOS. About 116 million women worldwide (3.4%) may be impacted by PCOS, according to data from the World Health Organization (WHO). This is a heterogeneous endocrine condition that manifests as insulin resistance, increased testosterone levels, swollen and malfunctioning ovaries, and other symptoms. This paper covers the information about the polycystic ovary syndrome, its causes, symptoms, pathogenesis and its management in brief. External causes include genetic mechanism, diet and environmental factors while insulin resistance, inflammation, hyperandrogenism and obesity are the internal causes. Irregular periods, hirsutism, acne & oily skin, mood swings, weight gain, heavy bleeding, hair thinning, diabetes, pelvic pain, sleep problems and skin darkening are the main signs and symptoms of the PCOS. Pathogenesis of PCOS involves alteration in insulin secretion, change in gonadotropin – releasing hormone and excess androgen level. When treating PCOS, more focus should be placed on the patient's adherence to treatment.

Keywords: Endocrine; Hyperinsulinemia; Androgen; Hirsutism; Acne

1. Introduction

Polycystic ovarian syndrome (PCOS) was formerly known as Stein-Leventhal syndrome [1]. PCOS is the most common endocrine and metabolic disorder in women of reproductive age. This syndrome is a heterogeneous endocrine disorder characterized by enlarged and dysfunctional ovaries, excess androgen levels, resistance to insulin, etc. Approximately 10% of women are thought to have PCOS before to menopause and experience difficulties from it [2]. According to the WHO, PCOS affects approximately 8%–13% of women in their reproductive years. Some tribes are more prone to PCOS and are likely to have complications particularly related to metabolic problems [3]. The World Health Organization (WHO) data suggests that approximately 116 million women (3.4%) are affected by PCOS globally [4]. According to the National Health Portal of India, the prevalence rate of PCOS in Maharashtra was found to be 22.5%. Another previous report from South India, which included adolescents, showed an incidence of 9.13% [5]. PCOS leads to disturbances in the levels of reproductive hormones like luteinizing hormone (LH), Follicle-stimulating hormone (FSH), estrogen, testosterone, which interrupt the normal menstrual cycle and would lead to oligomenorrhoea and amenorrhea like irregularities. A high ratio of luteinizing hormone to follicle-stimulating hormone and increased frequency of gonadotropin-releasing hormone (GnRH) are considered as the underlying causes of PCOS [6]. Also, there are some external and internal factors that may cause PCOS, such as insulin resistance (IR), hyperandrogenism (HA). The genetic mechanism is included in external factors while environmental factors include genetics, and epigenetics. PCOS increases the risk of further complications like cardiovascular diseases, type 2 diabetes mellitus [7,8], metabolic syndrome [8], depression, and anxiety [9]. PCOS is diagnosed with hyperandrogenism, menstrual irregularities, and varying sizes of cysts in the ovaries [10]. Half of the individuals suffering from PCOS are overweight. So, it is crucial to lose weight and

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have healthy balanced diet combined with regular exercise, which increases their metabolism rate, improves insulin sensitivity, and helps them lose weight [11]. This review highlights the causes, symptoms, pathogenesis, and management of PCOS.

2. Causes of PCOS

There are various external, environmental and internal factors that cause the PCOS.

2.1. External factors

Genetic mechanism: The gene types implicated in the development of PCOS are classified as follows: genes involved in the steroidogenesis of the ovary and adrenal glands, genes involved in the actions and regulation of steroid hormones, genes involved in the action and secretion of insulin, genes affecting energy homeostasis, and genes implicated in chronic inflammation [12]. Thus some particular alterations in some genomes is the reason for development of PCOS. Some examples of genes involved in development of PCOS are Calpain 10 (CAPN10), Cytochrome p450, Insulin gene, Androgen Receptor (AR), Fat Mass Obesity (FTO), and Follicular stimulating hormone receptor (FSHR) [13].

2.2. Environmental factors

Exposure to Endocrine Disrupting Chemicals (EDC) may also play a role in development of PCOS. The Endocrine Society defines Endocrine Disrupting Chemicals as "an exogenous chemical, or mixture of chemicals, that interfere with hormonal action." These chemical substances can affect the endocrine system and results in adverse effects [14]. Bisphenol A (BPA), perchlorate, dioxins, phthalates, phytoestrogens, polychlorinated biphenyls (PCB), polybrominated diphenyl ethers (PBDE), triclosan, perfluoroalkyl and polyfluoroalkyl substances (PFAS), pesticides such as dichlorodiphenyltrichloroethylene (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE), organophosphorus compounds, alkyl phenols (surfactants), parabens, methoxychlor, diethylstilbestrol (DES), fungicide vinclozolin, and natural hormones are the commonly used EDC. [14,15]. EDCs work as agonists or antagonists by binding to hormone receptors and leading to increase, decrease, or prevent the activity of the hormones [16]. Women who are exposed to air pollutants, such as particulate matter (PM) 2.5, sulphur dioxide, nitrogen oxides, and polycyclic aromatic hydrocarbons (PAHs), may have an increase in inflammatory mediators, which alters normal steroidogenesis and causes PCOS to develop [17].

2.2.1. Diet

Diet rich in fat, mainly saturated fatty acids and intake of foods with a high glycemic index increases the risk of insulin resistance and its related complications including obesity and PCOS [18].

2.3. Internal factors

- Insulin resistance: PCOS is frequently characterized by insulin resistance and compensatory hyperinsulinemia. Some studies indicate that hyperinsulinemia contributes to the hyperandrogenism of the condition by raising ovarian androgen production and impairing ovulation. This is the effect of insulin inducing ovarian cell, called as theca cell, that are responsible for androgen biosynthesis to produce testosterone [19].
- Hyperandrogenism: It results from overproduction of androgens produced due to abnormal ovarian function and insulin resistance. Hyperandrogenism hinders the growth of follicles, which are the sacs in the ovaries where eggs get develop, and inhibits normal ovulation [10].
- Inflammation: The imbalance between pro-inflammatory and anti-inflammatory cytokines, as well as cytokine gene polymorphisms, may influence etiology of PCOS. Thus, inflammatory reactions serve as mediators in the development and aggravation of the metabolic features of PCOS. Adipocytes have the ability to increase the production of pro-inflammatory chemicals, which can result in chronic inflammation [20]. Inflammation directly stimulates overproduction of androgens in the ovaries. The degree of hyperandrogenism may have an effect on the development of abdominal adiposity, which contributes to the inflammatory load in PCOS [21]. Research has linked elevated levels of androgen to inflammation [22].
- Obesity: Obesity activates the theca cells that stimulate luteinizing hormones which leads to ovarian androgen excess. High androgen levels lead to improper periods and obesity [23].

3. Symptoms of PCOS

Most of ladies are not even aware that they have PCOD. For an early identification of the issue, it is critical to pay attention to these signs [24]. PCOS symptoms might appear in early adulthood, although they can also start soon after

puberty. Anovulation causes irregular or absent menstruation in many PCOS-affected women, however some may develop ovarian cysts [25].

It has many signs and symptoms:

- Irregular periods: This is the most typical PCOD symptom. PCOD first manifests as irregular or frightening periods. Observe your monthly cycle closely in order to identify PCOD [24, 25].
- Excessive facial and body hair (Hirsutism): Excessive facial hair growth is known as Hirsutism. Women with PCOD have excessive hair growth because their ovaries secrete a large amount of the masculine hormone androgens [24, 25]. Up to 70% of women with PCOS experience Hirsutism, a frequent clinical manifestation of hyperandrogenism. The face, arms, back, chest, thumbs, toes, and abdomen are among the areas that may be impacted by excessive hair growth, which is linked to PCOS because of hormonal fluctuations [24].
- Acne and Oily Skin: Acne and other facial issues are caused by hormone disruption in PCOD. Acne is a result of an overabundance of male hormones. PCOD causes severe cystic acne in certain women [25]. The inflammatory condition known as acne that affects the hair follicle and the sebaceous and apocrine glands that are connected to it. The main issue for female acne sufferers is elevated sebum production while serum androgen levels are frequently not elevated [26].
- Mood Swings: Hormonal imbalance and irregular periods are brought on by PCOD. Abrupt mood swings are caused by this hormone imbalance. Depression and anxiety are common symptoms [27].
- Weight gain: High amounts of male hormones and insulin in women are produced by the body in PCOD such women experience this weight gain suddenly. An abundance of fat in the lower abdomen is a typical sign of PCOD [24]. The frequency of overweight and obese women in PCOS communities varies greatly between nations. In Italy, 10% of women with PCOS are overweight but not obese, while in Kuwait, the percentage is 37%. According to research done in the US and Australia, the highest rates of obesity are found among women with PCOS, of whom 61% to 76% are obese [25].
- Heavy Bleeding: The uterine wall has increased accumulation since the periods are irregular. This causes more bleeding each time a period occurs [22, 24].
- Hair Thinning: Hair loss is a common symptom of PCOD in females. For some women, hair loss is completely total. Hormone imbalance within the body is the cause of this. Hair loss or scalp thinning is brought on by an excess of androgens [24].
- Diabetes: Insulin levels are higher in women with PCOD, which raises their risk of diabetes. [24]. Insulin resistance is one of PCOS's primary traits. Significant evidence has been found through epidemiologic studies connecting PCOS to an increased risk of type 2 diabetes, impaired glucose tolerance (IGT), and gestational diabetes mellitus (GDM). PCOS and GDM are related to each other. A recent meta-analysis indicates that women with PCOS are generally three times more likely to have the condition, despite the fact that there hasn't been much research on prevalence to date [25].
- Pelvic Pain: Along with severe bleeding and headaches, pelvic discomfort can also happen during menstruation [24].
- Sleep problems: Sleep issues including sleeplessness are common complaints from women with PCOS. A sleep apnea disorder known as PCOS has been associated with it [22, 24]. Breathing pauses during the night is a common symptom of sleep apnea, which interferes with sleep [22].
- Skin Darkening: Dark patches may appear on the skin of the body, including the neck, groyne, and beneath the breasts [22].

4. Pathogenesis

Excessive adrenal androgen secretion and/or ovarian secretion are the characteristics of PCOS. The overproduction of ovarian androgen is caused by both intrinsic ovarian factor such as altered steroidogenesis and external factor hyperinsulinemia [28]. Theca cells in the ovary support developing follicles physiologically, aiding in the production of mature oocytes. Patients with PCOS experience ovarian hyperthecosis due to the hyperresponsiveness of theca cells to stimulatory actions of insulin. The symptoms of PCOS are exacerbated by insulin resistance in peripheral tissues, which increases the androgenic potential in theca cells. Furthermore, an additional factor contributing to hyperandrogenism in PCOS is the increased sensitivity of theca cells to gonadal steroid gonadotropin activation [29]. A number of factors, including changes in adipose cell activity, inflammatory factors, neuroendocrine function, metabolism, steroidogenesis, ovarian folliculogenesis, insulin production, and insulin sensitivity may have impact on the pathophysiology of this illness [30].

Pathophysiology Theories of PCOS

Pathophysiology theories of PCOS has been explained by a number of theories:

4.1. Alteration in insulin secretion

Alteration in insulin secretion and insulin action leads to insulin resistance and hyperinsulinemia.

A change in the gonadotropin-releasing hormone causes a rise in the release of luteinizing hormone. An excess of androgen produced by the ovaries due to a malfunction in androgen synthesis [31]. Insulin interferes with every aspect of the hypothalamus-hypophysis-ovary axis. Insulin resistance leads to decrease in metabolic signalling, but maintains mitogenic and steroidogenic activity, which promotes hyperandrogenism. This appears to be the primary pathophysiologic mechanism behind PCOS development.

4.2. Insulin Resistance / Hyperinsulinemia

The pathophysiology of insulin resistance in PCOS involves an interaction of non-heritable intrauterine and extrauterine environmental factors, genetic influences, and alternate responses to excess energy. A number of molecular processes, including elevated free fatty acids, elevated cytokine secretion, elevated testosterone, and impaired post-receptor insulin function, are responsible for insulin resistance in PCOS [32]. Insulin resistance (IR) is a metabolic condition marked by a reduction in cellular reactivity to insulin signalling and seems to be a necessary pathophysiologic mechanism in the development of any PCOS metabolic consequence. Women with PCOS frequently have insulin resistance and hyperinsulinemia. Diabetes mellitus type 2 and poor glucose tolerance are two conditions that develops in the women with PCOS.

Hyperinsulinemia associated with insulin resistance leads to thickening of theca cells in ovaries which causes anovulation and infertility [33,34]. Insulin stimulates the corresponding trophic hormones to encourage steroidogenesis in steroidogenic organs like the ovary and the adrenal cortex. Hyperinsulinemia is the main cause of excessive ovarian or adrenal androgen secretion as it stimulates the action of LH. Also the hyperinsulinemia decreases the synthesis of sex hormone binding globulin (SHBG), which is a vital circulatory protein that controls testosterone levels, resulting into increased free circulating testosterone concentration [4].

4.3. Abnormal Androgen Secretion / Hyperandrogenism

Hyperandrogenism is a state characterized by the overproduction of androgen, which is usually presented by acne, hirsutism or frontal alopecia. Androgens are a member of the steroid family that are primarily produced by the adrenal and ovarian glands. Pregnenolone is derived from cholesterol and undergoes a sequence of enzymatic reactions to be converted into steroid hormone [35]. Hyperandrogenism is caused by excessive androgen synthesis by ovaries as well as the adrenal gland. Excessive androgen synthesis is due to the abnormal function of ovaries and adrenal gland. Excess androgens promote the development of primordial follicles and an increase in antral follicles during the early gonadotropin stage. The pituitary releases gonadotropin hormones in response to the hypothalamus producing gonadotropin-releasing hormones (GnRH). The LH receptor is activated by luteinizing hormone (LH) to boost androgen production in ovarian theca cells. Simultaneously, FSH receptor in ovarian granulosa cells is activated by follicle-stimulating hormone (FSH) to transform androgens into estrogen, which promote the formation of new follicles. It is believed that, in women with PCOS, imbalances in the hypothalamic-pituitary-ovarian (HPO) axis result from dysregulation of the neuroendocrine system, which then leads to an excess of gonadotropin. An increase in GnRH causes the body to produce more LH than FSH, which causes the LH: FSH ratio to rise significantly. Because of increased LH stimulation, theca cells in the ovaries undergo hyperplasia. Additionally, follicular fluid accumulates and forms cystic structures along the periphery, giving the appearance of a string of pearls. This occurs primarily in the prenatal and antral stages, when a large number of follicles in the theca cells of ovaries become stopped. Overproduction of androgens occurs as a result of an increase in follicles and the expression of vital enzymes involved in androgen synthesis [36]. The dysregulated secretion of the gonadotropins, LH and FSH, which regulates ovarian steroidogenesis, follicular dynamics, and ovulation, plays an important role in pathogenesis of PCOS. Women with PCOS have been known to exhibit enhanced LH pulse frequency and/or amplitude, elevated circulating LH levels, elevated LH: FSH ratios, and comparatively lower FSH levels [37]. Insulin-resistant hyperinsulinemia synergizes with androgen to prematurely luteinize granulosa cells, increases adipogenesis, and acts on theca cells to intensify hyperandrogenism. Excessive LH is triggered by increasing hyperandrogenism that acts on theca and luteinized granulosa cells to worsen hyperandrogenism [38,39].

4.4. Decreased Sex Hormone Binding Globulins (SHBGS)

Sex hormone-binding globulin (SHBG), a glycated homo-dimeric plasma transport glycoprotein made by hepatocytes, binds to sex hormones and regulates their levels in the bloodstream. Through management of their individual metabolic

clearance rates, it controls the bioavailability of testosterone in plasma. One important factor influencing the ability of sex steroids to enter target tissues and be metabolically cleared is their content of SHBG. SHBG receptors (RSHBG) are expressed in tissues and cells that are dependent on sex steroids, including the endometrial, prostate, colon, hypothalamus, breast, placenta, liver, epididymis, immune system, and cardio myocytes. SHBG levels are good indicator for insulin resistance because they are decreased in insulin resistance. Women with PCOS often have abnormally low serum SHBG levels, which can contribute to hyperandrogenic symptoms such virilization, acne, hirsutism, and androgenic alopecia [40]. Several studies have demonstrated that reducing insulin resistance will eventually lead to a decrease in androgens and an improvement in the illness state [41].

5. Management of PCOS

PCOS has a complicated etiology, therefore therapy is rarely nontherapeutic; instead, it is individualized depending on the patient's indications and symptoms. For the management and treatment of PCOS, a number of alternative treatments have been proposed [42]. The medical treatment of polycystic ovarian syndrome (PCOS) in acute treatment involves three components such as managing infertility, treating hirsutism, and controlling irregular menstruation while that of in chronic treatment involves managing insulin resistance syndrome [43]. A comprehensive strategy is used to treat PCOS, with the goal of treating the condition's symptoms as well as its underlying hormonal abnormalities. The following is a thorough summary of PCOS treatment techniques:

- Lifestyle Modifications: Lifestyle adjustments are seen to be the primary line of treatment for PCOS, especially in overweight or obese individuals. These includes lowering androgen levels, reducing insulin resistance, and restoring monthly regularity [44]. Attaining and maintaining a healthy weight requires both diet and activity. Research has demonstrated that even small weight reduction (5–10% of body weight) can increase a woman's ability to conceive and regulate her menstrual cycle as well as her insulin sensitivity. A person's reproductive and metabolic fitness can be improved by setting realistic and attainable weight loss goals since these indices can be significantly improved with only a modest (2–5%) reduction in body weight [45].
- Genetics: Using the three primary PCOS associated variables ovulatory dysfunction (OD), hyperandrogenism (HA), and polycystic ovarian morphology (PCOM) - a meta-analysis of genome-wide association (GWAS) data revealed a strong genetic relationship between PCOS susceptibility variants. This finding supported the hypothesis that different variations can cause PCOS through distinct mechanisms [46].
- Hormonal Therapy: For the treatment of PCOS and maintaining the regularity in the menstrual cycle, birth control tablets are frequently prescribed. They are safe to take, particularly in cases where the patient wishes to avoid pregnancy. If lifestyle modifications fail to alleviate PCOS symptoms or long-term cardio metabolic risk factors, or if symptoms must be immediately managed, consideration should be given to pharmacological treatment. For years, oral contraceptive pills (OCPs) have been the only treatment for PCOS when fertility is not an issue. They remain the mainstay of PCOS treatment since they effectively regulate menstrual periods, offer a reversible method of contraception, lower the risk of endometrial cancer, and treat acne and hirsutism. However, OCPs are recognized to be more vulnerable [47].
- Medical Treatment: PCOS are treated with the following medications
  - Metformin: Diabetes type II is treated with the medication metformin (Glucophage, Fortmet). Enhancing insulin levels is another way to treat PCOS [22]. In PCOS patients, metformin is helpful to induce insulin resistance (defined as high fasting glucose or fasting glucose/insulin ratios). For women with PCOS and hyperandrogenism, the standard formulation of metformin proved helpful at doses ranging from 1275 to 2550 mg/day for ovulation [47].
  - Pioglitazone and Rosiglitazone: Pioglitazone and Rosiglitazone are other helpful medications.
  - Thiazolidinediones: Like metformin, or may be even more so, TZDs seem to be useful medications for helping PCOS-affected women regain regular menstrual cycles and ovulation; as a result, they may be used to treat oligo menorrhea [47].
  - Inositols: Among the more recent insulin-sensitizing drugs, the use of inositols in the PCOS treatment regimen has shown to be quite beneficial in managing the associated metabolic and endocrine abnormalities. For the treatment of PCOS patients, the inositol isomers myo-inositol (MI) and D - chiro-inositol (DCI) may be used as effective therapeutic options. They serve as supplementary messengers for insulin and modulate its various actions. Despite its similarities, the functions that MI and DCI play in the genesis and management of PCOS vary. The conversion of MI into an inositol Phosphoglycan (IPG) insulin second messenger (MI-IPG) is responsible for the absorption of glucose by cells, whereas the conversion of DCI into an IPG insulin second messenger (DCI - IPG) is crucial for the production of glycogen [48].
  - GLP-1 agonists: GLP-1 receptor agonists are a class of antidiabetic drugs that imitate the actions of incretins. Incretins are gastrointestinal hormones that cause the pancreas to release more insulin in response to eating [49]. Liraglutide and Exenatide are two GLP-1 receptor agonists that have been investigated in PCOS patients. In

overweight PCOS women, ligarglutide treatment (1.8 mg/kg) improved ovulation rate, decreased weight (by 5.2 kg), and boosted testosterone levels [50]. Another GLP-1 receptor agonist that has been shown to have effects on the central nervous system, decrease food absorption, and cause weight loss is eventide [48].

- Statins: Women diagnosed with PCOS often have dyslipidaemia, a condition marked by elevated LDL-C, TG, and low HDL-C values that is a strong indicator of cardiovascular risk. Thus, lowering the morbidity of cardiovascular disease and optimizing the lipid profile are essential components of the efficient therapy of PCOS [1]. Statins are among the most recent treatments that have been included to PCOS treatment regimens. They are helpful in treating PCOS because they lower the synthesis of sex steroids, improve dyslipidaemia, and lower the production of ovarian androgen by preventing the creation of androgen by theca cells [48].
- Acupuncture: In the age-old medical practice of acupuncture, somatic afferent neurons that innervate the skin and muscles are stimulated sensory stimuli using needles. Acupuncture has been recommended as a helpful treatment for an ovulatory dysfunction, insulin resistance, and hyperandrogenism in PCOS by a number of clinical and pre-clinical studies [48].

6. Conclusion

PCOS is most common and complex disorder in women of reproductive age. It is caused due to various factors including environmental factors, genetic mechanism, diet, obesity, insulin resistance, hyperandrogenism, etc. and manifests as irregular periods, hirsutism, increased testosterone levels, weight gain, acne, mood swings etc. Depending on the cause of PCOS, multiple techniques are used to treat this condition. This review provides the information about PCOS, its causes, symptoms, pathogenesis and its management to raise the awareness among women to prevent and manage this complicated condition.

Compliance with ethical standards

Disclosure of conflict of interest

Conflict of interest: Nil

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