

The Complex Landscape of Polycystic Ovarian Syndrome: From Causes to Cutting-Edge Treatments

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ABSTRACT

Polycystic ovarian syndrome (PCOS), or hyperandrogenic anovulation (HA), is a common endocrine condition in 4-10% of women of reproductive age globally. PCOS is diagnosed when these symptoms substantially compromise the quality of life. The etiology of the condition is multifactorial and includes genetic and environmental causes such as hormonal dysregulation, chronic low-grade inflammation, insulin resistance, and hyperandrogenism. These disrupt folliculogenesis and heighten the potential for comorbidities such as type II diabetes and endometrial cancer.

New research points to dysbiosis of gut microbiota in the pathophysiology of PCOS, with disturbed microbial patterns playing a role in metabolic and hormonal dysfunction. Microbiota-directed therapy, including fecal microbiota transplantation (FMT), probiotics, synbiotics, and prebiotics, have been found to have promise in enhancing hormonal homeostasis and decreasing inflammation.

This review summarizes the risk factors affecting PCOS development, prevalence, and modulation and discusses novel therapeutic approaches such as IL-22 and miRNA therapy. It highlights the importance of gut dysbiosis and examines microbiota-based treatments that may assist in the management of the heterogeneous phenotypes of PCOS, providing new directions for enhancing patient outcomes.

Keywords: Polycystic Ovarian Syndrome (PCOS), Insulin Resistance, Hyperandrogenism, Gut Microbiota Dysbiosis, Targeted Therapies

1. INTRODUCTION

Hyperandrogenic anovulation (HA) or Stein-Leventhal syndrome are other names for polycystic ovarian syndrome (PCOS), one of the most common endocrine system disorders affecting women of reproductive age [1]. This chronic and diverse condition can show itself as obesity, hirsutism, acne, infertility, and irregular menstruation [2]. It illustrates a state in which at least one ovary possesses an ovarian volume of over 10 millilitres and at least one ovary develops an estimated ten tiny cysts that range in diameter from 2 to 9 mm [3]. It is typically only identified when issues arise that substantially lower a patient's quality of life (e.g., hair loss, alopecia, acne, and problems associated with infertility) [4].

According to extensive screening of women employing the National Institutes of Health (NIH) diagnostic criteria, 4–10% of women of reproductive age all over the world are likely to have PCOS [5]. According to estimations from the World Health Organization (WHO), 116 million women worldwide (3.4%) suffered from PCOS in 2012 [7]. This high prevalence highlights PCOS's substantial financial cost, as does its association with irregular menstruation and ovulation, infertility, hair loss, and metabolic problems [2]. While PCOS can develop at any age, starting with menarche, most cases are seen in people

between the ages of 20 and 30 [6]. Around the world, 1.55 million women of reproductive age suffer from PCOS, which causes 0.43 million disability-adjusted life years (DALYs). Compared to 2007, the age-standardized incidence rate of PCOS in women of reproductive age was 1.45% higher in 2017 (82.44 per 100,000) [8].

Previously believed to be a condition that only afflicted adult women, a recent study shows that PCOS is a lifelong syndrome that initially appears during pregnancy [9]. A mix of hereditary and environmental variables is believed to be the main cause of this multifactorial condition, while the precise reason is unknown. Hormonal imbalance, chronic low-grade inflammation, insulin resistance, and hyperandrogenism are the main pathophysiological factors of PCOS. These factors hinder folliculogenesis and raise the risk of associated comorbidities such as type II diabetes and endometrial cancer. International guidelines state that ovarian morphology, anovulation, and hyperandrogenism are the three primary criteria used to diagnose PCOS [10].

Various environmental factors, including geography, nutrition and diet, socioeconomic position, and environmental contaminants, may influence the development, occurrence, and treatment of PCOS [12]. The microbiome and PCOS have been linked in recent years, and this is thought to have had a role in the development of the condition. One possible pathogenic element in the onset and progression of PCOS may be dysbiosis of the gut microbial community brought on by environmental risk factors. Distinct microbiota contributes to distinct pathogenic elements of PCOS, and there are crucial pathways connecting their involvement in the start of diverse PCOS clinical symptoms. Introduce fresh approaches to treatment for the illness [11]. Fecal microbiota transplantation (FMTs), probiotics, synbiotics, and prebiotics improve eubiotics and lessen the effects of changed microbial profiles, which helps control the range of phenotypes linked to PCOS. Treatments mediated by microbiota may help PCOS women's hormonal, inflammatory, and metabolic traits [16].

The risk factors for PCOS development, prevalence, and modulation are compiled in this review, along with potential therapeutic strategies such as IL-22 and miRNA therapy. We also discuss the importance of gut dysbiosis in the pathophysiology of PCOS and look at many microbiota-focused treatment approaches that may help with its management [16].

Phenotypes of PCOS

Based on the three main characteristics of PCOS—anovulation, hyperandrogenism, and polycystic ovaries—the medical profession has established four phenotypes that might be considered variations of PCOS (Table 1) [14]. Along an axis of metabolic and ovarian dysfunction, the four phenotypes consistently range from the most severe (phenotype A) to the least severe (phenotype D).

Table 1: Four major phases in phenotypes of PCOS

Feature	Phenotype A	Phenotype B	Phenotype C	Phenotype D
Biochemical/clinical hyperandrogenism	+	+	+	–
Chronic anovulation	+	+	–	+
Polycystic ovaries	+	–	+	+

Disease Pathophysiology

Based on the diagnostic criteria, PCOS affects 8% to 20% of women of reproductive age worldwide each year [15]. Changes in steroidogenesis, ovarian folliculogenesis, neuroendocrine function, metabolism, insulin sensitivity, insulin production, adipose cell activity, inflammatory factors, and sympathetic nerve function all play a role in the pathogenesis of this disorder [13]. According to Barre et al., excessive carbohydrate intake, hyperinsulinemia, hyperandrogenemia, and persistent low-grade inflammation are the four primary drivers of pathophysiological alterations in PCOS [20].

Hyperandrogenism

Hyperandrogenism, the biochemical hallmark of PCOS, presents clinically as hirsutism, acne, and baldness. Seventy-five to ninety percent of PCOS patients with oligomenorrhea have excessive amounts of androgens, and these levels usually rise as the phenotype gets worse. Hyperandrogenism is caused by the ovaries and adrenal glands producing too much androgen [19]. Hyper androgen dependence is characterized by elevated levels of free (unbound) testosterone, a key hormone involved in the pathophysiology of PCOS. The excessive production of androgens results from impaired adrenal or ovarian functions. Poor folliculogenesis is the first consequence of excessive androgens interfering with normal androgen production in PCOS. Excessive androgens promote the development of primordial follicles and an increase in antral follicles during the early gonadotropin stage [17]. GnRH synthesis in the hypothalamus causes the pituitary to discharge gonadotropin chemicals.

Luteinizing hormone (LH) stimulates the LH receptor to boost testosterone production in ovarian cells, theca. At the same time, androgens are changed into estrogens, which promote follicle growth, by activating the FSH receptor in ovarian granulosa cells. An excess of gonadotropin is believed to result from an imbalance in the hypothalamic–pituitary–ovarian (HPO) axis caused by the dysregulation of the neuroendocrine system. The creation of LH is promoted above FSH by the rise in GnRH, which causes a significant hormonal spike in the LH: FSH ratio in PCOS [18]. Excessive LH stimulation induces the ovaries' theca cells to hyperproliferate. It ultimately results in a follicular fluid accumulation that forms cystic structures around the ovary's edge, giving it an appearance of a pearl string. This is because, particularly during the preantral and antral stages, a large number of follicles in the ovaries' theca cells become arrested. An increase in follicles and the expression of essential enzymes involved in androgen synthesis are the causes of the overproduction of androgens [16].

Hyperinsulinemia

The primary hormone responsible for glucose homeostasis and lipogenesis is insulin.

Insulin affects the metabolism of proteins, lipids, and carbs and acts as a mitogenic hormone. The actions of insulin are mediated by insulin receptors, which are found in numerous tissues of the HPO axis. In steroidogenic organs like the ovary and the adrenal cortex, insulin increases the relevant trophic hormones to promote steroidogenesis [15]. Hyperinsulinemia is the primary root cause of increased androgen production because insulin directly mimics the action of LH and indirectly increases GnRH. Insulin reduces sex hormone binding globulin (SHBG), a crucial circulatory protein that controls testosterone levels. As a result, reduced SHBG would raise free androgen levels, which result in PCOS clinical symptoms such as hirsutism, alopecia, and acne [17]. Several studies have demonstrated that reducing the insulin resistance will eventually lead to lower testosterone levels and an improvement in the ailment [21].

Causes and Risk Factors

Because of its intricately interconnected pathophysiology, it is challenging to pinpoint the underlying causes of this multifactorial illness. Genetic factors, obesity, gut dysbiosis, environmental contaminants, and dietary and lifestyle decisions can all affect the genesis, prevalence, and modulation of the PCOS phenotype. These variables may contribute to the development of insulin resistance, partial folliculogenesis arrest, excessive androgen secretion by the ovaries, and the long-term low-grade release of inflammatory mediators from white blood cells, all of which can worsen metabolic syndrome.

Etiological Role of Environmental Pollutants

Multiple studies demonstrate the substantial impact that environmental contaminants such as pesticides, heavy metals, and endocrine-disrupting chemicals (EDCs) have upon human reproduction and health. There is growing evidence that environmental contaminants play a role in PCOS development. According to Takeuchi and Kandarakis et al., hyperandrogenic women with PCOS had higher serum BPA levels than both non-hyperandrogenic PCOS women and healthy controls [22]. According to a different study, PCOS women's serum testosterone levels were favourably correlated with increases in blood BPA levels compared to healthy women [22]. Higher serum levels of perfluorooctanoate and perfluoro octane sulfonate were found in women with PCOS, according to case-control research conducted by Vagi et al. to determine the association between different environmental contaminants and PCOS [23]. The research team also observed a negative correlation between PCOS and phthalate body burden. More specifically, women with PCOS had reduced levels of monophenyl phthalate (mBzP) in their urine [23]. Indicating an impaired xenobiotic metabolism. It had been thought that EDCs, such as BPA and phthalates, primarily impacted the nuclear hormone system's thyroid, oestrogen, progesterone, and androgen receptors. Fortunately, later studies have shown that EDCs can affect non-nuclear hormone receptors, orphan receptors, and neurotransmitter receptors as well as other reproductive pathways. They can also directly alter steroidogenesis and hormonal metabolism [24]. EDCs are a class of common contaminants that have been extensively researched as potential environmental factors that influence the pathophysiology of PCOS. This condition is associated with increased oxidative stress and inflammation, which in turn lead to insulin resistance, obesity, and infertility—all of which can be directly or indirectly linked to exposure to EDC. Furthermore, PCOS exhibits changes in neurotransmitter profiles that are comparable to those observed in animals exposed to EDCs [25]. In vitro and animal studies, endocrine disruptors are linked to the production of metabolic and reproductive disorders that mimic PCOS symptoms [26]. All things considered, EDCs may disrupt the local paracrine and autocrine systems, along with the hypothalamic-gonadal hormone balance, ultimately leading to PCOS pathogenesis.

Several studies have discovered a positive relationship between smoking, exposure to cigarette smoke, and the incidence of PCOS. With a study including oligo-anovulatory women with PCOS, women with normal anovulation with PCOS, and healthy controls, smoking was discovered to be dose-dependently linked to ovulatory dysfunction [27]. PCOS and smoking are closely linked to an inflammatory condition marked by an increase in mononuclear cells, mitochondrial dysfunction, a decrease in GSH (glutathione) and oxygen intake, and an oxidative state with lower antioxidant levels [28]. Theca cells may undergo steroidogenesis as a result of these inflammatory stimuli changing their enzymes. The majority of air pollutants which are positively connected with the threat of PCOS are polycyclic aromatic hydrocarbons (PAHs), which are created by burning coal, gas, wood, trash, cigarette smoke, and high-temperature-cooked meat [29]. PCOS may occur as a result of exposure to air pollutants such as nitrogen oxides, sulphur dioxide, PAHs, and particulate matter, or PM 2.5, which may alter

normal steroidogenesis and increase inflammatory mediators in exposed women. According to the findings of a Taiwanese population-based cohort study, a higher incidence of PCOS was linked to greater exposure to fine air pollutant particles and pollutant gases, including SO₂, NO, NO₂, NO_x, and PM_{2.5} [30]. Experimental animals also show a link between environmental contaminants and PCOS. Recent studies have shown that direct exposure of pregnant rats to the insecticides DDT or the fungicide vinclozolin was linked, through epigenetic processes, to the development of ovarian anomalies typical of PCOS in three generations afterwards [31].

Role of Diet and Lifestyle

Though they are not a substitute for pharmaceutical therapy, lifestyle modifications are the mainstay of care for women with PCOS. In addition to being advised in professional guidelines for several conditions, regular physical activity, maintaining a healthy bodyweight, following the prevention and treatment of metabolic diseases depend heavily on eating a balanced diet and giving up smoking.

A lack of exercise and high calorie diets may be contributing factors to the worsening of PCOS. By changing gut flora, causing chronic inflammation, raising insulin resistance, and increasing androgen production, high-sugar diets may be a contributing factor to PCOS. Gaining weight and obesity exacerbate the syndrome's defining characteristics. Low-GI (LGI) diets decreased the waist circumference, total and LDL-C, TGs, fasting insulin, and total testosterone in PCOS patients compared to high-glycaemic index (HGI) meals. However, there was no effect on fasting glucose, HDL-C, weight, or the free androgen index. In addition, HDL, SHBG production, and body fat loss were enhanced by a combination of an LGI diet, exercise, and/or omega-3 supplements [32]. According to Gonzales et al., eating saturated fat increases the production of peripheral leukocytic suppressor of cytokine-3 (SOCS-3) and TNF in the blood, which in turn causes LPS-mediated inflammation and insulin resistance in PCOS [33].

Therefore, cutting saturated fats out of these individuals' diets is essential. Through the sex steroid hormone–microbiota inflammation axis, dietary linolenic acid-rich flaxseed oil reduced PCOS in rats; however, additional linolenic acid sources are probably going to have a comparable impact [34]. Overweight and PCOS are intimately associated, according to epidemiological data and, more recently, genetic research [35]. Obesity exacerbates PCOS, mostly by making insulin resistance (IR) severe. Because of the abnormal activation of the HPO axis, obesity has been connected to the development of PCOS. The condition known as hyper, which is linked to obesity, exacerbates the lipid profile and glucose intolerance of PCOS patients. Obesity raises androgen production by inducing LH, which leads to hyperandrogenism [36]. The gut flora profits metabolically from fermentable Fiber, which causes SCFAs to be released [37]. Ghrelin and glucagon, two hormones that regulate appetite, may shift brought on by low-GI foods. In women with PCOS, low-GI meals lowered ghrelin while increasing glucagon [38]. While not metabolic changes in PCOS, high fructose consumption (HFC) worsened endocrine changes, suggesting that HFC can worsen endocrine-related PCOS phenotypes [39]. A meta-analysis and systematic review concluded that an LGI diet is an effective, acceptable, and safe intervention for IR relief, and that professional dietary counselling should be provided to all PCOS patients [40]. A ketogenic diet (KD), which limits total carbohydrate intake in favour of plant-based fat, seems to be another low-GI dietary modification. A KD enhances the menstrual cycle, reduces body weight and blood sugar, enhances liver function, and treats fatty liver in obese women with PCOS and liver dysfunction [41]. Paoli et al. found even more fascinating outcomes in PCOS-afflicted women after using KDs for 12 weeks [42]. Anthropometric and body composition measures revealed a considerable decrease in body weight, BMI, and fat-free body mass. Blood insulin and glucose levels significantly decreased, and HOMA-IR scores significantly improved. While HDL levels rose, TGs, total cholesterol, and LDL levels all sharply declined. Furthermore, blood levels of LH/FSH ratio, LH total, free testosterone, and DHEAS sharply declined, whilst levels of oestradiol, progesterone, and SHBG rose [42]. Patients and medical experts are increasingly acknowledging and accepting the benefits of physical exercise in the treatment of PCOS [43]. Activity amplifies the effects of insulin sensitivity by enhancing glucose transport and metabolism. A new meta-analysis found that the amount of exercise has a greater impact on physical health than dose. The results of the analysis demonstrate the health benefits of exercise and indicate that intense exercise may have the greatest impacts on insulin resistance, body composition, and cardiorespiratory fitness [44]. Resistance workouts and intense aerobic exercise are recommended for women with PCOS to increase their androgen levels and insulin sensitivity [45].

Role of Genes and Genetics

It has been demonstrated that certain genes, gene–gene interactions, or interactions between genes and the environment may influence an individual's susceptibility to developing PCOS, a polygenic and complex condition [46]. Numerous genetic investigations have shown that a range of PCOS symptoms are linked to multiple putative genes that have single-nucleotide polymorphisms or mutations. All genes and mutations that affect the ovaries directly or indirectly are associated with PCOS [47]. Genes encoding signaling components linked to steroidogenesis, steroid hormone action, gonadotrophin action and regulation, insulin action and secretion, energy metabolism, and chronic inflammation are most commonly implicated in the pathogenesis of PCOS [48] (Figure 1). The genetic architecture of this complicated condition must be defined by identifying important gene variations that could change a gene's expression or subsequent protein function. Genetic marker discovery could improve this condition's diagnosis, allowing for more individualized treatment plans and early intervention in co-

morbidities linked to the illness and its symptoms.

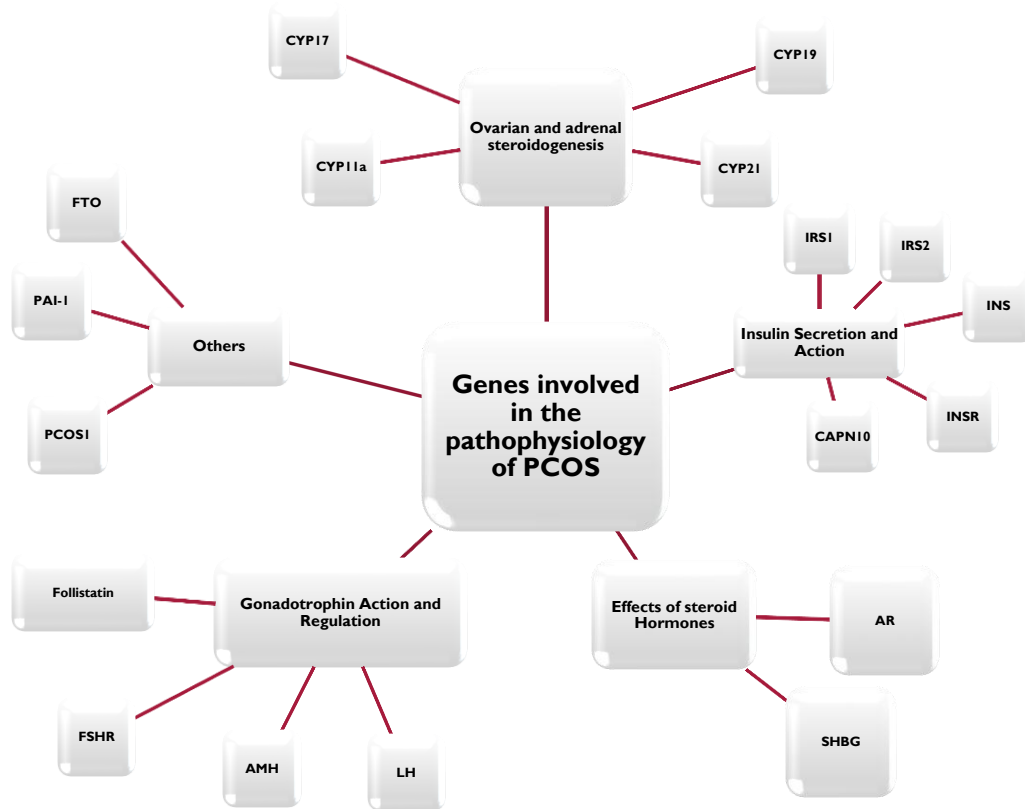


FIGURE 1: Summary of the genes involved in the pathophysiology of PCOS

Gut Microbiota Dysbiosis: Critical Correlation

The gut microbiome is an "organ" in and of itself, consisting of roughly 10^{13} – 10^{14} bacteria with a combined gene count nearly 200 times greater than the human genome [49]. Inflammation and changes in gut permeability, which seem to be caused by gut dysbiosis, may impact a host's health. The gut microbiota and the host maintain a delicate equilibrium under physiological settings that affects immunological function, metabolism, nutrition, and physiology. It also plays a major role in preventing several disorders. Significant differences exist in the composition of the microbiomes of healthy people, and these differences may increase a person's vulnerability to specific illnesses.

In recent years, many studies have examined the connection between PCOS and alterations in the gut flora [50]. These studies showed that the gut microbiota composition of PCOS patients differed significantly from that of healthy controls. Insulin resistance, sex hormone levels, and obesity may have an impact on the variety and structure of the gut microbiota in women with PCOS, according to studies [43]. PCOS is closely linked to gut microbiota and its metabolites. There were notable variations in the quantity of species and metabolites generated between PCOS and the control group. Primarily demonstrated by a reduction in microbial diversity, which was marked by an increase in dangerous bacteria (*Escherichia* and *Shigella*) and a decrease in helpful bacteria (*Lactobacilli* and *Bifidobacteria*) [50]. Dietary substrates can be broken down by the gut microbiota, which also produces metabolites that can either directly affect the intestines or enter the bloodstream and have an impact on numerous host tissues, including the skeletal muscle, liver, adipose tissue, and ovary, whose activities are changed in PCOS. A few gut bacterial metabolites that will be modified in PCOS include trimethylamine (TMA), short-chain fatty acids (SCFAs), and secondary bile acids [51]. Although 16S rRNA and metagenomic gene sequencing data vary widely, numerous human and rodent model studies have demonstrated a correlation between changes in gut microbiota and PCOS, including a decrease in biodiversity and changes in specific bacterial taxa. Research has shown that patients with PCOS have different bacterial species, including Firmicutes and Bacteroidetes, in terms of diversity and balance. The dysbiosis of gut microbiota (DOGMA) theory of PCOS explains three fundamental features of the syndrome: anovulation/menstrual irregularity, hyperandrogenism (acne, hirsutism), and the development of multiple tiny ovarian cysts [52]. The DOGMA theory states that gut microbiota dysbiosis brought on by a poor diet may enhance the gut mucosa's permeability, which will facilitate the bloodstream's uptake of lipopolysaccharides (LPS) from Gram-negative colonic bacteria.

Because the immune system disrupted insulin receptor function, blood insulin levels rise, ovaries produce more androgens,

and normal follicle formation is disrupted [52].

Treatment and Management

PCOS treatments need to be customized for each patient; possible objectives include reducing hyperandrogenic symptoms, triggering ovulation, controlling menstruation, and avoiding cardiometabolic issues. The three most upsetting symptoms for women with PCOS are infertility, hirsutism, and irregular menstruation. Because PCOS has a complicated etiology, treatment is rarely monotherapeutic; instead, it is tailored to the patient's specific indications and symptoms. For the management and treatment of PCOS, some alternative therapies have been proposed. The cornerstone of managing PCOS is thought to be dietary and lifestyle modifications. The most common symptoms of PCOS, including irregular menstruation, androgen-related symptoms, and anovulation that causes infertility, can be alleviated with a variety of pharmaceutical and non-pharmacological treatments. Many therapeutic options may be useful for controlling metabolic comorbidities in PCOS, but it's important to recognize that no single treatment may completely address the variety of metabolic abnormalities in women with PCOS. Compared to monotherapies, combining lifestyle modifications with drugs for various conditions improves metabolic comorbidity parameters and yields larger metabolic benefits. In addition, treatment should also consider elevated levels of anti-Müllerian hormone (AMH), plasma metabolomics, and gut microbiota composition, which are extreme features of PCOS, alongside emphasis on primary traits.

Oral Contraceptives and Anti-Androgens

For women with PCOS, oral contraceptives (OCs) are the first-line treatment for hirsutism/acne and irregular menstruation [53]. To minimize hyperandrogenism and lessen androgen synthesis in the ovaries, OCs work by promoting negative feedback on LH secretion. They decrease blood levels of free androgens while increasing SHBG generated by the liver. Additionally, OCs function by binding DHT to androgen receptors, preventing the peripheral conversion of testosterone into dihydrotestosterone (DHT), and reducing the release of adrenal androgens [54]. OC medicines can have different risk-benefit ratios depending on their dosages and drug combinations. The majority of OC preparations contain anti-androgens such as cyproterone acetate (CPA), drospirenone, norgestimate, levonorgestrel, and desogestrel, as well as estrogen (ethinylestradiol) [55]. Consequently, it's being utilized to treat hyperandrogenism medically. Antiandrogens are commonly used to treat PCOS since they help with androgen-related problems like hirsutism. Although the anti-androgens work in slightly different ways, they all prevent testosterone from doing its job. Anti-androgen receptor medications have shown promise in treating the symptoms of PCOS. Because OCs affect the pituitary and hypothalamus in addition to ovarian steroidogenesis, their primary effect is a reduction in hyperandrogenism [56]. Because of these characteristics, it is a useful pharmaceutical intervention for treating PCOS-related androgenic alopecia, hirsutism, acne, and irregular menstruation [57]. It has been demonstrated that third-generation combination OCs, which comprise antiandrogenic drugs, enhance patients' lipid, adipokine, and PCOS metabolic characteristics [58]. Flutamide, the most common competitive antagonist of ARs, has been demonstrated to help PCOS-affected women by lowering acne and hirsutism.

Flutamide-treated PCOS patients also reported better regular menstrual cycles and ovulation [59]. Furthermore, flutamide therapy demonstrated that, independent of weight changes, flutamide improved the lipid profiles of PCOS-afflicted women, with a significant reduction in total cholesterol, LDL, and TGs in both obese and lean PCOS women [60]. CPA and spironolactone are examples of steroidal AR blockers that compete with T and DHT for binding to ARs [61]. It has been discovered that both of these AR blockers significantly lessen acne and hirsutism in PCOS patients. Additionally, one experiment found that spironolactone therapy improved metabolic parameters in people with PCOS [62]. Another medication used to successfully treat hirsutism and lessen hyperandrogenic symptoms in PCOS patients is finasteride, a 5- α reductase inhibitor that prevents the conversion of T into DHT [63]. When taken as a whole, research on the use of anti-androgenic drugs, either by themselves or in combination, in PCOS patients has demonstrated that the targeted decrease in hyperandrogenism and, by extension, androgenic activity, has a favourable impact, improving many PCOS characteristics. Women with PCOS should undergo thorough screening to determine risk factors for serious OC side effects, including a history of smoking, obesity and hypertension, and a history of clotting problems, to mention a few crucial variables [64].

Insulin Sensitizers

PCOS has a pathogenesis that includes impaired insulin secretion and function. Hyperinsulinemia and insulin resistance are recognized to have an impact on the high androgen levels in PCOS. Insulin controls ovarian function, and high insulin levels can impair ovarian function. Theca cells release a lot of androgens in response to too much insulin, which stops follicular development and raises the likelihood of polycystic ovarian morphology, a symptom of PCOS [65]. Insulin resistance not only contributes significantly to the pathogenesis of PCOS but also adversely impacts PCOS patients by making them more susceptible to chronic conditions including type 2 diabetes and cardiovascular disease. A therapy strategy that targets insulin resistance, involving medication and lifestyle modifications, is crucial for the optimal management of PCOS. Insulin sensitizers raise insulin sensitivity in target tissues by decreasing insulin production and maintaining glucose tolerance [66]. It has been shown that by lowering insulin resistance, insulin sensitizers like metformin and thiazolidinediones (TZDs) can induce ovulation. The usage of the biguanide metformin is associated with better ovulation, lower levels of androgens in the blood, and increased menstrual cyclicity [54]. It works by boosting peripheral tissues' sensitivity to insulin, decreasing

hepatic glucose production, and increasing glucose absorption. In a study comparing lifestyle modifications with metformin in women with PCOS, both groups saw a significant drop in BMI; only the metformin group saw a drop in testosterone levels [67]. Metformin dramatically decreased BMI without requiring lifestyle modifications, according to another RCT assessing the medication's effect on body weight in obese and extremely obese PCOS women [68]. Several studies have demonstrated that metformin significantly reduces dyslipidaemia. It either directly influences how free fatty acids are metabolized by the liver or indirectly improves dyslipidaemia by reducing hyperinsulinemia [69]. Furthermore, TZDs (pioglitazone and rosiglitazone) decrease blood levels of androgens by improving insulin sensitivity, which in turn lowers insulin levels [70]. A meta-analysis evaluating the efficacy of pioglitazone and metformin in treating PCOS revealed that the pioglitazone group significantly improved menstrual cycle and ovulation [71]. The results of a meta-analysis of 22 studies for women with PCOS suggest that metformin with TZD is superior to metformin alone in reducing total testosterone levels and improving lipid metabolism and insulin resistance [72].

Ovulation Inducers

One of the diagnostic criteria for PCOS patients is ovulatory dysfunction, and ovulation induction is a successful treatment for PCOS patients who need to become fertile. The stoppage of antral follicle growth in its late phases of maturation and low FSH levels are linked to anovulation in PCOS. This process may be influenced directly or indirectly by the overproduction of LH, androgens, and insulin, which promotes steroidogenesis while inhibiting follicular development. The partially selective estrogen receptor modulator clomiphene citrate (CC) remains the first-line treatment for ovulation induction [73]. By blocking negative feedback in the estrogen signaling pathway, CC, an antagonist of the estrogen receptor, raises the availability of FSH. Follicle growth brought on by elevated FSH is followed by an LH surge and ovulation. Low-dose gonadotropin therapy can also be utilized to induce mono-follicular development and ovulation [74]. It is believed that women with PCOS produce fewer follicles that are necessary for efficient ovulation because they have a relative decrease in aromatase. Since they selectively prevent androgens from being converted into estrogens in ovarian follicles, peripheral tissues, and the brain, aromatase inhibitors (AIs) are thought to induce ovulation. This results in a positive feedback loop with the estrogen of the HPO axis, which triggers the endogenous release of GnRH, encourages the secretion of FSH, and stimulates follicular growth. Letrozole and anastrozole are examples of selective AIs that have been proposed as primary and secondary therapy for ovulation induction [75]. One benefit of letrozole is that it promotes mono-follicular growth while avoiding peripheral antiestrogenic effects on the endometrium [76].

Calcium and Vitamin D Supplements

Vitamin D affects AMH signaling, FSH sensitivity, and progesterone synthesis in human granulosa cells, which all have physiological implications for reproduction, including ovarian follicular development and luteinization. Among its many other roles, it affects glucose homeostasis. Several possible effects of vitamin D on glucose homeostasis include the presence of a particular vitamin D receptor (VDR) in skeletal muscle and pancreatic cells, the expression of the enzyme 1-hydroxylase, which can catalyze the conversion of 25-hydroxyvitamin D [25(OH)D] into 1,25-dihydroxyvitamin D, and the presence of a vitamin D response element in the human insulin gene promoter [77]. Infertility, hyperandrogenism, insulin resistance, irregular menstruation and ovulation, obesity, and PCOS symptoms can all be made worse by low 25(OH)D levels. They can also raise the risk of cardiovascular disease. Vitamin D supplementation can boost blood anti-inflammatory soluble receptors for advanced glycation end products while lowering abnormally elevated serum AMH levels in vitamin-D-deficient PCOS patients. Specifically, in PCOS patients, vitamin D and calcium supplements combined with metformin therapy may enhance ovulation, hyperandrogenism, follicular development, and regular menstruation [78,79]. PCOS-afflicted women have abnormal ovarian folliculogenesis due to elevated AMH levels. When serum AMH levels are restored by vitamin D therapy, folliculogenesis may improve [80]. A meta-analysis's findings demonstrated that taking metformin along with a calcium/vitamin D supplement enhanced follicular maturation and menstrual regularity, significantly decreased fasting blood sugar (FBS), serum insulin levels, and homeostasis model assessment insulin resistance (HOMA-IR), and significantly raised the quantitative insulin sensitivity check index (QUICKI). Furthermore, it reduced blood TG and VLDL-C levels, cholesterol, LDL levels, hirsutism, and testosterone levels in PCOS patients [81].

Surgical options

Ovarian Drilling (Laparoscopic Ovarian Surgery):

Laparoscopic ovarian drilling is a surgical procedure that can induce ovulation in women with polycystic ovary syndrome (PCOS). Electrocautery or a laser is used to kill ovarian tissue. This operation is not widely utilized. However, it may be a possibility for women who are still not ovulating despite decreasing weight and using reproductive medications.

Ovarian drilling is typically performed through a tiny incision (laparoscopy) under general anesthesia. The surgeon makes a tiny incision in the abdomen near the belly button. The surgeon next inserts a tube into the belly to inflate it with a small amount of carbon dioxide gas, allowing him or her to implant the viewing instrument (laparoscope) without damaging the internal organs.

Surgical equipment can be placed through the same incision or smaller incisions in the pelvic area. Because of the little

incisions, laparoscopy is often referred to as "Band-Aid surgery". LOD is mainly used for women with PCOS who have difficulty ovulating and who do not respond to medications like clomiphene citrate or letrozole [82].

2. CONCLUSION

Polycystic ovarian syndrome (PCOS) is a common and multifactorial endocrine disorder that occurs in millions of women globally. It is marked by hyperandrogenism, insulin resistance, and persistent inflammation and has significant effects on reproductive health and metabolic function. The etiology of PCOS, though highly prevalent, is still not well understood, with genetic, environmental, and hormonal influences playing pivotal roles.

Traditional therapies like insulin sensitizers and oral contraceptives manage the symptoms rather than the etiology. The newly emerging treatments, like miRNA-based treatment, IL-22, as well as the targeted approaches such as fecal microbiota transplantation (FMT) and probiotics, represent encouraging directions toward a more complete management.

Targeting the gut microbiome and optimizing hormonal and metabolic balance, such new therapies potentially can decrease symptomatology and mitigate risk for associated comorbidities such as type II diabetes and endometrial cancer. In the future, tailored treatments that take phenotypic individuality and life style into consideration will be important to optimize the outcome in women with PCOS and to better improve quality of

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