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REPRODUCTIVE ENDOCRINOLOGY: REVIEW

A Comprehensive Review on Recent Advancements in Navigating the Complexities of Polycystic Ovarian Syndrome (PCOS)

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Abstract

Polycystic Ovarian Syndrome (PCOS) is a complex endocrine disorder whose pathophysiology extends beyond classical mechanisms of insulin resistance and hyperandrogenism. This review critically synthesizes recent advances from the past seven years that challenge conventional views and highlight emerging concepts. Key controversies such as the differing metabolic and reproductive phenotypes of lean versus obese PCOS, the causal versus associative role of gut microbiota dysbiosis, and the bidirectional link between psychological disorders and endocrine imbalance are examined in light of current evidence. We integrate insights from molecular, metabolic, and neuroendocrine research to illustrate how these interrelated mechanisms influence ovulatory function, oocyte competence, and fertility outcomes. Emerging therapeutic directions, including GLP-1 receptor agonists, insulin sensitizers, and neurobehavioral interventions, are discussed with attention to safety, reproductive implications, and long-term efficacy. Overall, this review advances a framework that connects metabolic, reproductive, and psychological dimensions of PCOS, emphasizing the need for individualized, mechanism-based management strategies.

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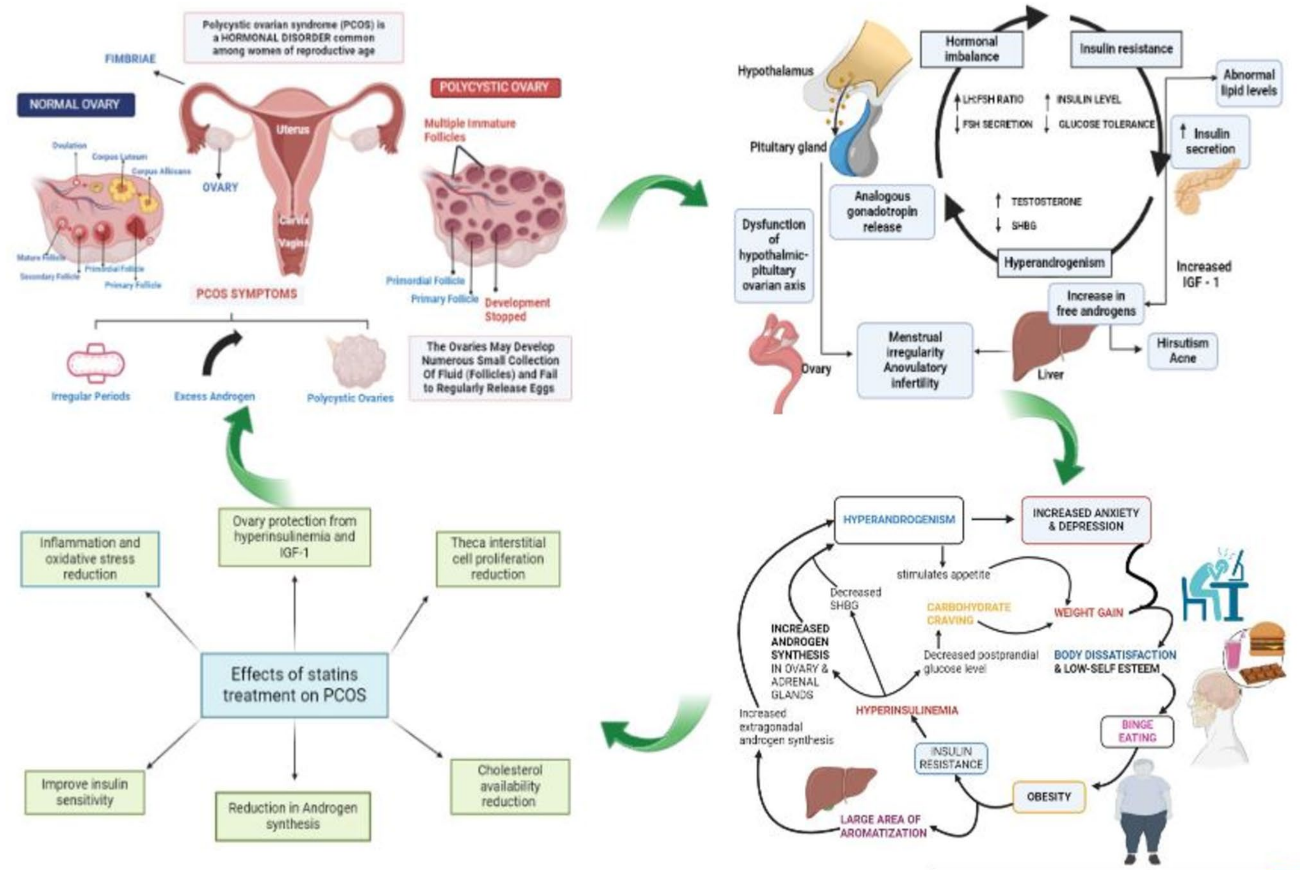
Graphical Abstract



Keywords Polycystic ovarian syndrome · Hyperandrogenism · Metabolic implications · Therapeutic approaches · Pathophysiology

Abbreviations

AMPK	AMP activated protein kinase
ANGPTLs	Angiopoietin-like proteins
BED	Binge eating disorder
BMI	Body mass index
EE	Emotional eating
FFA	Free fatty acids
FSH	Follicle-stimulating hormone
GLUT4	Glucose transporter 4
GnRH	Gonadotropin-releasing hormone
HPO	Hypothalamus-pituitary-ovarian
IL-6	Interleukin-6
INSR	Insulin receptor gene
IR	Insulin resistance
MS	Metabolic syndrome
PCOS	Polycystic ovarian syndrome
SHBG	Sex hormone-binding globulin
T2DM	Type 2 diabetes mellitus
TNF-α	Tumor necrosis factor-alpha
WC	Waist circumference

Introduction

An endocrine disorder first described by Stein and Leventhal in 1935, included clinical presentations of enlarged ovaries, menstrual irregularities, obesity infertility and pilosity, now which is termed as polycystic ovarian syndrome [1]. Polycystic ovarian syndrome is a disease characterized by excessive production of androgens causing hormonal imbalance and hence disturbing normal functioning of female reproductive system. PCOS is commonly known to be an ailment of females of reproductive age with a 9 to 18% prevalence [2–4]. International guidelines 2018 set up a diagnosis criterion for PCOS, presence of any of the following two symptoms would be a strong indicator of PCOS: a) Hyperandrogenism either clinical or biochemical b) oligo-anovulation (>35 days duration of menstrual cycle or < 8 menstrual episodes per year) c) polycystic ovaries seen in ultrasound [5, 6]. Besides its reproductive indications, PCOS is also identified as the metabolic syndrome (MS) a cluster of medical conditions such as hypertension, hyperglycemia, abnormal cholesterol levels and excessive abdominal fat deposition. It has strong relationship with insulin resistance (IR) and type 2 diabetes mellitus (T2DM) [7].

Obesity is known to cause PCOS rather than just be one of its symptoms [8]. Recent studies have suggested that women diagnosed with PCOS have fivefold increase chances of presenting with insulin resistance when compared to the normal population and a 4.35-fold risk of Type 2 Diabetes Mellitus (T2DM) along with 23.46-fold risk of developing metabolic syndrome (MS) [9, 10]. Furthermore, the body of patients with PCOS and obesity is more inclined to develop insulin resistance and most of the women with this condition are found to be overweight or obese. Particularly, a number of mechanisms that are mainly associated with impaired post-receptor signaling and reduced insulin receptor beta subunit in skeletal muscle, liver, adipose tissue, and kidneys been known to have been responsible for the development of tissue insulin resistance [11]. It is conceivable that the perturbation of PCOS could be involved in the genesis of hyperinsulinemia, the increase of testosterone levels, and the altered synthesis of ghrelin and CKK [5]. Interestingly, the prevalence of PCOS in thin females is a signal that there are more factors linked to PCOS and insulin resistance (IR) than obesity [12, 13].

Genetical predisposition in obese females stimulates the development of PCOS [14]. The latest theory indicates the possibility of maternal obesity and stress being the determinants in the uterus that trigger PCOS during adolescence [15, 16]. Besides metabolic impairment and hirsutism, PCOS is associated with a gamut of emotional torments—sadness, fear, and mood disorders [9]. The possible determinant factors are lack of self-esteem, bad body image due to medicinal transition e.g. obesity, acne, and hirsutism. Also, problems with womanhood and difficulty with fertility might be indicated, as well as dysfunction in sexual and relational relationships [17, 18]. These conditions of depression and anxiety may be problems in EE and BED and also in later obesity which complicate PCOS (polycystic ovarian syndrome) [19, 20].

This study examines the complex interplay between obesity and Polycystic Ovary Syndrome (PCOS), noting that obesity worsens insulin resistance and hyperandrogenism. Insulin resistance disrupts glucose balance and raises insulin levels, exacerbating PCOS symptoms. The review also highlights that PCOS can affect women of varying body weights, revealing its diverse causes. Emphasizing the need for further research, it calls for a focus on genetic, metabolic, and psychological factors, including the heightened anxiety and depression commonly experienced by women with PCOS. This approach is crucial for developing comprehensive, personalized treatment strategies.

This review synthesizes evidence published within the past years (2018–2025) to distinguish classical from emerging paradigms in PCOS research. By critically comparing established mechanisms such as insulin resistance and HPO-axis dysfunction with newer findings on gut–brain interactions, microbiome alterations, and psychological determinants, this article aims to provide an integrated conceptual framework that reflects the evolving complexity of PCOS. A summary schematic contrasting traditional and emerging models is presented to highlight unresolved controversies and guide future inquiry.

Polycystic Ovarian Syndrome (PCOS)

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder that affects reproductive-aged women, characterized by hormonal imbalance, menstrual irregularities, and often, the presence of cysts on the ovaries [21, 22]. While the exact cause of PCOS remains elusive, it is believed to involve a combination of genetic, environmental, and lifestyle factors. Understanding the pathophysiology of PCOS (Fig. 1) is crucial for both diagnosis and treatment. Furthermore, disturbances in gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus and subsequent dysregulation of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion from the pituitary gland contribute to the pathogenesis of PCOS [23]. Elevated LH levels relative to FSH are commonly observed in women with PCOS, disrupting normal ovarian follicle development and leading to anovulation. One of the key features of PCOS is hyperandrogenism, an excess of androgens (male hormones) in the female body [24]. This imbalance can lead to symptoms such as hirsutism (excessive hair growth), acne, and male-pattern baldness. The source of these androgens in PCOS can be multifactorial, involving increased production by the ovaries, as well as by the adrenal glands and peripheral tissues [25]. Insulin resistance is another hallmark of PCOS, with many individuals exhibiting impaired glucose tolerance and compensatory hyperinsulinemia [26]. Insulin resistance can exacerbate hyperandrogenism by stimulating ovarian androgen production and reducing sex hormone-binding globulin (SHBG), leading to elevated free androgen levels [27].

Also, it is crucial to say that chronic interpersonal stress such as low self-esteem issues, conflictual relationships with friends or/and family, and discrimination may serve as the reasons of the onset of emotional eating (EE) and binge eating disorder (BED) both of which are mental illnesses related to abnormal behavior of eating [28]. Furthermore, it is not only the hypothalamic–pituitary–adrenal axis which is activated by chronic stress, but adrenal androgen production

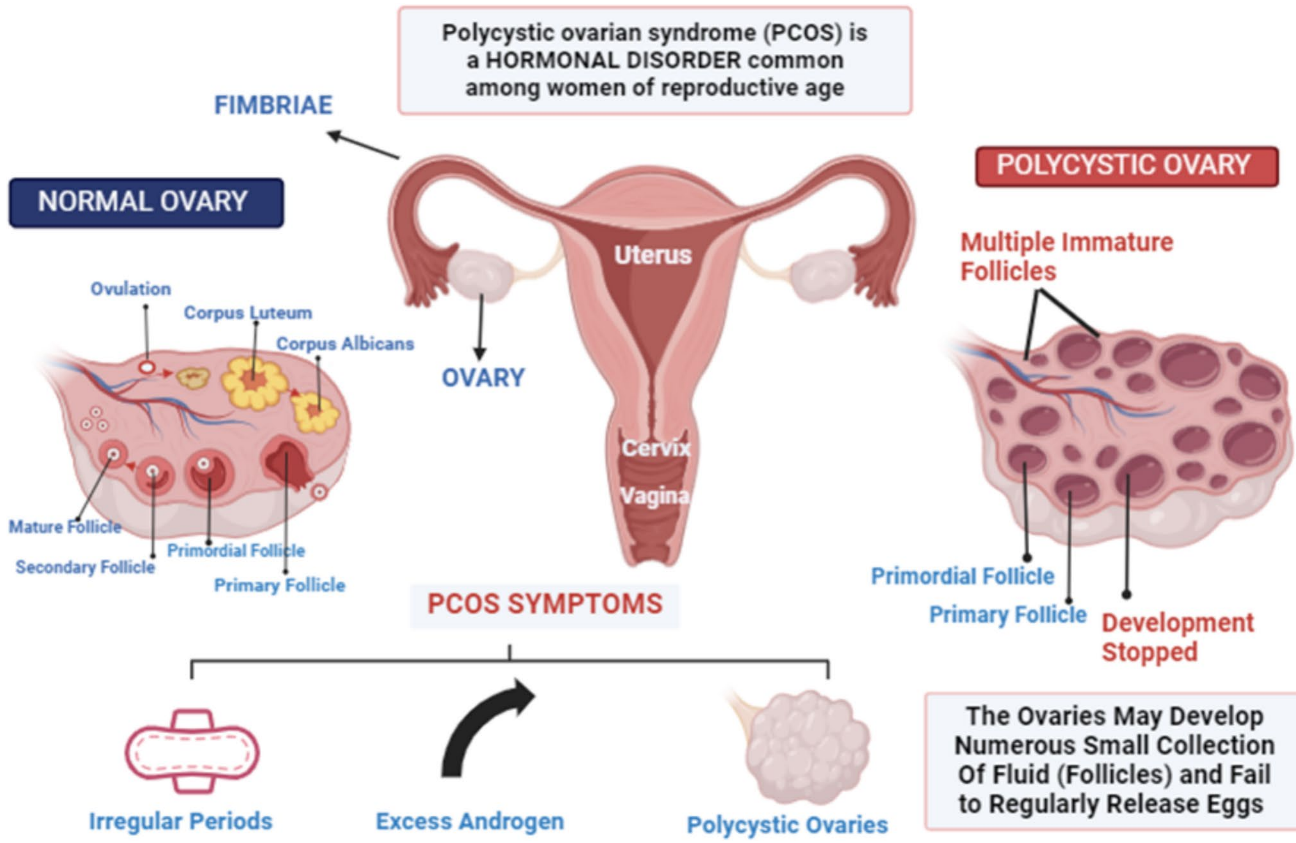


Fig. 1 Pathophysiology of PCOS

is also stimulated by the process [29]. It has been well-established, through several studies, that there's a surge in depression, anxiety, and post-traumatic stress among children/adolescents during the COVID-19 pandemic a reasonable growth in the incidence of EE and BED can also be expected at the end [30]. It can therefore be the reason of increasing proportion of PCOS related reproductive challenges among the teenage girls and the female patients of reproductive age group [31]. The combination of emotional [32] and psychological problems lowers a person's impulse control and consequently favors binge eating patterns and food cravings that are known to spur weight gain and insulin resistance [33].

Recent studies anticipated that women with PCOS have higher level of psychological distress than that of healthy cohorts [34]. It has been found that impairment of the women's fertility, weight gain, hirsutism and acne may be among the features of this disease, and further weakening the mental and psychological state of these women [35]. Additionally, disruptions in gut microbiota have a substantial impact on behavior and brain function. In particular, they lead to a decrease in serotonin synthesis, which has a direct impact on mood and behavior. It relates to emotional activities like anxiety and depressive disorders [36]. Emerging research challenges the long-held notion that psychological symptoms are merely secondary to PCOS. Elevated cortisol and altered serotonergic signaling may themselves contribute to ovarian dysfunction, suggesting a bidirectional relationship where psychological distress both arises from and perpetuates endocrine imbalance. This evolving model underscores the need for integrated psycho-neuroendocrine approaches in PCOS care [37].

To highlight conceptual evolution, Table 1 contrasts classical mechanisms of PCOS with emerging perspectives reported over the past years, emphasizing ongoing controversies such as lean versus obese phenotypes, gut microbiota causality, and the bidirectional influence of psychological factors.

Metabolic and Hormonal Dearrangements Predisposing to Food Disorders in Women with PCOS

Obesity

The fact that thin women can still get PCOSs is not a bar to the condition whose major risk factor is obesity and accounts for up to 80% of cases in females [7, 12]. Obesity in women

Table 1 Evolution of PCOS understanding: classical vs emerging perspectives (2018–2025)

Domain	Classical views	Emerging views	Key unresolved questions	Ref
Insulin resistance (IR)	Considered a secondary effect of obesity and hyperinsulinemia	Observed even in lean PCOS phenotypes; may be a primary defect independent of adiposity	Does IR arise from intrinsic genetic or inflammatory triggers rather than obesity alone?	[38]
Hyperandrogenism	Attributed mainly to ovarian theca cell dysfunction and excess LH stimulation	Now linked with systemic inflammation, gut microbiota metabolites, and chronic stress	How do inflammatory cytokines and gut–brain signals regulate androgen synthesis?	[39]
Gut microbiota	Historically under-recognized in PCOS pathogenesis	Dysbiosis shown to influence insulin signaling and androgen production, but directionality remains unclear	Is microbial imbalance a cause or a result of metabolic dysfunction?	[39]
Psychological disorders	Viewed as consequences of infertility, hirsutism, and cosmetic concerns	Recent evidence suggests bidirectional links psychological stress may worsen hormonal and metabolic imbalance	Can early psychological interventions improve endocrine outcomes?	[40]
Phenotypes (lean vs obese PCOS)	Obesity regarded as central to pathogenesis	Lean PCOS exhibits distinct hormonal and metabolic profiles, suggesting different underlying mechanisms	Should lean and obese PCOS be treated as distinct subtypes?	[23]
Treatment approaches	Centered on metformin, OCPs, and lifestyle modification	GLP-1 receptor agonists, microbiome modulation, and combined psychometabolic therapy emerging	What are the reproductive safety profiles and long-term benefits of these novel therapies?	[41]

often leads to irregular menstruation and irregular ovulation—which causes infertility in women of the broader population [13]. Research regarding teenagers and girls is aimed at establishing the relations of obesity and PCOS and finding out which one is the start point of that vicious circle [42]. A group of investigators has stated that the more weight (BMI) baby girls have during infancy, then there is a higher their risk of getting oligomenorrhea and a PCOS diagnosis in their early adult years [43]. However, it's unclear, though, if these girls displayed symptoms of PCOS when they were young [14]. A study was carried out to find out if obesity in teenagers with PCOS is predicted. At the age of 14, 12 out of 30 (or 40%) oligomenorrheic girls had PCOS, according to the Rotterdam criteria. Compared to 8.4% of girls without PCOS, 33% of girls with PCOS had class III obesity by the age of 24 [44]. In another study, 244 girls who had reached puberty were randomly selected to look at the impact of obesity on the abnormal development of ovaries. 61.1% of the obese girls and 2.1% of the subjects with normal weight developed PCOS, according to the data [45]. These studies show that obesity and PCOS are likely to be related or that one can led to another. It is yet unclear the exact way obesity, in turn, affects PCOS pathophysiology. Elevated tissue fat negatively impacts the hypothalamus-pituitary-ovarian axis (HPO) which is a hormonal system regulating reproductive function via communication between hypothalamus, ovaries and pituitary gland [46]. Hence, it is well established that increased levels of insulin and insulin resistance are closely related to obesity.

Resistance to Insulin

The increase in blood glucose level after eating food triggers the release of insulin from the beta cells of pancreas [47]. Insulin is a hormone involved in homeostasis of glucose by increasing the uptake of glucose by cells and adipose tissues, promoting the synthesis of proteins, inhibiting lipolysis, and reduces the liver's gluconeogenesis [48]. It binds to the tyrosine kinase surface receptors and activates AKT serine/threonine kinase 2 which opens GLUT-4 channels promoting the translocation of glucose into the cells and glycogen synthesis via glycogen synthetase [49]. In certain conditions there is an abrupt insulin signaling via diacylglycerol mediated protein kinase C theta activation [50, 51]. In contrast there is an increased sequestration of AKT2 via protein kinase C zeta which impairs the normal functioning of AKT2 i.e. less GLUT-4 channels opening and more blood glucose level [52]. Consequently, there is an increase beta cell activation to overproduce the insulin which provokes increased insulin resistance (IR) occurs. At least in the early stages of the disease, hyperinsulinemia has been certified to be of the greatest significance in cases of insulin resistance [53].

Obesity induces lipolysis of subcutaneous and visceral adipose tissues depicted by increased levels of free fatty acids (FFA) and their metabolites inside the cells, which disrupt the working of the AKT2 regulator protein [31]. Together with it the studies indicate the disturbance of adipokine level e.g. adiponectin [54]. AMP activated protein kinase (AMPK) is activated by attachment to adiponectin, increases the oxidation of fats, and thus, insulin sensitivity improved [55]. There is low adiponectin levels in women with PCOS as compared with the control group which makes IR even worse [56]. Adipokine or hepatokine proteins are a group of proteins secreted usually by the liver. These proteins have an important role in the metabolism of fat and carbohydrates and in the etiology of IR [57–59]. It is fascinating that even though some hepatic biomarkers such as fetuin-A, B, selenoprotein P(SEPP1), Hepassocin, lipocalin 2 and 13 (LCN2, LCN13) enhance IR severity and some hepatokines such as fibroblast growth factor 21(FGF-21) and sex hormone-binding globulin (SHBG) and angiopoietin-like proteins (ANGPTLs) decrease the IR severity. According to the research done by Giannouli et al., the concentration of SHBG and selenoprotein P is lower in patients with PCOS than healthy people which was control group. It also demonstrated an association between levels of selenoprotein P and testosterone, also showed significant positive correlations with both the free androgens index ($r=0.361$, $p=0.002$) and testosterone ($r=0.325$, $p=0.007$). Furthermore, it was revealed that in PCOS patients the FGF21 levels were positively correlated with disease risk A study was done using 42 healthy volunteers that ranged in age from 18 to 45. This group was compared to 45 PCOS patients. The results of the study confirmed high level of Hepassocin and CRP in the PCOS group. In addition, the study suggested that both Hepassocin, a hormone related to menstrual cycle and LH, a gonadotropin that simulates mature Leydig cells, were positively correlated [60]. Furthermore, both had a very negative association with body mass index (BMI), waist circumference (WC), fat ratio, and HbA1c.

The serum levels of C-reactive protein (CRP) a marker of inflammation have been related with IR [61]. And interestingly, there is a back-and-forth relationship that can be demonstrated between inflammatory molecules, for example, cytokines, that are present during inflammation and infections and IR. Pro-inflammatory cytokines were measured to be present prior to the outbreak of inflammatory response; this means that the said response can worsen the effects of inflammatory response more [62]. Cytokines can either directly or indirectly inhibit the AKT signaling pathway by inducing lipolysis, which leads to the accumulation of FFA. In response, administration of FFP may weaken the inside activity of PI3K and AKT [63].

In response to hyperinsulinemia and IR, pituitary gland secretes the LH (luteinizing hormone) in large amount, thereby increasing production of ovarian androgens [64, 65]. Insulin can also stimulate the androgen production by ovarian theca cells directly and hence worsen the situation as shown in Fig. 2 [66]. It is noticeable that both IR and hyperandrogenemia have a bidirectional relation. Excessive exposure to testosterone has proved to have the deleterious effect on islets of Langerhans's which impairs pancreatic metabolic processes and thereby results in hyperinsulinemia [53, 67]. An imbalance in testosterone levels was found to be one of the independent risk factors for developing metabolic syndrome (MS) and IR in patients infected with PCOS

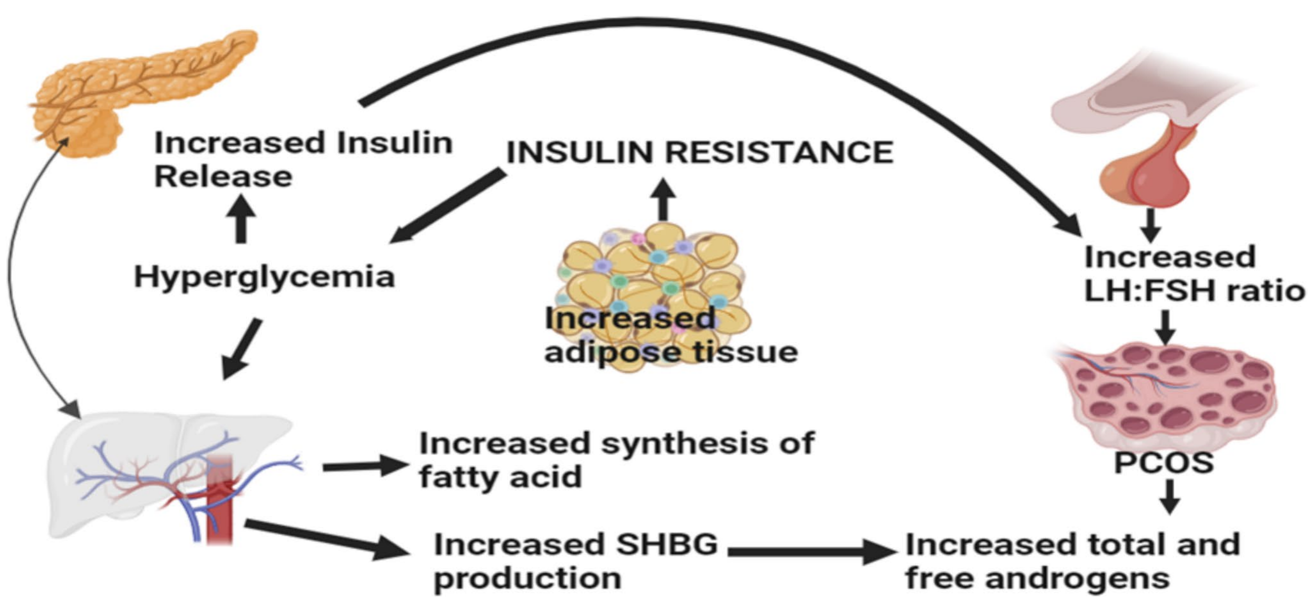


Fig. 2 Insulin resistance and PCOS

as depicted in Fig. 3 [68, 69]. Once BMI has been used as the controls, PCOS women who have MS were still observed to have significantly higher free testosterone than PCOS women without the metabolic syndrome. Close association between IR and androgens have been found in women with gender reassignment. Subsequently, to the cytokine secretion, after four months of intramuscular injection with testosterone esters, a state of insulin resistance was reached [70]. Thereafter, very much like the healthy, premenopausal women, oral methyltestosterone caused insulin resistance on the 10th day (i.e., equivalent to 12 days), which was also measured by a clamp. The arcuate nuclei in hypothalamus is the center of activities that control hunger, digestion and weight balance [71]. Neurons of hypothalamus respond to level of glucose and fatty acids, the same phenomenon is repetitive with insulin, leptin, ghrelin, adiponectin and ovarian steroids [72].

Insulin regulates the satiety and energy balance by interacting with insulin receptors present in Hypothalamus [73]. The altered rhythm of food intake disturbs glucose metabolism, results in a late, blunted, brain response to insulin, that in turn increases eating and body mass and worsens peripheral IR [74]. The neuro-IR development mechanism is complicated and is affected by those mechanisms which are responsible for the peripheral IR pathogenesis [75]. The occurrence of obesity leads to it interference with producing LH (the lower pulsatile amplitude of LH among obese women and animal models, fed with a high fat diet) [76, 77]. Further, IR is also able to produce a local inflammatory response in the hypothalamus as can be seen in an increase in the number of macrophages in the hypothalamus of male rats. Finally, there is downregulation of the brain insulin receptors which are caused by hyperinsulinemia, as a result which makes them insensitive to the insulin signals provoking insulin resistance [78].

Although the molecular explanations involving AKT2, PKC, and GLUT4 signaling provide mechanistic insight, most of this evidence originates from experimental models rather than large-scale human studies [79]. Clinical research primarily demonstrates an association between insulin resistance and hyperandrogenism but does not fully confirm causality [80]. Therefore, while the pathways described are biologically plausible, they should be interpreted as hypothesis-driven mechanisms that still require validation through interventional and tissue-level human studies.

Eating Disorders in PCOS

The PCOS syndrome is associated with eating disorders as well as psychological conditions such as extreme anxiety,

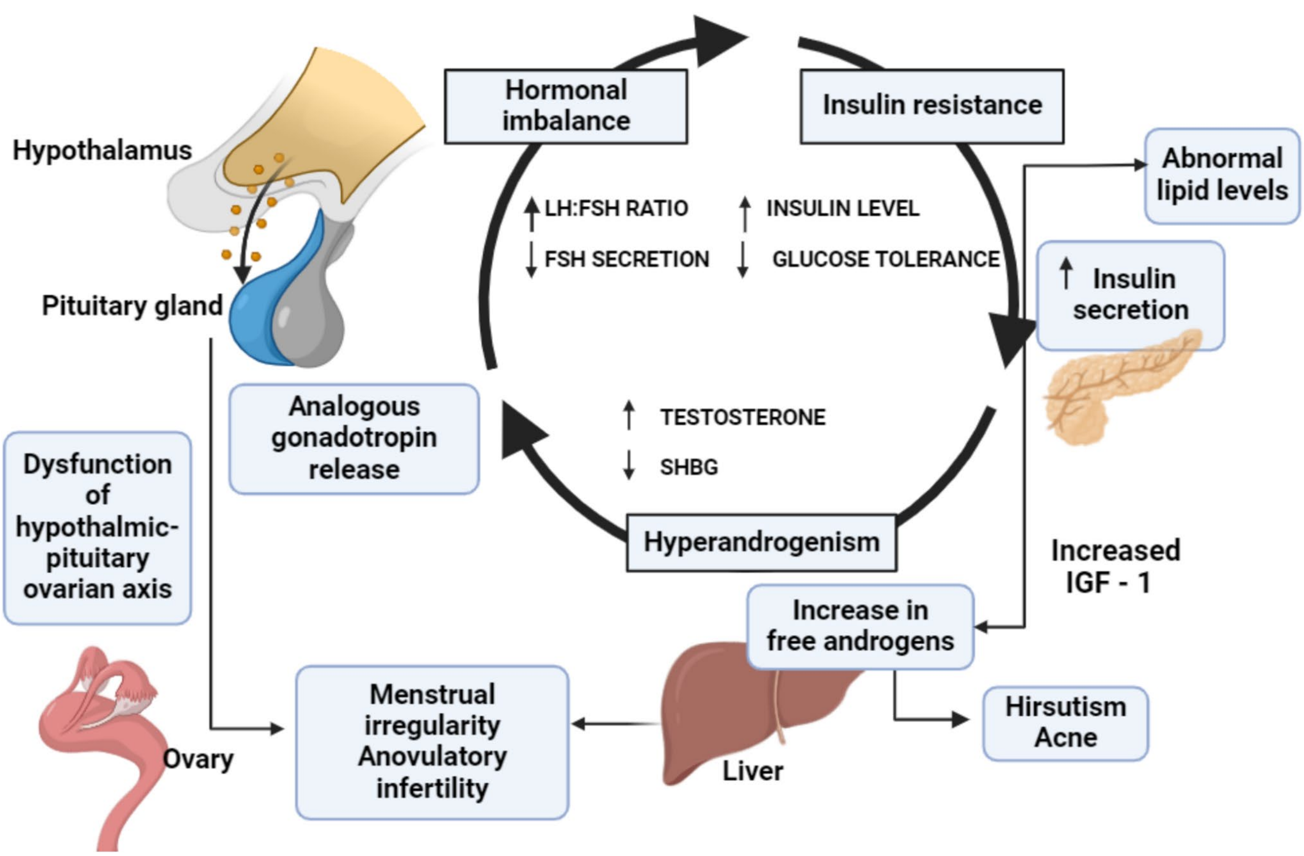


Fig. 3 Relationship between hormonal imbalance, insulin resistance and hyperandrogenism

severe depression, mood swings, food cravings, binge eating, night eating syndrome, anorexia nervosa (AN), bulimia nervosa (BN), and emotional eating [81]. The pathogenesis of eating disorders (ED) among PCOS patients is complicated and multi-faceted (Fig. 4). PCOS patients experience high stress levels or feel often negative about their bodies due to obesity, acne, hirsutism, or irregular menstruation, may have the risk of developing ED [82, 83]. Adding to the condition, the excess of androgen hormone influences ED in terms of increasing the appetite, stages of bulimia such as nervousness and despair [38].

To the contribution of facial hirsutism, a specific feature of the hyperandrogenism, which was examined by the Morgan et al. study [84], 36.3% of women with this symptom had poor social adjustment, rejection, panic and low self-esteem. The hypothalamus inability to carry out its function may be major culprit, with metabolic disturbances, hyperandrogenism and psychosocial factors among the many other reasons. Insulin resistance and resulting increased level of insulin elicit low levels of post prandial glucose which in turn provoke binge eating, more carbohydrate consumption [85]. In the end, mood problems along with anxiety and depression are mainly responsible for being related to obesity and hyperandrogenism [86]. Bulimia and over eating as well as obesity, IR and mood problems are implemented due to brain IR, brain leptin resistance, and the declining in postprandial production of CCK [87, 88].

However, it is important to note that most available data linking PCOS and eating disorders are derived from cross-sectional or self-reported studies, limiting causal interpretation. Very few interventional trials have directly examined whether correcting metabolic abnormalities reduces disordered eating behavior. Hence, the relationship between PCOS and psychological eating patterns appears bidirectional rather than unidirectional, emphasizing the need for longitudinal evidence [89].

Gastrointestinal Hormones

Leptin, a protein that increases energy consumption while suppressing appetite, is repressed also is a feature of PCOS [90]. Body mass index (BMI), HOMA-IR (Homeostatic Model Assessment of Insulin Resistance), and QUICKI (Quantitative Insulin Sensitivity Check Index) are methods to determine level of leptin and insulin sensitivity in insulin resistant individuals [91]. They are leveled up in women with PCOS (whether they are lean or obese patients, barring IR), among which some might have PCOS even without being obese [92]. But while despite increased levels, leptin cannot make people stop eating [56]. Originally, this finding was considered as the reason of reduction in leptin receptors in hypothalamus whereas it is responsible for leptin resistance.

Another hormone that rules appetite by controlling how much food is consumed is known as ghrelin [91]. Ghrelin, a hormone that is mostly involved in regulating satiety, is still being studied although it is generally accepted that this hormone is higher before pregnancy and acts in a way to stimulate the appetite while it falls after pregnancy to inhibit eating [93]. Though there is an ongoing debate on whether women with PCOS have low ghrelin levels as compared to body mass index-matched healthy controls. On the other

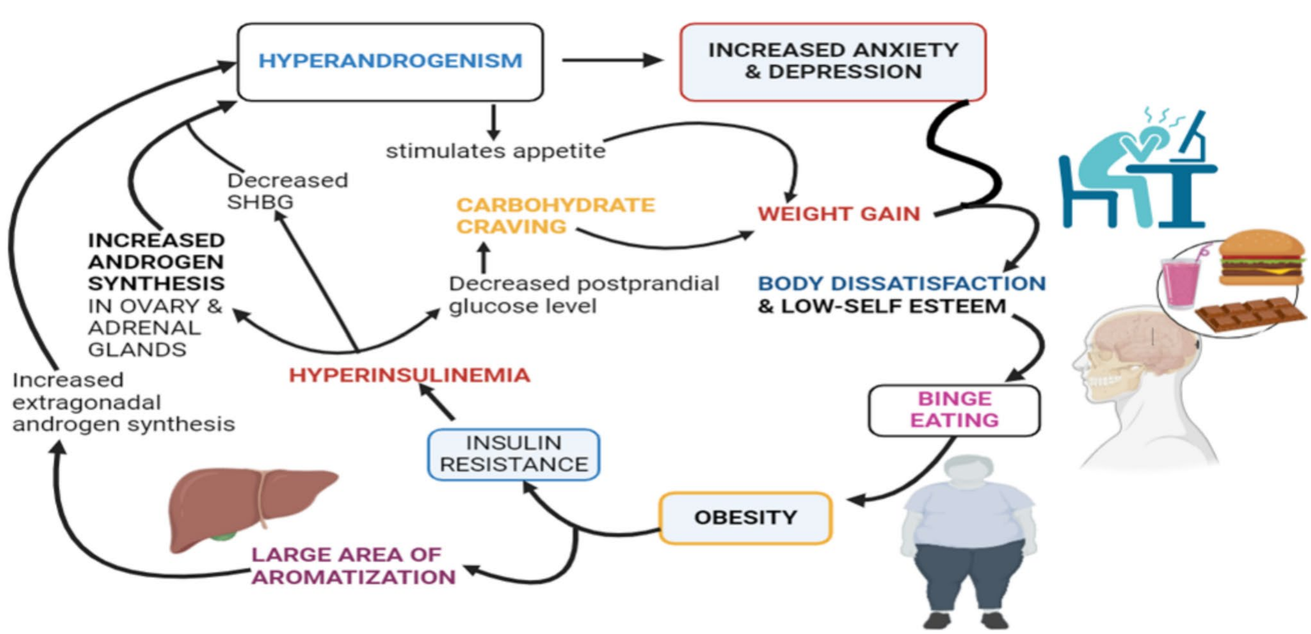


Fig. 4 Binge eating and PCOS

hand, Saydam et al. have also shown that fasting levels as well as postprandial ghrelin suppression are either unaffected or lowered in PCOS patients compared to healthy ones in comparison against healthy controls [64]. This anomaly raises the consumption of excessive food, which is also possible. In parallel, with research on animals, we know that CCK and estradiol (E2) acting together have been reported to induce apetite of the solitary tract by their binding to receptors located within Nucleus Tractus Solitarius [94]. The normal role of CCK which is suppressed after eating is thought to be related to the raised testosterone level in the PCOS patients [95]. The CCK and E2 gained are not only their synergy but also the possibility of inhibiting binge eating by activating the serotonin neurons of the dorsal raphe nuclei and promoting anorexia model in animals [96]. Despite these hormonal associations, findings across studies remain inconsistent. Differences in population characteristics, BMI, and diagnostic definitions of PCOS contribute to variability in leptin and ghrelin results. Furthermore, there is insufficient interventional evidence to establish whether modulating these hormones improves metabolic or reproductive outcomes, indicating that these findings remain largely correlative [97].

Brain Reward System

The main components of the mesolimbic system are the hippocampus, prefrontal cortex, striatum and amygdala respectively, and it is also commonly known as the reward system. It forms the natural pathway to favorable rewards, which are stimuli that a brain sees as value, feelings, events, or activities. These processes occur in both a physical as well as an intellectual way. An activation of this process makes a person modify his or her behavior to get their point over and receive a reaction that is favorable to them [98]. The reward system has dopamine as a key player in the saving of food value, but the reward system also activates other neurotransmitters, including serotonin (5-HT) and endocannabinoids, to be released [99]. A number of studies have shown that stress can result in an inhibition of dopamine release in the blood reward system due to an elevated cortisol by activation of the hypothalamic–pituitary–adrenal (HPA) axis in both acute and chronic stress [100]. While Estrone E3 shows negative influence on dopamine release of serotonin, Estradiol E2 has stimulating effect on the same [72]. Stressors of hypothalamus–pituitary–adrenal interactions are increased ratio of testosterone in the PCOS [101]. In addition to that, the altered dopamine metabolism has been revealed to be associated with brain IR and the consequences, which include behavioral disorders and eat irregularities [102]. Although neuroimaging and neuroendocrine studies suggest altered dopamine and serotonin activity in PCOS, most data arise from small sample sizes and animal models. The direct translation of these findings to human reproductive outcomes remains uncertain [103]. Future studies combining neuroimaging with hormonal profiling are needed to clarify whether reward-system dysregulation is a cause or consequence of PCOS-related behavioral changes.

Hyperandrogenism

The major pathological factor of PCOS is hyperandrogenism, that leads to the development of hyperinsulinemia and IR [104]. The insulin action on ovary stimulates the formation of androstenedione by binding the insulin to the insulin receptors on theca cells. Also, in the ovary, excessive insulin works with the adrenal to produce more androgens [105–107]. Furthermore, the pituitary hormone LH binds to its receptor of CYP17A1 and increases its enzymatic activity, thereby stimulating the production of androgens via intracellular action mediated by hCG and LH [108, 109]. Moreover, insulin promotes higher degrees of free and physiologically active testosterones in the body through the inhibition of Hepatic Synthesis of Sex Hormone-Binding Globulin (SHBG) [110, 111].

The Impact of Gut Microbiota

The link between gut microbiota and PCOS has garnered considerable attention in recent studies. Dysbiosis, an imbalance in gut microbiota, has been identified as a critical factor in the metabolic and hormonal disruptions commonly seen in PCOS [112, 113]. Research has shown that dysbiosis can lead to increased intestinal permeability [114]. This increased permeability allows bacterial components like lipopolysaccharides to cross into the bloodstream, potentially causing systemic inflammation [115]. According to Li et al., this relationship between inflammation and insulin resistance is key to understanding PCOS. They found that inflammation driven by LPS can worsen insulin resistance, which then stimulates ovarian theca cells to produce more androgens, contributing to hyperandrogenism, a common characteristic of PCOS [116]. Song et al. noted that gut microbiota also influences glucose and lipid metabolism. When dysbiosis occurs, it can lead to decreased insulin sensitivity and hyperinsulinemia, resulting in increased androgen production. This hormonal imbalance is disruptive to the normal follicular development and ovulation cycle, which are hallmarks of PCOS [116].

Sun et al. pointed out that dysbiosis can lead to reduced production of short-chain fatty acids (SCFAs), essential for maintaining insulin sensitivity and glucose homeostasis. A decrease in SCFAs can worsen insulin resistance, causing higher insulin levels, leading to reduced sex hormone-binding globulin (SHBG) production. This reduction results in more free testosterone, which further exacerbates hyperandrogenism and disrupts hormonal balance in PCOS [117]. Beyond insulin resistance, dysbiosis can also impact bile acid metabolism, contributing to obesity, which is a known aggravating factor in PCOS [118, 119]. Obesity, in turn, can lead to a cascade of hormonal and metabolic imbalances. Furthermore, Guo et al. indicated that the gut-brain axis, which connects gut microbiota with neurological functions, plays a role in PCOS. Altered neurotransmitter levels due to dysbiosis can affect mood, appetite, and behavior, potentially leading to mood disorders and increased appetite [120]. Mitrea et al. emphasized that addressing gut microbiota could be key to managing the psychological aspects of PCOS. They suggested that treating dysbiosis could yield positive effects on both physical and mental health in PCOS patients [121]. Obesity can further exacerbate insulin resistance and hyperandrogenism, reinforcing the metabolic and hormonal disturbances in PCOS. Moreover, the gut-brain axis, which connects gut microbiota with neurological functions, plays a role in PCOS. Dysbiosis can impact neurotransmitter production, affecting mood, appetite, and behavior. Altered serotonin levels, often linked with gut microbiota imbalances, can contribute to mood disorders and increased appetite, complicating the management of PCOS [115, 122].

While numerous studies report microbial dysbiosis in PCOS, the directionality of this association remains controversial. Some evidence supports a causal role where microbial-derived lipopolysaccharides induce systemic inflammation and insulin resistance; whereas other studies suggest dysbiosis is a downstream effect of obesity and altered metabolism. Clarifying whether microbiota alterations precede or follow hormonal disturbances remains a major gap in current understanding [123].

Key Genetic Factors in PCOS

Genetic factors are key contributors to the development and progression of PCOS [124, 125]. Studies have shown that various genes involved in insulin resistance, steroidogenesis, and inflammation can impact PCOS [46, 59, 126–130]. For example, Khazamipour et al. highlighted the role of the insulin receptor gene (INSR) in insulin resistance, a common characteristic of PCOS. Variants in INSR can lead to reduced insulin sensitivity, causing hyperinsulinemia and stimulating androgen production, leading to hyperandrogenism [131].

Similarly, Shaaban et al. noted that mutations in the IRS1 gene, which encodes insulin receptor substrate 1, can exacerbate insulin resistance. This can lead to a cascade of effects, including impaired glucose metabolism and elevated androgen levels, further complicating the PCOS condition [132]. Unluturk et al. discussed the implications of mutations in genes related to steroidogenesis, such as CYP17A1 and CYP11A1. These genes can result in increased androgen production, contributing to PCOS symptoms like hirsutism and acne. Furthermore, variations in the LHCGR gene, which encodes the luteinizing hormone receptor, can disrupt ovulation, leading to the formation of polycystic ovaries [133]. Inflammation-related genes also play a significant role in PCOS. Thomas et al. and other researchers have found that genetic variations in TNF-α and IL-6 can increase systemic inflammation. This increase in inflammation can worsen insulin resistance, leading to additional metabolic complications and further complicating PCOS [53, 134].

Lifestyle and Environmental Factors

A diet rich in refined carbohydrates and sugars has been linked to insulin resistance, a key characteristic of PCOS [135, 136]. High blood glucose levels from such diets prompt the pancreas to secrete more insulin, triggering a series of biochemical events involving phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt). These pathways aim to promote glucose uptake by muscle cells, but when insulin resistance develops, this process becomes inefficient, leading to hyperinsulinemia [137, 138]. This high insulin level can stimulate ovarian theca cells to produce more androgens, exacerbating hyperandrogenism, a defining feature of PCOS [139]. Physical inactivity is another significant factor [140]. Prolonged sedentary behavior contributes to decreased insulin sensitivity and increased adiposity, leading to elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These cytokines can interfere with insulin signaling pathways, further worsening insulin resistance and contributing to the hormonal imbalance seen in PCOS [141].

Endocrine-disrupting chemicals (EDCs), such as bisphenol A (BPA), can mimic estrogen and bind to estrogen receptors, leading to disruption in hormonal signaling. This can affect the hypothalamic-pituitary-ovarian axis, impacting gonadotropin-releasing hormone (GnRH) and downstream effects on luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Disrupted hormonal signaling can lead to irregular ovulation and contribute to ovarian cyst formation [136]. Stress is another factor impacting PCOS. Chronic stress can activate the hypothalamic–pituitary–adrenal (HPA) axis, leading to increased cortisol production. High cortisol levels contribute to insulin resistance, potentially worsening PCOS symptoms. Elevated cortisol can also affect ovarian function by influencing androgen production and ovulation. Various other factors involved in promoting the PCOS in females are shown in Fig. 5.

Evidence Quality and Knowledge Gaps

Across mechanistic domains, the strength of evidence in PCOS research varies considerably. Insulin resistance and hyperandrogenism are robustly supported by clinical and biochemical data, while links involving gut microbiota, gastrointestinal hormones, and neural reward pathways remain largely correlational [142]. Many foundational studies rely on small samples, non-standardized diagnostic criteria, or animal models, making causal inference challenging [143].

Future research must integrate multi-omic profiling, longitudinal designs, and interventional trials to validate proposed mechanisms. Establishing whether emerging biological pathways such as gut, brain signalling or psychological stress modulation translate into measurable reproductive and metabolic improvements will be critical for refining precision treatment strategies [144].

Medical Interventions

GLP-1 Receptor Agonists

GLP-1 receptor agonists (GLP-1RAs) are gaining recognition for their effectiveness in managing Polycystic Ovary Syndrome (PCOS), offering significant benefits in reducing body weight, improving metabolic health, and addressing insulin resistance. These medications work by mimicking the action of glucagon-like peptide-1, a hormone that stimulates insulin secretion, reduces glucagon production, and helps regulate appetite. A Study by Siamashvili et al. have shown that GLP-1RAs, such as exenatide and liraglutide, can reduce body mass index (BMI), waist circumference, and insulin resistance in women with PCOS [145]. This effect on body weight is particularly beneficial for PCOS patients, who often struggle with obesity and associated metabolic complications. The findings from Jensterle et al. suggest that GLP-1RAs are more effective than metformin in reducing these parameters, highlighting their therapeutic potential for PCOS management [41].

Zhang et al. have reported that GLP-1RAs can reduce local (ovarian) and systemic inflammation in PCOS mice, which may contribute to improved insulin sensitivity and

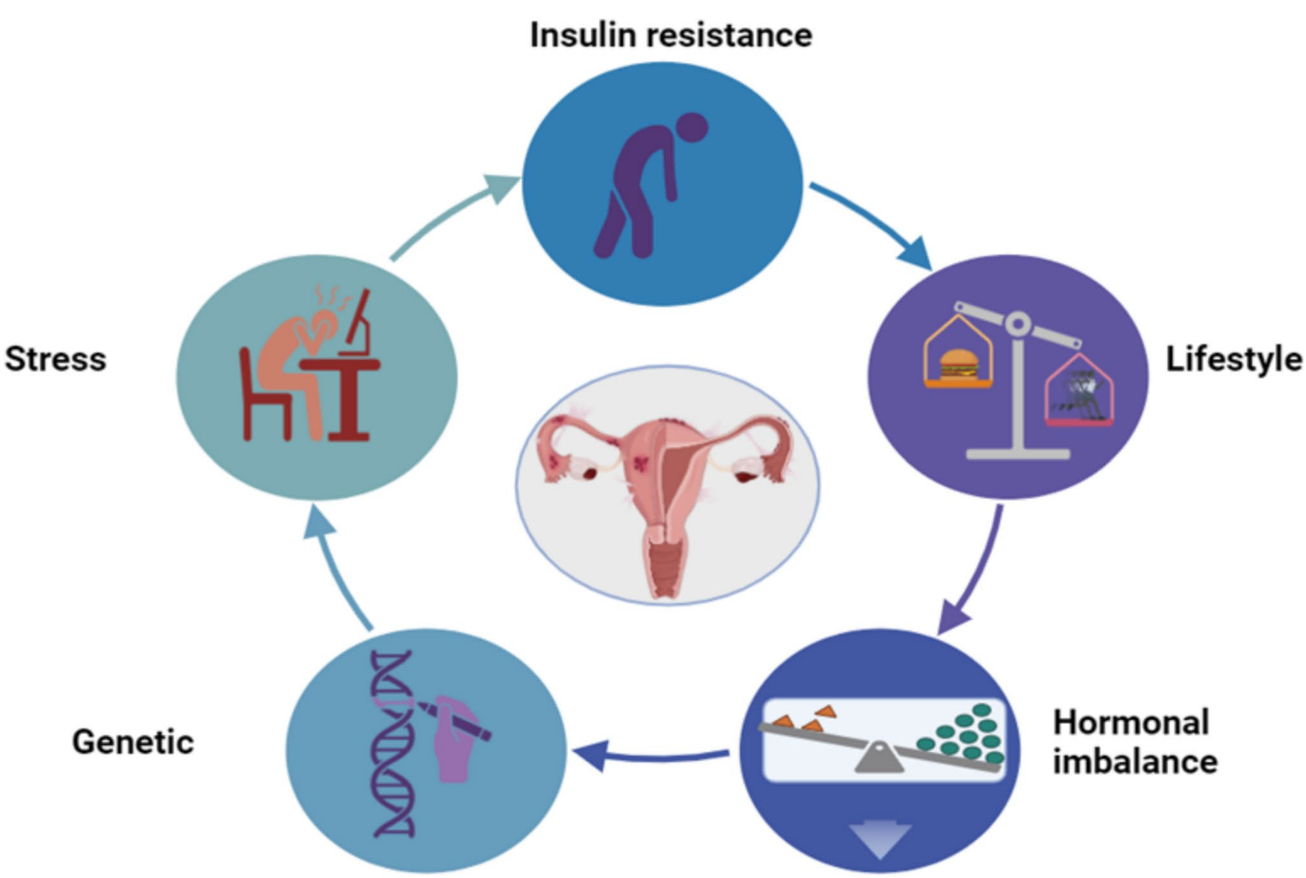


Fig. 5 Multiple factors promoting PCOS

reduced androgen levels [96]. This reduction in inflammation can lead to improved reproductive health, including enhanced menstrual cyclicity and potentially increased pregnancy rates in women with PCOS. GLP-1RAs may also play a role in reducing cardiovascular risk factors in PCOS. Papaetis et al. noted that these medications can improve cholesterol levels and blood pressure, which is crucial for long-term cardiovascular health [146]. Additionally, by impacting body fat distribution, GLP-1RAs offer a multifaceted approach to managing PCOS symptoms, ultimately improving quality of life for those affected by the condition. While GLP-1RAs show promising metabolic and reproductive benefits, their reproductive safety profile remains underexplored. Data on pregnancy exposure are limited, and most regulatory agencies currently advise discontinuation prior to conception. Long-term studies assessing ovulation outcomes, live birth rates, and fetal safety are required before routine use in women seeking fertility [147].

Insulin Sensitizers

Metformin is widely recognized as a key insulin sensitizer for managing Polycystic Ovary Syndrome (PCOS). Its mechanism of action revolves around the activation of AMP-activated protein kinase (AMPK), a crucial regulator of cellular energy balance. When AMPK is activated, it leads to a cascade of downstream effects that improve cellular insulin sensitivity. For instance, it stimulates the translocation of glucose transporter 4 (GLUT4) to the cell membrane, increasing glucose uptake into muscle and adipose tissue. Additionally, AMPK reduces hepatic gluconeogenesis by phosphorylating key transcription factors, such as CREB-regulated transcription coactivator 2 (CRTC2), thus inhibiting the expression of gluconeogenic enzymes like glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (PEPCK) [148]. Dumitrescu et al. highlighted that metformin's benefits extend beyond insulin sensitivity; it also reduces serum lipid and androgen levels, aiding in the management of hyperandrogenic symptoms like hirsutism and acne. This multi-faceted impact underscores metformin's role in improving various biochemical pathways, leading to better overall management of PCOS [149].

Thiazolidinediones (TZDs), such as pioglitazone, are another class of insulin-sensitizing agents used in PCOS. As Kim et al. indicated, TZDs activate peroxisome proliferator-activated receptor gamma (PPARγ), which is crucial in regulating glucose metabolism and fatty acid storage. Upon activation, PPARγ induces genes responsible for adipogenesis and fatty acid storage, enhancing insulin sensitivity in peripheral tissues. TZDs also redistribute fat from visceral to subcutaneous adipose tissue, reducing inflammation and improving metabolic profiles in women with PCOS [150]. Recent studies have further shown that insulin-sensitizing agents, including metformin and TZDs, have significant therapeutic potential in treating PCOS and its associated complications. These findings suggest that these agents not only address insulin resistance but also reduce androgen levels and improve metabolic profiles, offering a comprehensive approach to managing PCOS [151]. Although metformin is widely used and generally regarded as safe during ovulation induction and early pregnancy, its long-term reproductive effects are still debated. Pioglitazone and other thiazolidinediones, on the other hand, are not recommended in women attempting conception due to limited human safety data [152]. Clinicians should therefore individualize therapy, balancing metabolic benefits against reproductive goals and pregnancy risk.

Statins

Statins are being explored for their effects on Polycystic Ovary Syndrome (PCOS) due to their role in cholesterol regulation and potential impact on hyperandrogenism. According to Cassidy-Vu et al., statins work by inhibiting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, leading to a reduction in cholesterol production, which can indirectly lower androgen synthesis. This decrease in androgen levels might help manage hyperandrogenic symptoms commonly associated with PCOS, such as hirsutism, acne, and menstrual irregularities [153]. Sathyapalan et al. discussed the effects of statins on PCOS in a review, highlighting the underlying mechanism by which statins might reduce androgen production. Their study suggested that the reduction in cholesterol synthesis by statins could lead to lower androgen levels, potentially offering therapeutic benefits for hyperandrogenism in women with PCOS [154].

Chen et al. conducted a systematic review showing that statins can decrease androgen levels in PCOS patients, with atorvastatin being particularly effective in lowering serum testosterone. This evidence suggests that statins could be a useful therapy for managing PCOS-related hyperandrogenism [154]. Statins' anti-inflammatory properties might also offer a means of reducing the low-grade inflammation commonly seen in PCOS (Fig. 6). Akre et al. demonstrated that statins could reduce inflammation markers and improve insulin sensitivity, contributing to improved metabolic health in women with PCOS [155]. Statins may reduce hyperandrogenism and improve metabolic parameters, yet their use in reproductive-age women is constrained by teratogenic potential. Current guidelines contraindicate statins during pregnancy, and treatment should be stopped at least one to three months before conception attempts. Evidence for improvement in ovulatory or fertility outcomes remains

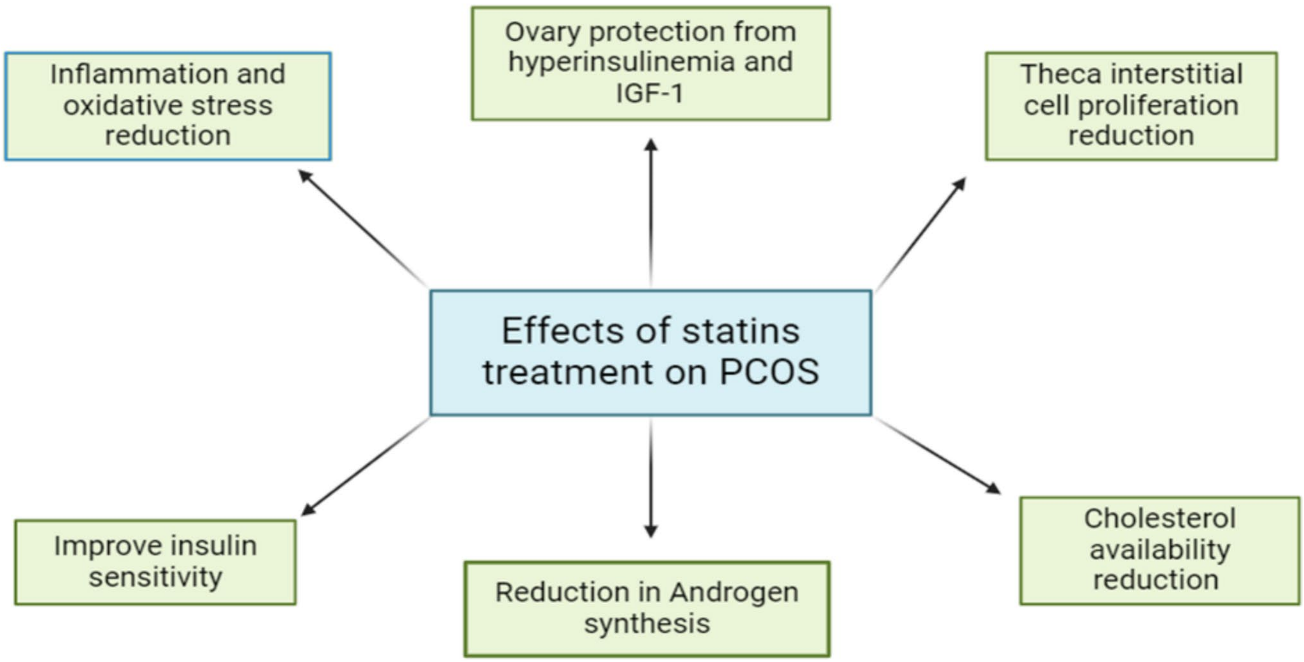


Fig. 6 Effect of statins treatment on PCOS

inconclusive, emphasizing the need for controlled reproductive studies [156].

Bupropion/Naltrexone and Behavioral Therapy

The combination of bupropion, a norepinephrine-dopamine reuptake inhibitor, and naltrexone, an opioid receptor antagonist, has emerged as a promising treatment for binge eating and food cravings, especially in women with Polycystic Ovary Syndrome (PCOS). A study by Grilo et al. explored the effectiveness of this combination in a randomized double-blind trial, revealing significant improvements in reducing binge eating disorder (BED) episodes when the combination therapy was used in conjunction with behavior therapy [157].

The therapeutic rationale behind this combination involves targeting the hypothalamic reward pathway, which is often implicated in binge eating behaviors. Bupropion's action on norepinephrine and dopamine pathways, coupled with naltrexone's modulation of opioid receptors, creates a synergistic effect that has shown greater benefits in reducing binge eating and cravings compared to using either drug alone [158]. Burnatowska et al. also reported that this combination therapy could positively affect other aspects of PCOS-related eating disorders, like emotional eating. The research indicated that when bupropion-naltrexone is combined with behavioral therapy, it can significantly reduce the frequency of binge eating and emotional eating episodes [1]. The bupropion–naltrexone combination has shown benefit in weight management and appetite control among women with PCOS; however, reproductive data are scarce. Both agents are classified as pregnancy category C, with potential fetal risks at high doses. These drugs should be avoided in women pursuing pregnancy, and behavioral or nutritional interventions remain the safer first-line approach for fertility optimization [159].

Herbal and Natural Interventions

Recent studies suggest that herbal and natural interventions play an increasingly significant role in managing Polycystic Ovary Syndrome (PCOS). In particular, myo-inositol, a naturally occurring compound, has drawn attention to its role in insulin signaling and its potential to improve ovarian function while reducing insulin resistance. Smith et al. demonstrated that myo-inositol can activate the phosphatidylinositol 3-kinase (PI3K) pathway, leading to increased insulin sensitivity through enhanced glucose uptake [160]. This process ultimately contributes to better ovarian function and reduced insulin resistance in women with PCOS.

Similarly, in a study conducted by Jones and colleagues, myo-inositol supplementation was found to improve ovulatory function and restore regular menstrual cycles in women with PCOS [161]. This observation supports the hypothesis that natural interventions can positively impact the hormonal imbalances and metabolic disturbances characteristic of PCOS. These results indicate a promising direction for non-pharmaceutical interventions in PCOS management, providing a more holistic approach that may complement traditional pharmacological treatments. Evidence for herbal and nutraceutical therapies remains preliminary. Most studies use small samples, variable formulations, and non-standardized dosages, limiting clinical translation. Myo-inositol and D-chiro-inositol appear most supported, but even these require consistent dose standardization and pregnancy-safety evaluation [162]. Future research should adopt randomized, placebo-controlled designs with defined endpoints such as ovulation rate, oocyte quality, and live birth outcome.

Addressing Misconceptions

Common misconceptions about PCOS treatment must be addressed, such as the belief that treating obesity will resolve all PCOS symptoms or that weight loss will always lead to improved insulin sensitivity. It's crucial to understand that PCOS involves complex biochemical pathways, and comprehensive treatment approaches are required to address hormonal imbalances and insulin resistance. Metformin, for example, does not inherently cause weight loss; instead, it enhances insulin sensitivity through specific biochemical pathways.

Reproductive Implications of Therapeutic Strategies

Given that PCOS is a leading cause of anovulatory infertility, evaluating therapeutic success should include reproductive endpoints rather than metabolic outcomes alone [163]. Insulin sensitizers such as metformin have shown moderate improvements in ovulation and menstrual cyclicity, yet benefits on live birth rates remain variable [164]. Emerging agents like GLP-1RAs demonstrate potential to restore ovulatory function through weight reduction and hormonal balance, but reproductive safety data are insufficient for routine fertility use [41].

Future research should systematically examine how each pharmacologic or nutritional approach influences folliculogenesis, oocyte competence, and endometrial receptivity. Trials that include assisted reproductive technology (ART) outcomes will be crucial to determine the translational relevance of metabolic improvements to actual fertility success [165].

Recent Advancements in PCOS

The recent advancements along with their primary outcomes have been described in Table 2

Future Perspective

Polycystic Ovary Syndrome (PCOS) represents a complex endocrine disorder affecting millions of women worldwide, characterized by hormonal imbalance, irregular menstruation, and often, infertility. Over the years, advancements in research and clinical practice have significantly improved the management of PCOS. However, the quest for more effective and personalized treatment options continues to evolve, promising a brighter future for those affected by this multifaceted condition. The future of PCOS treatment lies in personalized, precision medicine approaches. By leveraging genetic, molecular, and phenotypic data, clinicians can tailor therapies to individual patients, optimizing outcomes and minimizing side effects. Advances in genomic profiling and biomarker identification hold promise for identifying subtypes of PCOS, allowing for targeted interventions based on specific pathophysiological mechanisms.

Precision medicine holds immense potential in tailoring therapies to individual phenotypes, optimizing efficacy while minimizing side effects. Furthermore, the integration of novel pharmacological agents targeting insulin resistance, androgen excess, and ovulatory dysfunction offers hope for more targeted and efficacious treatments. Lifestyle interventions, including personalized nutrition plans and behavioral modifications, continue to play a pivotal role, augmented by technological innovations such as mobile health apps and wearable devices. Moreover, emerging non-invasive fertility preservation techniques and multidisciplinary care models underscore a holistic approach to managing PCOS and improving patient outcomes. In the ever-evolving landscape of PCOS research, delving into the intricate interplay between genetic predispositions, environmental triggers, and hormonal imbalances emerges as a paramount focus. By unraveling these complex interactions, tailored treatment modalities can be tailored, offering newfound hope for individuals grappling with PCOS. Furthermore, shedding light on epigenetic mechanisms holds immense promise in uncovering novel therapeutic avenues. This exploration into the molecular underpinnings of PCOS pathogenesis could unveil transformative interventions, addressing the root causes of this enigmatic condition. As we navigate the complexities of PCOS, embracing these future perspectives promises to transform the landscape of care, offering personalized, effective, and patient-centered treatments for individuals affected by this syndrome."

Table 2 Recent Studies on PCOS and their primary outcomes

Recent studies	Primary outcome	Reference
Treatment of lean PCOS teenagers: a follow-up comparison between Myo-Inositol and oral contraceptives	Because Myo-Ins treatment can improve weight, BMI, and metabolic parameters, it is advised for younger adolescents with PCOS. This may delay the need for pharmacological medication during adolescence	[166]
Short-term effects of metformin and myoinositol in women with polycystic ovarian syndrome (PCOS): a meta-analysis of randomized clinical trials	The meta-analysis's findings show that MET and MI had similar effects on PCOS patients' temporary fluctuations in hormone levels PCOS women find MI more acceptable for the restoration of their androgen and metabolic profile since it is more tolerable	[167]
Melatonin treatment may be able to restore menstrual cyclicity in women with PCOS: a pilot study	In PCOS-afflicted women, melatonin treatment increased follicle-stimulating hormone levels, reduced androgen, and markedly lowered anti-Mullerian hormone serum levels. Menstrual cycle improvement was observed in over 95% of cases, suggesting that melatonin may be a useful treatment in the future for PCOS-affected women. This is the first study to examine how clinical, endocrine, and metabolic features are affected by exogenous oral melatonin treatment	[168]
Use of metformin to treat pregnant women with polycystic ovary syndrome (PregMet2): a randomized, double-blind, placebo-controlled trial	In a 487-person study, 10% of women treated with a placebo and 55% of women treated with metformin had premature deliveries and late miscarriages. Metformin or a placebo was administered to the individuals at random. There were no notable variations observed in secondary outcomes, like the occurrence of gestational diabetes. Compared to 10% of women receiving a placebo, 55% of metformin-treated women had late miscarriages or premature deliveries in a post-hoc pooled study	[169]
Evidence summaries and recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome: assessment and treatment of infertility	There are new suggestions for pharmacological treatment, such as letrozole, gonadotrophins, anti-obesity drugs, and bariatric surgery, in the international guidelines for ovulation induction for women with PCOS. IVF is a third-line therapy that may be suggested if first or second-line treatments don't work. Metformin medication in addition to controlled ovarian hyperstimulation can increase the likelihood of pregnancy and lower the risk of OHSS	[170]
Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome	Physicians can follow 166 guidelines found in the International Guideline for the Assessment and Management of Polycystic Ovary Syndrome (PCOS). It highlights how crucial lifestyle changes, education, empowerment, and interdisciplinary treatment are to managing weight. The recommendation is that adults and adolescents with insulin resistance use the Rotterdam PCOS Diagnostic Criteria, even if it is not yet clinically indicated	[171]
Metformin versus myoinositol: which is better in obese PCOS patients? A randomized controlled crossover study	The research validates the advantageous outcomes of extended metformin therapy on the clinical, biochemical, and metabolic traits of PCOS. It does, however, draw attention to the 21% prevalence of side effects and recommends treating metabolic disorders with a combination of myoinositol and metformin at lower dosages. Additionally, the study indicates that in overweight/obese hyperinsulinemia PCOS individuals, metformin is superior to myoinositol. More randomized clinical trials are needed to compare the two compounds in a bigger population	[172]
The efficacy of 24-month metformin for improving menses, hormones, and metabolic profiles in polycystic ovary syndrome	The study shows that women with PCOS with varying BMI/testosterone phenotypes respond differently to metformin treatment. The percentage of normal menses at M6 was similar for all four BMI/testosterone categories, although at baseline, the NW-ET subgroup had a lower percentage of normal menses. The NW-ET segment showed the most significant improvement, whereas the OW-NT grouping had the longest recovery period and the highest rate of regular menses after therapy. Using GEE models, assessing the longitudinal design, and classifying patients according to their testosterone and BMI phenotypes are some of the study's strong points	[173]
Women with polycystic ovary syndrome (PCOS) have reduced melatonin concentrations in their follicles and have mild sleep disturbances	To investigate the relationship between melatonin and follicular growth in PCOS, we evaluated the melatonin concentrations in a sample of women with and without the disease. We observed milder sleep problems and decreased melatonin concentrations in large leading follicles in PCOS individuals. Due to the intricate relationship between melatonin and ovarian function regulation, extensive basic research on clinical and pathophysiological pathways is required	[174]
Metabolic and hormonal effects of melatonin and/or magnesium supplementation in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial	Total, our study demonstrated that giving PCOS women co-supplements of melatonin and magnesium for eight weeks increased their total testosterone levels and quality of sleep. Moreover, it was found that the PSQI score significantly decreased when melatonin was administered on its own. Moreover, supplementing with melatonin and magnesium together was more successful in raising insulin, HOMA-IR, LDL-C, HDL-C, and serum cholesterol levels, among other metabolic indicators To obtain more results, longer-term, large-scale research is required	[175]

Table 2 (continued)

Recent studies	Primary outcome	Reference
Effects of melatonin administration on mental health parameters, metabolic and genetic profiles in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial	Melatonin supplementation for 12 weeks improved the mental health status, insulin levels, HOMA-IR, QUICKI, and the expression of the PPARγ and LDLR genes among PCOS women who were candidates for IVF; however, it had no effect on other metabolic profiles or the expression of the GLUT-1 gene This implies that women with PCOS may benefit therapeutically from melatonin administration. For longer periods of time and with additional subjects, more research is required to ascertain the advantages of melatonin administration	[176]
Intrauterine metformin exposure and offspring cardiometabolic risk factors (PedMet study): a 5–10 year follow-up of the PregMet randomised controlled trial	The purpose of this study was to ascertain how offspring anthropometrics are affected by polycystic ovarian syndrome (PCOS). The primary outcome was the BMI Z score, which predicts cardiometabolic risk factors. The following were regarded as secondary variables: body fat, muscular mass, head circumference, weight, waist-to-height ratio, and other traits. The study used BMI cutoffs and metabolic syndrome criteria for children and adolescents from the International Obesity Task Force. The impact of polycystic ovarian syndrome on children's anthropometrics was also evaluated in this study	[177]
Prevalence and symptomatology of polycystic ovarian syndrome in Indian women: is there a rising incidence?	Young Indian women are experiencing PCOS at a higher rate than previously. Serious difficulties may arise as the adolescent ages if Polycystic Ovarian Syndrome and consequently Insulin Resistance are not detected. Globally, PCOS and its related problems are increasing the cost of healthcare. In order to save these young women before PCOS worsens into a full-blown metabolic syndrome, it is imperative that we identify them and treat their hormonal and metabolic disorders as soon as possible. To prove a real rising trend, perhaps more extensive research in other locations is required	[178]
Perceptions and experiences of lifestyle interventions in women with polycystic ovary syndrome (PCOS), as a management strategy for symptoms of PCOS	Clinical practice guidelines state that women with PCOS who live in the community report regularly following a range of dietary and physical activity regimens and feeling that their health objectives are only partially met. Exercise and nutrition plans may seem ineffective to oneself, but this could be because there is a lack of solid evidence to support their efficacy. Pragmatic RCTs that evaluate lifestyle interventions on outcomes important to PCOS-affected women using community-based samples may enhance the quality of the evidence	[179]
Barriers and facilitators to weight management in overweight and obese women living in Australia with PCOS: a qualitative study	Women with PCOS struggle to control their weight because of a lack of professional help, as well as societal, environmental, and emotional barriers Long-term efforts are also hampered by low self-esteem and a preponderance of negative ideas. Future studies should examine the psychological and emotional toll that PCOS takes, as well as create a lifestyle solution that targets the psychosocial side of the disease	[180]
Challenges in diagnosis and health care in polycystic ovary syndrome in Canada: a patient view to improve health care	For those with polycystic ovarian syndrome (PCOS), there is a deficiency in prompt diagnosis, resources, symptom management choices, and multidisciplinary care in Canada, especially in Alberta. Patient involvement in healthcare and research, education, specialist referrals, and patient education are some examples of patient-focused insights and improvement recommendations. Improving the quality of healthcare requires the establishment of specialized clinics and increased public awareness of PCOS	[181]
What can be done to improve polycystic ovary syndrome (PCOS) healthcare? Insights from semi-structured interviews with women in Canada	In order to diagnose and treat PCOS in a timely manner, the study highlights how important it is to comprehend its biopsychosocial components, diagnosis, and management. To lessen loneliness, it suggests giving women access to support groups, evidence-based information, and referrals. Women also recommend that the medical community prioritize and pay more attention to women's health	[182]
"I felt like she didn't take me seriously": a multi-methods study examining patient satisfaction and experiences with polycystic ovary syndrome (PCOS) in Canada	Improving patient experiences can be accomplished by raising PCOS awareness, supporting diagnosis guidelines, and offering reliable medical information. Women with PCOS face many obstacles while seeking a diagnosis. Women can navigate their path with the assistance of skilled and attentive physicians, but patients should also trust their doctors to act as their champions for healthcare	[183]
The challenges with managing polycystic ovary syndrome: A qualitative study of women's and clinicians' experiences	The study emphasizes the difficulties in treating PCOS, such as the scarcity of information, the absence of effective treatments, and the differences in expectations between women and doctors. It recommends employing many diagnostic categories, addressing women's expectations for patient-centered care, and providing customized risk counseling in addition to better communication	[184]

Table 2 (continued)

Recent studies	Primary outcome	Reference
Women's experiences of diagnosis and management of polycystic ovary syndrome: a mixed-methods study in general practice	The study investigates women's encounters with PCOS diagnosis, care, and treatment in the United Kingdom. It was discovered that while the lady or a family member frequently made the diagnosis, GPs or specialists made the most of the diagnoses. Women believed that medical professionals trivialized their situation and frequently disregarded weight reduction. They thought that further data and investigation were required. While some women felt that PCOS received too much attention as a "reproductive health" problem, fertility remained crucial. Women's conversations with general practitioners on mental health and fertility were similarly influenced by their ethnicity	[185]
'I'm usually being my own doctor': women's experiences of managing polycystic ovary syndrome in Canada	The study's lived experiences indicate that Canada's support system for PCOS-affected women needs to be improved. The medical community might need to learn more about PCOS. In Canada, medical professionals are urged to educate patients about PCOS and its biopsychosocial ramifications by providing a wealth of information (such as brochures and reputable websites). In order to help patients achieve their health objectives, patients require guidance in managing their lifestyle, which includes making referrals to allied health providers	[186]

Conclusion

Polycystic Ovarian Syndrome (PCOS) represents a multifactorial disorder that bridges endocrine, metabolic, and psychological domains, demanding an integrated clinical approach. The coexistence of insulin resistance, hyperandrogenism, and emotional dysregulation underscores the need for multidisciplinary management that combines metabolic control with reproductive and mental health optimization. Clinically, interventions should move beyond weight reduction alone to include targeted therapies such as GLP-1 receptor agonists, insulin sensitizers, and individualized behavioral strategies that address both metabolic and psychological contributors to anovulation and infertility. Clinical management should equally prioritize metabolic control and reproductive success, emphasizing individualized treatment strategies that are safe for conception and pregnancy.

From a reproductive standpoint, future studies must clarify how metabolic and inflammatory pathways impair folliculogenesis, oocyte quality, and endometrial receptivity, and how emerging therapies influence these outcomes. Long-term, multicenter randomized trials are needed to evaluate the safety of novel pharmacologic agents on fertility, pregnancy, and offspring health. Advancing PCOS management will require personalized medicine approaches that integrate genetic, microbiome, and neuroendocrine insights to guide evidence-based, fertility-centered care. By bridging molecular mechanisms with clinical translation, future research can redefine therapeutic strategies and improve both reproductive success and quality of life in women with PCOS.

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Data Availability All the data are contained in the manuscript.

Declarations

Ethics Approval N.A.

IRB Approval N.A.

Conflict of interest The authors declare no competing financial interest.

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