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Physiopathology of polycystic ovary syndrome in endocrinology, metabolism and inflammation

Pingping Su[1,2], Chao Chen[3] and Yun Sun[2*]

Abstract

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder characterized by elevated androgen levels, ovarian cysts, and impaired ovulation in females. This condition is closely linked with various reproductive health issues and has significant impacts on endocrine and metabolic pathways. Patients with PCOS commonly exhibit hyperandrogenaemia and insulin resistance, leading to complications such as acne, hirsutism, weight fluctuations, and metabolic disturbances, as well as an increased risk for type 2 diabetes, cardiovascular disease, and endometrial cancer. Although extensive research has identified several mechanistic aspects of PCOS, a thorough understanding of its pathophysiology remains incomplete. This review aims to provide a detailed analysis of the physiological and pathological aspects of PCOS, covering endocrine, metabolic, and inflammatory dimensions, to better elucidate its etiological framework.

Keywords Polycystic ovary syndrome, Endocrinology, Metabolism, Inflammation, Physiopathology

Introduction

PCOS is a prevalent reproductive endocrine disorder characterized by distinctive polycystic ovarian morphological changes, including the accumulation of numerous immature follicles. It affects a significant proportion of women of reproductive age globally, with an incidence ranging from 10 to 13% [1]. This pathological condition disrupts the regularity of the menstrual cycle, commonly presenting as oligomenorrhea or secondary amenorrhea. In severe cases, PCOS can lead to infertility and miscarriage, significantly impacting reproductive function [2]. Since its initial description by Stein and Leventhal in 1935, PCOS has also been known as Stein–Leventhal syndrome [3].

The pathophysiology of PCOS is multifactorial and involves impaired gonadotropin-releasing hormone (GnRH) pulsatility, increased pituitary luteinizing hormone (LH) secretion [4], elevated androgen levels, insulin resistance, obesity [5], and chronic low-grade inflammation [6]. Hyperandrogenism is a key diagnostic feature characterized by elevated androgenic hormones, leading to clinical manifestations such as acne, hirsutism, and alopecia [7]. Additionally, insulin resistance, which reduces the cellular responsiveness to insulin and impairs glucose uptake and metabolism, is prevalent among PCOS patients. This can lead to obesity and is closely linked with the development of type 2 diabetes [8]. In addition to reproductive system abnormalities, PCOS is associated with various nonreproductive health issues,

*Correspondence:
Yun Sun
sunyun7304@outlook.com
[1]Wenzhou Graduate Joint Training Base, Zhejiang Chinese Medical University, Hangzhou, China
[2]Department of Gynecology, Wenzhou TCM Hospital of Zhejiang Chinese Medical University, Wenzhou, China
[3]Department of Traditional Chinese Medicine, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China

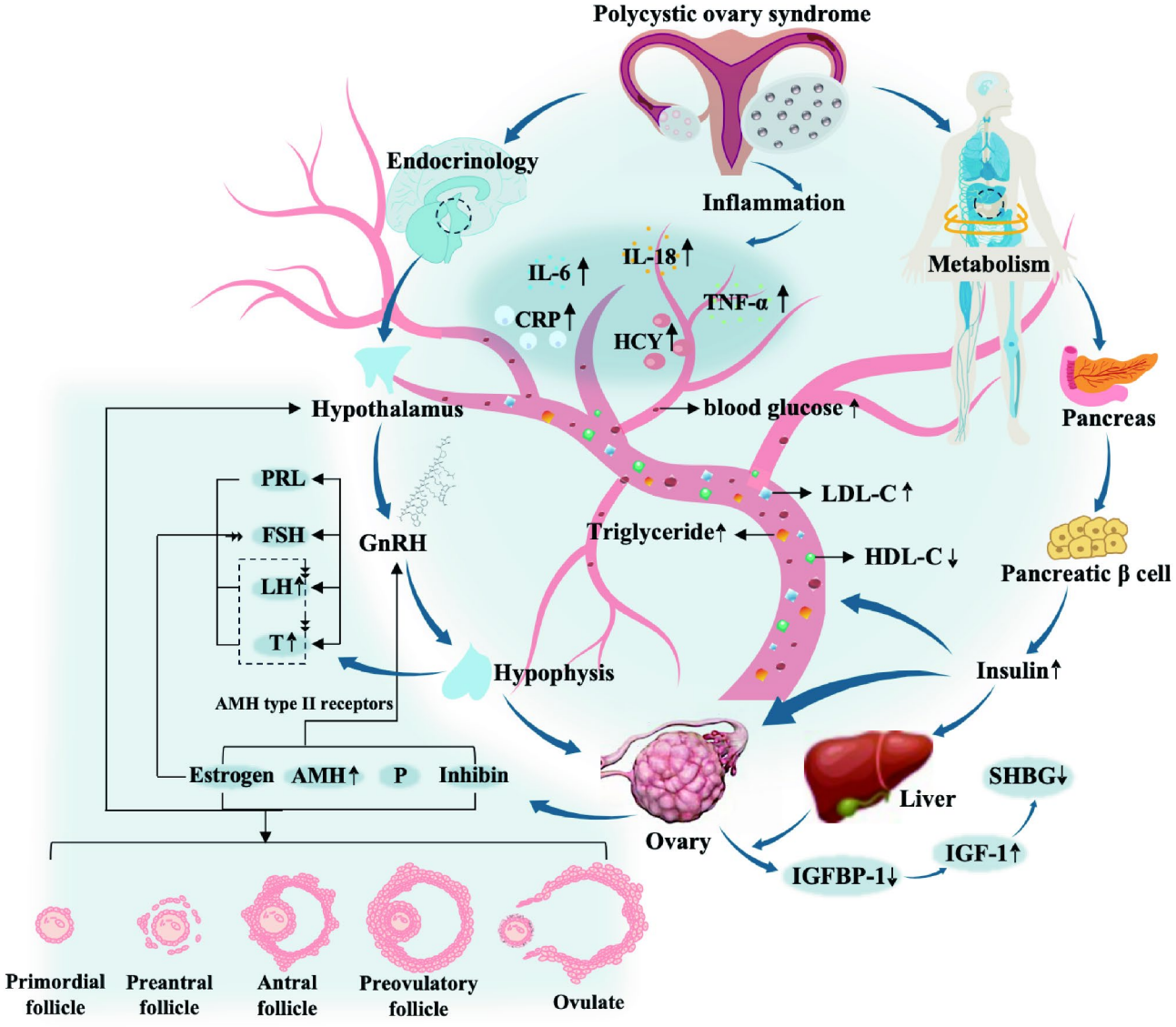

Fig. 1 Polycystic ovary syndrome in endocrinology, metabolism and inflammation

including cardiovascular diseases [9] and type 2 diabetes [10].

Despite substantial research elucidating several critical pathways involved in the pathogenesis of PCOS, a comprehensive understanding of its pathophysiology remains incomplete. This review aims to synthesize and integrate both fundamental and clinical research findings regarding the physiological and pathological mechanisms underlying PCOS. By identifying key factors, we examined endocrine alterations associated with PCOS, including hypothalamic–pituitary–ovarian (H–P–O) axis dysregulation and elevated levels of anti-Müllerian hormone (AMH), androgens, and prolactin. Additionally, we address metabolic disturbances such as insulin resistance and dyslipidemia and evaluate the role of elevated inflammatory markers in PCOS pathogenesis. This review elucidates the interconnections among endocrine, metabolic, and inflammatory processes, illustrating how these mechanisms collectively contribute to the manifestation and complications of PCOS. Furthermore, we highlight existing gaps and unresolved questions within the domains of endocrinology, metabolism, and immunology and propose future research directions to bridge these knowledge deficits. Emphasizing the convergence of endocrinology, metabolomics, and immunology, this review advocates for interdisciplinary research collaboration to enhance communication and integration across research fields, thereby advancing a holistic understanding of PCOS. (Fig. 1)

PCOS and endocrinology

H-P-O axis disorder

The H–P–O axis plays a crucial role in regulating the reproductive cycle by ensuring the periodic secretion of gonadotropins and steroid hormones necessary for reproductive function [11]. This sophisticated regulatory mechanism originates in the hypothalamus, where the arcuate nucleus releases GnRH in a pulsatile manner. GnRH travels through the hypothalamic–pituitary portal system to bind to specific receptors on the anterior pituitary gland. This interaction stimulates the synthesis and release of follicle-stimulating hormone (FSH) and LH [12], which subsequently interact with the ovaries. FSH primarily facilitates follicle development and maturation, thereby promoting estradiol production. As follicles reach a critical size, LH is triggered by a certain concentration of estradiol to initiate a positive feedback mechanism, increasing the LH release frequency while reducing its amplitude, ultimately leading to ovulation [13]. Postovulation, the formation of the corpus luteum in the ovary initiates progesterone production [14]. Oestradiol and inhibin B then exert negative feedback on the hypothalamus to reduce GnRH release and pituitary FSH secretion, thereby concluding the endocrine regulatory cycle [15]. This complex interaction of positive and negative feedback mechanisms is essential for maintaining the regularity of the menstrual cycle and ensuring the proper timing of ovulation.

Disruptions in the H–P–O axis can manifest as abnormalities such as an irregular GnRH pulse frequency, an elevated LH/FSH ratio, and excessive androgen production from the adrenal glands or ovaries. Studies have shown that approximately 75% of patients with PCOS exhibit elevated LH levels, with 94% demonstrating a significantly increased LH/FSH ratio [16]. This condition primarily arises from increased sensitivity of the pituitary gland to GnRH, resulting in excessive LH secretion. Elevated LH then stimulates the ovarian stroma and theca cells to produce excess androgens, disrupting follicular maturation and inhibiting dominant follicle formation. Despite this, small follicles in the ovaries continue to secrete estradiol at levels similar to those observed in the early follicular phase. Oestradiol exerts a robust feedback effect on both the hypothalamus and pituitary gland to regulate the H–P–O axis [12]. Additionally, androstenedione is converted to estrone in peripheral tissues, leading to elevated estrone levels. Persistent estrone secretion, along with elevated estradiol, exerts a positive feedback effect on LH production, resulting in increased amplitude and frequency of LH secretion and sustaining high LH levels without cyclical fluctuations, which leads to anovulation [17]. Conversely, elevated estrogen levels suppress FSH secretion, resulting in relatively low FSH levels and an increased LH/FSH ratio. High LH levels further stimulate ovarian androgen secretion, and prolonged low FSH levels prevent the development of dominant follicles. This creates a detrimental cycle characterized by elevated androgen levels and persistent anovulation, ultimately leading to polycystic ovarian alterations.

Research indicates that an inappropriate elevation in the LH/FSH ratio is a significant contributor to the persistent anovulation observed in PCOS. Specifically, an LH/FSH ratio exceeding 1 is associated with optimal sensitivity and specificity for diagnosis [18]. While LH/FSH ratio is partially incorporated into the diagnostic criteria for PCOS in certain regions, such as China and Japan, it is not involved in the Rotterdam diagnostic criteria [19–21]. This discrepancy underscores the absence of a universally accepted threshold for clinical practice, which hampers the effective application of the LH/FSH ratio in PCOS diagnosis. Moreover, variability in definition criteria across different studies complicates the use of the LH/FSH ratio as a diagnostic marker. Therefore, future investigations should leverage extensive datasets to establish a widely recognized optimal range for the LH/FSH ratio, thereby enhancing the differentiation of PCOS from other gynecological conditions and healthy populations. Furthermore, it is important to consider that discrepancies in LH and FSH measurements may arise due to variations in laboratory equipment, reagents, and detection methodologies. To maximize the utility of the LH/FSH ratio as a diagnostic biomarker and improve the accuracy of PCOS diagnoses, it is crucial to establish a definitive cut-off value for this ratio and address the challenges posed by differing experimental conditions.

Elevated levels of AMH

AMH plays a crucial role in maintaining the dynamic balance of the reproductive endocrine system, underscoring the need for continued investigation into its complex interactions with neuroendocrine factors. Initially, identified by Fallat et al. in 1997, significantly elevated serum AMH levels were noted in women with PCOS [22]. Subsequent studies have validated these observations, revealing a two- to threefold increase in serum AMH concentrations among PCOS patients compared with those with ovarian function and regular menstrual cycles, particularly in those with anovulatory symptoms [23, 24]. Tehrani et al. (2006) observed that in females diagnosed with PCOS, elevated levels of AMH are associated with fluctuations in fertility. These individuals may experience a prolonged potential reproductive lifespan (the time span of being able to conceive) relative to normo-ovulatory individuals [25]. Furthermore, Homburg et al. (2010) confirmed a positive correlation between the severity of PCOS symptoms and the abundance of small ovarian follicles, thereby reinforcing the central regulatory role of

AMH in the pathophysiological mechanisms of anovulation in PCOS [26].

As a member of the transforming growth factor β (TGF-β) family, AMH is integral to the regulation of GnRH neuron function under physiological conditions. Research has identified AMH type II receptors on GnRH neurons, indicating the ability of AMH to bind to these receptors and exert direct or indirect effects on GnRH neurons in the hypothalamus [27]. In pathological states, elevated serum AMH levels may activate hypothalamic pathways through distinct signalling mechanisms, leading to changes in GnRH secretion frequency or magnitude and contributing to hyperandrogenism. Additionally, AMH has been shown to inhibit factors that promote granulosa cell-mediated follicular development, primarily affecting follicles destined for dominance [28]. Compared with their wild-type counterparts, follicles in AMH gene knockout murine models exhibit increased sensitivity to FSH, suggesting that AMH indirectly inhibits follicular growth by decreasing FSH sensitivity in granulosa cells and suppressing aromatase activity [29].

The 2023 international evidence-based guidelines in PCOS highlight the critical role of AMH in the diagnostic framework, officially recognizing it as a key diagnostic marker [30]. According to the revised guidelines, AMH is particularly useful in assessing the presence of polycystic ovary morphology, especially in adult women.

Hyperandrogenism

Hyperandrogenism is a defining characteristic of PCOS [31]. Livadas et al. (2014) explored the prevalence of hyperandrogenism in women with PCOS, highlighting its significant impact on overall health and emphasizing the strong association between androgen levels and PCOS features [32]. Evidence suggests that more than 75% of women with clinically diagnosed PCOS exhibit clinical signs of hyperandrogenism, including hirsutism, severe acne, and alopecia [33]. The etiology of these symptoms is linked to dysregulation of the neuroendocrine system, particularly the H–P–O axis. In individuals with PCOS, increased sensitivity of the pituitary gland to GnRH results in elevated LH levels relative to FSH levels due to the increased frequency and amplitude of LH pulses. Recent findings suggest that hyperandrogenism may disrupt the negative feedback of gonadal steroids on LH, leading to increased GnRH release from the hypothalamus and consequently increased LH and androgen levels [34]. Elevated LH persistently affects stromal and granulosa cells in the ovary, driving excessive production of testosterone and other androgens, which intensifies hyperandrogenic symptoms and contributes to the reproductive and metabolic disturbances observed in PCOS patients.

Elevated androgen levels activate the endoplasmic reticulum (ER) stress response in granulosa cells (GCs), ultimately leading to cellular apoptosis through death receptor 5 (DR5) [35]. DR5, a transcriptional target of C/EBP homologous protein (CHOP), enhances the signalling cascade of secreted death ligands, playing a crucial role in ER stress-mediated cell apoptosis [36]. Recent studies have demonstrated that ER stress in ovarian cells impacts oocyte maturation, follicular formation, and ovulation [37, 38]. Research utilizing PCOS mouse models highlights the involvement of ER stress in GCs in follicular atresia and anovulation [39]. The function of granulosa cells is intricately linked to the anovulation and metabolic disturbances observed in PCOS [40]. Wu et al. (2017) reported that ER stress induces apoptosis in GCs and disrupts ovarian angiogenesis, resulting in abnormal follicular development [41]. Harada et al. (2015) emphasized the role of the unfolded protein response (UPR) and ER stress in coordinating follicular development and maturation in the ovary [42]. Park et al. (2018) reported that ER stress affects cumulus cell proliferation and oocyte maturation in porcine models [43]. Li et al. (2019) identified a direct link between elevated serum testosterone levels and the expression of autophagy-related genes, suggesting that increased androgens promote autophagy and apoptosis in granulosa cells, negatively impacting ovarian function [44]. Azhary et al. (2019,2020) reported that hyperandrogenaemia activates ER stress, leading to the apoptosis of antral follicle granulosa cells via the upregulation of DR5 [30, 34]. Additionally, testosterone was found to upregulate receptor for advanced glycation end products (RAGE) and advanced glycation end products (AGEs) accumulation in granulosa cells through ER stress activation, disrupting the estrous cycle and increasing atretic antral follicle incidence [35, 39]. Jin et al. (2020) extensively explored the impact of androgens on granulosa cell function and reported that testosterone significantly induces ER stress and apoptosis in granulosa cells in vitro [45]. These findings highlight the apoptotic effects of androgens on granulosa cells in PCOS, demonstrating that elevated androgen levels are a significant factor in reproductive health issues and increase the risk of PCOS development in offspring [46].

It is important to recognize that not all women who fulfill the diagnostic criteria for PCOS will present with pronounced symptoms of androgen excess. The Rotterdam criteria encompass a diagnosis of hyperandrogenism, which includes both biochemical alterations characterized by elevated androgen levels and clinical manifestations such as hirsutism, acne, and androgenetic alopecia [21]. Consequently, women may be diagnosed with PCOS even in the absence of detectable high hormone levels if they exhibit the aforementioned clinical signs. Therefore, when employing the Rotterdam criteria

for PCOS diagnosis, it is essential to take into account a comprehensive evaluation of both biochemical indicators and clinical manifestations. This approach facilitates the identification of patients who may not demonstrate typical biochemical profiles but do experience significant hormone-related symptoms.

Hyperprolactinemia

Szosland et al. (2015) demonstrated that the prevalence of hyperprolactinemia in females with PCOS does not significantly differ from that in healthy controls [47]. This finding underscores the need for further research to explore the etiology of hyperprolactinemia within the context of PCOS, recognizing the potential for these conditions to cooccur. Davoudi et al. (2021) reported that 37% of a cohort of 330 PCOS patients exhibited hyperprolactinemia, with many receiving diagnoses within the study's scope [48]. Dehghan et al. (2022) further suggested that PCOS is a common underlying factor in hyperprolactinemia among women with infertility [49]. Notably, hyperprolactinemia is often a causative factor of ovulatory dysfunction, potentially related to the stimulatory effect of thyrotropin-releasing hormone (TRH) on prolactin secretion. In cases of primary hypothyroidism, excessive TRH can disrupt GnRH pulsatility, affecting the endocrine balance of the H–P–O axis [11]. However, there is no compelling evidence that PCOS patients benefit therapeutically from reduced prolactin levels due to GnRH agonist-induced pituitary desensitization [50]. Current research indicates that PCOS patients with hyperprolactinemia often have lower insulin levels and higher homeostatic model assessment-insulin resistance (HOMA-IR) scores than those with prolactin levels do, suggesting a potential interplay between these metabolic factors [48, 51].

The 2018 international evidence-based guidelines in PCOS emphasize the necessity of excluding other conditions that may present with symptoms similar to those of PCOS, including hyperprolactinemia, prior to establishing a diagnosis [52]. While prolactin levels are not utilized as direct diagnostic criteria for PCOS, the guidelines advise that clinicians consider the potential presence of other endocrine disorders, such as thyroid dysfunction or hyperprolactinemia, during the evaluation of patients with PCOS. Nonetheless, a definitive physiological and pathological relationship between PCOS and hyperprolactinemia remains to be established in the literature.

PCOS and metabolism

Insulin resistance and hyperinsulinaemia

Insulin resistance, a critical indicator of metabolic dysfunction, is characterized by a reduced responsiveness of cells to both endogenous and exogenous insulin, leading to inadequate glucose regulation and persistent hyperglycemia [53]. In the complex landscape of PCOS, a multifaceted endocrine disorder, insulin resistance emerges as a primary metabolic anomaly [54]. Moller et al. (1988) investigated a PCOS patient with insulin resistance, acanthosis nigricans, and classic type A insulin resistance and revealed a genetic variant in the insulin receptor gene [55]. Epidemiological studies indicate that 50-70% of PCOS cases are associated with insulin resistance, which is often accompanied by compensatory hyperinsulinaemia [56]. This association highlights a significant and widespread pathological link between insulin resistance and PCOS.

Notably, even in PCOS patients with or slightly elevated body weights, insulin resistance typically occurs. This condition reflects a decreased physiological response of various tissues to insulin, which disrupts effective glucose regulation. As a result, pancreatic beta cells exhibit increased insulin secretion to maintain blood glucose homeostasis, leading to elevated insulin levels and compensatory hyperinsulinemia [57]. Over time, individuals may experience a gradual decline in beta cell function, marked by a reduction in insulin production, which exacerbates glucose metabolism disorders. This decline can lead to compromised blood glucose control and potentially progress to type 2 diabetes [8]. Within this pathological context, the diminished biological effectiveness of insulin critically impairs its capacity to facilitate glucose uptake and conversion, thus perpetuating hyperglycemia and sustaining a harmful cycle.

Theca cells within the ovarian follicle are the primary site for testosterone synthesis. The enzyme cytochrome P450c17, encoded by the CYP17A1 gene, is crucial for testosterone biosynthesis and affects both gonadal and adrenal cortical tissues [58]. In vitro studies have demonstrated that hyperinsulinaemia enhances LH receptor expression, which increases testosterone production in response to LH stimulation. Specifically, hyperinsulinemia increases LH binding sites and increases ovarian sensitivity to LH, thus promoting intraovarian testosterone synthesis. This effect is mediated through a synergistic interaction between LH and insulin, leading to elevated CYP450c17 mRNA expression [59–61]. Insulin directly influences the cytochrome P450c17 enzyme system by significantly increasing the activity of its critical active sites, 17-hydroxylase and 17,20-lyase, through the modulation of granulosa cell functions [59, 62]. This indirect enhancement results in increased androgen production within granulosa cells. Studies in animal models have shown that the lack of androgen receptors in hypothalamic neurons in female mice leads to insulin resistance in this region [63], suggesting that androgens may contribute to decreased insulin sensitivity through central nervous system pathways.

During hyperinsulinemia, a key physiological response is the suppression of insulin-like growth factor binding protein-1 (IGFBP-1) synthesis in the liver and ovaries, which increases the availability of insulin-like growth factor-1 (IGF-1). This change enhances insulin activity in the liver, reduces sex hormone-binding globulin (SHBG) levels, and amplifies insulin action in the ovaries [31]. Elevated insulin levels not only activate IGF-1 receptors in ovarian stromal cells but also directly bind to insulin receptors on theca cells. These two signaling pathways facilitate the synthesis of androgens, including testosterone [64]. Additionally, insulin exerts an inhibitory effect on the expression and activity of aromatase, a crucial enzyme responsible for the conversion of androgens into estrogens. When aromatase activity is suppressed, the conversion of androgens to estrogens is diminished, resulting in an elevated androgenic state [65, 66]. Furthermore, peroxisome proliferator-activated receptor γ (PPAR-γ) is an essential nuclear receptor that regulates insulin sensitivity and maintains reproductive function, particularly by modulating steroid hormone synthesis in ovarian granulosa cells. Experimental studies have shown that targeted deletion of the PPAR-γ gene in granulosa cells can cause abnormal follicle rupture, disrupt ovulation, and potentially result in ovulation disorders under severe conditions [67].

Dyslipidemia

PCOS is a common endocrine disorder in females and is frequently associated with dyslipidemia. According to Legro et al. (2001), individuals with PCOS typically exhibit hyperandrogenism and insulin resistance, leading to significant alterations in circulating lipid and lipoprotein profiles [68]. To investigate the connection between lipid profiles and carotid intima–media thickness in young women with PCOS, Saha et al. (2008) conducted an in-depth study. Their results revealed that even in relatively young individuals, PCOS is linked with an increased risk of atherosclerosis, suggesting early vascular compromise [69]. This finding highlights the extended cardiovascular risks inherent in PCOS.

In the PCOS patient population, dyslipidemia is a prevalent and critical comorbidity. It manifests in three key aspects: first, an elevated triglyceride level, known as hypertriglyceridaemia, which is a prominent indicator of lipid metabolism disruption; second, a progressive increase in low-density lipoprotein cholesterol (LDL-C), which increases cardiovascular risk; and third, a reduction in high-density lipoprotein cholesterol (HDL-C), which not only disrupts overall lipid metabolism but also increases the likelihood of long-term cardiovascular complications [70].

In individuals diagnosed with PCOS, hypertriglyceridaemia represents a notably significant and prevalent metabolic disorder that is frequently associated with insulin resistance mechanisms [71]. Reduced insulin sensitivity leads to decreased glucose utilization efficiency, which adversely impacts glucose metabolism, triglyceride synthesis, and metabolic clearance processes. Consequently, triglycerides experience insufficient breakdown and removal, resulting in their persistent accumulation in the circulatory system and elevated blood lipid levels [72]. Additionally, patients with PCOS commonly exhibit increased levels of LDL-C, often referred to as "bad" cholesterol [70]. LDL-C plays a critical role in transporting cholesterol to various tissues. Elevated concentrations of LDL-C facilitate the deposition of cholesterol along vascular walls, contributing to the formation of atherosclerotic plaques. Specifically, in PCOS patients, the elevated triglyceride content within LDL particles may lead to local lipid degradation into more harmful free fatty acids within the vascular intima, inducing mild chronic endothelial inflammation. Persistent elevations in LDL-C levels significantly increase the risk of atherosclerotic cardiovascular diseases, including coronary artery disease, myocardial infarction, ischemic stroke, and peripheral artery disease [73]. Conversely, HDL-C, known as "good" cholesterol, is recognized for its anti-inflammatory, antioxidant, and antithrombotic properties [74]. The Framingham Heart Study, conducted in 1960, first identified an inverse relationship between cardiovascular risk and circulating HDL-C levels [75]. This landmark discovery spurred extensive research into the protective mechanisms of HDL against atherosclerosis, elucidating the importance of the reverse cholesterol transport (RCT) pathway [76]. RCT involves the extraction of cholesterol from peripheral tissues, transport via the bloodstream to the liver, and eventual excretion through feces. The cardioprotective effects of HDL are primarily mediated through its role as a receptor for intracellular cholesterol and as a key cholesterol transporter within the RCT cascade. However, individuals with PCOS often present with lower HDL-C levels, impairing the efficiency of cholesterol transport from vessel walls to the liver. This impairment facilitates increased cholesterol accumulation in vessel walls, thereby increasing the risk of atherosclerosis development.

PCOS and inflammation

Low-Grade chronic inflammation

Despite incomplete elucidation of the precise pathophysiological mechanisms underlying PCOS, substantial evidence indicates that a complex interplay between chronic low-grade inflammation and the concurrent expression of proinflammatory and anti-inflammatory cytokines may play a crucial role in the onset and progression of this disorder [77]. Initial studies by Orio et al. (2005) revealed a significant elevation in white blood cell

count in individuals with PCOS, suggesting a substantial role for inflammation in the pathogenesis of this disorder [78]. These findings were further supported by Kelly et al. (2001), who reported elevated levels of serum C-reactive protein (CRP), a well-established marker of inflammatory activity, in PCOS patients [77]. Research has revealed increased levels of various inflammatory markers, including interleukin-6 (IL-6) [79], interleukin-18 (IL-18) [80], and tumor necrosis factor-alpha (TNF-α) [81], in the serum of individuals with PCOS. Sirmans et al. (2012) highlighted the therapeutic implications of addressing chronic inflammation in PCOS treatment, emphasizing the necessity of incorporating inflammatory considerations into treatment strategies [82]. Using a 5α-dihydrotestosterone-induced animal model, Milutinović et al. (2017) reported elevated inflammatory activity in visceral adipose tissue, suggesting a potential link between inflammation and the metabolic features of PCOS, even in the absence of impaired insulin signalling [83]. Additionally, Rudnicha et al. (2021) underscored the importance of targeting the inflammatory response in the comprehensive management of PCOS, reinforcing the importance of integrating anti-inflammatory interventions into treatment protocols [6]. The 2023 international evidence-based guidelines in PCOS as well as underscore the potential association between metabolic abnormalities in patients with PCOS and the presence of chronic low-grade inflammation [30].

The preservation of ovarian function is critically dependent on the precise regulation and balance of inflammatory markers. An imbalance between anti-inflammatory and proinflammatory cytokines can lead to ovarian dysfunction, abnormal steroid hormone synthesis, and impaired follicular development and maturation. C-reactive protein (CRP), an essential inflammatory biomarker, is an acute-phase reactant produced by hepatic cells in response to proinflammatory cytokines such as TNF-α and IL-6 [84]. Cytokines, which are crucial mediators of intercellular communication, are soluble proteins secreted by various cellular populations, including adipocytes. They play vital roles in numerous physiological and pathological processes, including the recruitment of macrophages to inflammation sites, the modulation of vascular smooth muscle cell proliferation, and the migration of these cells from the vascular intima to the media. Additionally, TNF-α plays a crucial role in inducing insulin resistance associated with obesity by inhibiting the phosphorylation of the insulin receptor tyrosine kinase, which impairs the effectiveness of insulin signalling [85]. IL-6, a multifaceted signalling molecule with various biological functions, is essential in reproductive physiology. Its roles extend beyond modulating gonadal steroidogenesis to regulate embryo implantation, corpus luteum maintenance, and embryo development [86]. IL-18, a potent proinflammatory cytokine, is closely associated with insulin resistance and metabolic syndrome. IL-18 not only stimulates the production of TNF-α, thus amplifying inflammatory responses but also positively regulates IL-6 synthesis [80]. These events collectively disrupt the metabolic equilibrium of the organism and require detailed investigation.

Hyperhomocysteinaemia

Homocysteine (Hcy), a metabolic intermediate in methionine catabolism, is a prevalent amino acid across various organisms. Elevated levels of Hcy, which are observed in pathological conditions, are closely associated with cellular dysfunction. This dysfunction is primarily linked to the upregulation of inflammatory cytokines, which represents a key molecular mechanism contributing to the cellular abnormalities observed in hyperhomocysteinaemia (HHcy) [87]. A detailed meta-analysis investigating oxidative stress markers in women with PCOS revealed a significant increase in Hcy levels—approximately 23% higher—than those in healthy controls [88]. Moreover, Kondapaneni et al. (2020) reported a notable association between HHcy and reproductive challenges in women with PCOS, including an increased risk of pregnancy loss and reduced ovulatory function [89].

Hcy serves not only as a biomarker for metabolic disturbances but also as a potent proinflammatory mediator, influencing the initiation and progression of inflammatory pathways both in vivo and in vitro [90]. Extensive epidemiological studies highlight the close relationship between HHcy and insulin resistance [91]. In vitro research has demonstrated that HHcy can impair the insulin sensitivity of adipose tissue by promoting the synthesis of proinflammatory cytokines [92]. Additionally, animal model studies have shown that HHcy is associated with an increase in inflammatory monocytes in peripheral tissues, along with elevated levels of proinflammatory markers such as TNF-α and IL-6 [93]. These findings emphasize the critical role of Hcy in modulating inflammatory processes and its impact on the pathological landscape of related conditions, including PCOS.

Conclusions

The pathophysiological underpinnings of PCOS constitute a multifaceted network of interactions. This review meticulously examines the endocrine alterations associated with PCOS, including disturbances within the H–P–O axis, as well as elevated levels of AMH, androgens, and prolactin. Additionally, it addresses metabolic anomalies, such as insulin resistance and dyslipidemia, and the increase in inflammatory markers and their contributions to PCOS pathogenesis. By elucidating the interplay among these endocrine, metabolic, and inflammatory factors, this review demonstrates their

collective influence on PCOS development, symptoms, and complications. Furthermore, it identifies existing knowledge gaps and proposes future research directions aimed at advancing the understanding of PCOS through interdisciplinary collaboration. Ultimately, the review underscores the necessity for integrative research across endocrinology, metabolomics, and immunology to foster a more comprehensive understanding of PCOS and advocates for enhanced interdisciplinary efforts in future studies.

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Author contributions
P.P.S. designed the study and wrote the manuscript. C.C. searched the related literature. Y.S. designed and provided support for this research, supervised the study, and reviewed and revised the manuscript. All the authors have read and agreed to the published version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Conflicts of interests
The authors declare that there are no conflicts of interest.

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