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Brief Review

Deciphering polycystic ovary syndrome: A brief overview from metabolic drivers to genetic and fetal origins

Mario Morales-Esponda[a], Ramón de los Santos-Aguilar[b], Raúl Villanueva-Rodríguez[b], Luis David Sol-Oliva[b], Carlos Alberto Aguilar-Salinas[c], Mayel Chirinos[b], Fernando Larrea[b,*]

[a] Departamento de Vigilancia Epidemiológica, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, CDMX, 14080 Mexico, Mexico
[b] Departamento de Biología de la Reproducción Dr. Carlos Gual Castro, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, CDMX, 14080 Mexico, Mexico
[c] Unidad de Investigación de Enfermedades Metabólicas, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, CDMX, 14080 Mexico, Mexico

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a multifactorial endocrine and metabolic disorder in women of reproductive age characterized by hormonal imbalances, menstrual irregularities, and changes in ovarian morphology. Excess body fat plays a significant role in the clinical development of PCOS. The complex relationship between adiposity and PCOS involves disruptions in hormonal balance and inflammatory processes, which both contribute to the clinical and phenotypic manifestations of the syndrome. Insulin resistance is a significant factor linking adiposity and PCOS. Moreover, reduced fertility is associated with adiposity in PCOS, with obesity exacerbating anovulation. Recent studies have raised questions about the role of androgen exposure during fetal life, including genetic factors related to PCOS identified in genome-wide association studies and Mendelian randomization studies. Managing PCOS should concentrate on addressing adiposity as a crucial target, positively impacting the syndrome, particularly regarding reproductive and fertility outcomes. This review aims to understand how metabolic conditions such as obesity and insulin resistance are linked to PCOS and how early prenatal androgen exposure is involved in its etiology. Particular attention is given to its role in developmental programming, fat distribution, and fat type, as well as how these factors contribute to the onset of metabolic disturbances in adulthood.

Introduction

Polycystic ovary syndrome (PCOS) is both a hormonal and metabolic disorder that affects many women of reproductive age. The Rotterdam criteria are often used to diagnose PCOS after ruling out other similar conditions.[1] These criteria require the presence of at least two of the following features: ovulatory dysfunction (OD), hyperandrogenism (HA), and polycystic ovary morphology (PCOM). These criteria can be presented in four phenotypes as shown in Table 1, and influenced by both genetic and ethnic factors.[2–5] More recently, significant progress has been made in understanding how adiposity, insulin resistance (IR), and hormonal alterations contribute to this condition.[6,7] Adiposity refers to the accumulation of body fat, particularly visceral fat, which surrounds internal organs. This type of fat plays a crucial role in overall health, as it is closely linked to IR,[8] inflammation,[9] and dyslipidemic factors that contribute to conditions like type 2 diabetes, cardiovascular disease, and other metabolic disorders, such as stroke, cancer, and other metabolic disorders.[10,11]

Moreover, the inflammatory and hyperandrogenic environment associated with IR affects oocyte quality, interfering with maturation, mitochondrial function, and chromosomal integrity. These factors contribute to reduced fertility and poor outcomes in assisted reproductive technologies (ART), such as in vitro fertilization (IVF).[12] Overall, fat distribution and IR are key drivers of reproductive impairment in PCOS, significantly affecting both natural and assisted fertility. Adipose tissue, which includes visceral fat, functions as an endocrine organ, releasing hormones and other factors that regulate appetite, energy metabolism, and inflammation. Several studies have demonstrated that adipose tissue expression in PCOS leads to an imbalanced adipokine profile, negatively impacting endocrine and reproductive systems.[13] Indeed, this condition, coupled with inflammatory responses and IR, is thought to contribute to the pathogenesis of PCOS, leading to obesity-related complications[11] as described above. Genetic and environmental factors, such as lifestyle (diet and physical activity), influence the degree of adiposity.[14] Tools like the body mass index (BMI) and the visceral adiposity index (VAI) help assess the risk of metabolic complications associated with body fat, with VAI offering a more precise measure than BMI.[15,16] Adiposity and IR are important associated conditions of PCOS.[17] IR and

* Corresponding author.
E-mail address: fernando.larreag@incmnsz.mx (F. Larrea).

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Table 1
PCOS diagnosis criteria.

	Hyperandrogenism	Ovulatory dysfunction	PCOM	Diagnosis
NIH (1990)	Required: clinical (hirsutism, acne) and/or biochemical (elevated total/free testosterone)	Required: oligo- or anovulation (mentrual cycles >35 days or fewer 8 cycles per year)	No required	Both hyperandrogenism and ovulatory dysfunction
Rotterdam (ESHRE/ASRM, 2003)	Optional: clinical and/or biochemical	Opcional: oligo- or anovulation	Optional: ≥12 follicles (2–9 mm) in each ovary and/or ovarian volume ≥10 mL	Any 2 of 3 criteria
AE-PCOS (2006)	Required: clinical and/or biochemical	Optional: oligo- or anovulation	Optional: PCOM as defined by Rotterdam	Hyperandrogenism plus either ovulatory dysfunction or PCOM
International evidence-based guideline (2023)	Opcional: clinical (hirsutism) and/or biochemical (elevated total/free testosterona or free androgen index)	Opcional: oligo- or anovulation defined by NIH	Optional: follicle numer per ovary ≥20 in at least 1 ovary and/or ovarian volume ≥10 mL. AMH useful	Any 2 of 3 criteria, plus exclusion of other etiologies

PCOM: polycystic ovary morphology; NIH: National Institutes of Health; ESHRE: European Society of Human Reproduction and Embryology; ASRM: American Society for Reproductive Medicine; AE-PCOS: Androgen Excess and PCOS Society.

compensatory hyperinsulinemia, for example, are prevalent in 45–70% of women with PCOS.[18] Interestingly, a group of women with PCOS often exhibits metabolic dysfunction despite having a normal BMI, a phenomenon linked to changes in the structure and function of adipose tissue.[19] Studies show that subcutaneous abdominal adipose tissue in these women may be hypertrophic, insulin resistant, and pro-inflammatory, demonstrating impaired adipogenic and mitochondrial gene expression in adipose-derived stem cells. These alterations can reduce lipid storage capacity, promote the deposition of ectopic fat, and contribute to systemic insulin resistance. Therefore, rather than fat mass alone, dysfunction in adipose tissue plays a crucial role in the metabolic disturbances observed in normal-weight PCOS. The relationship between abdominal adiposity and PCOS is particularly significant because visceral adiposity leads to androgen production.[20] Viceral fat through a feedback loop in which hyperinsulinemia (resulting from IR amplifies ovarian androgen production by reducing levels of sex hormone-binding globulin (SHBG) and directly stimulating the ovary's theca cells[21] (Fig. 1). The result is an increase in circulating free androgens, contributing to hyperandrogenism characterized by hirsutism, acne, and alopecia, which are important clinical features of PCOS.[22–24] Ovulatory dysfunction has also been associated with fetal or perinatal exposure to androgens, with studies indicating that female fetuses subjected to high androgen levels during critical developmental stages may experience prenatal programming that predisposes them to PCOS.[25] Furthermore, recent research has uncovered new dimensions of PCOS, including chronic inflammation, mitochondrial dysfunction, and various metabolic alterations, providing valuable insights into the complexity of this condition.[26–28] Thus, this review aims to explore how obesity affects reproductive and endocrine functions in women with PCOS, to support more accurate diagnoses and effective management strategies.

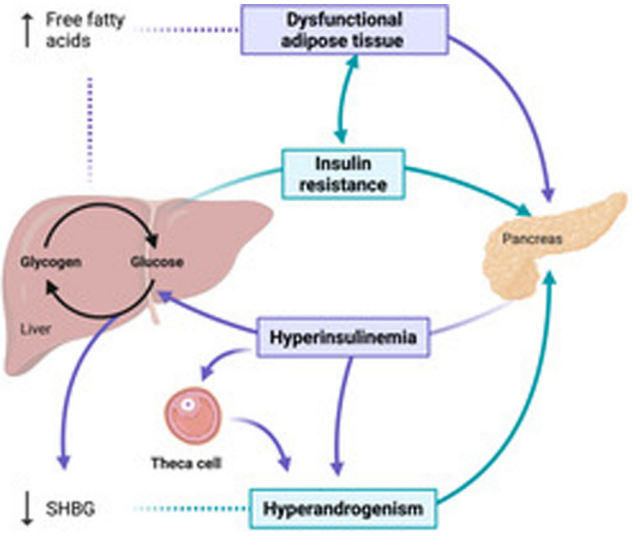

Fig. 1. Determinants of PCOS phenotype heterogeneity. Genetic and epigenetic factors during prenatal life, including gene polymorphisms and fetal exposure to hyperandrogenism, influence PCOS development. At puberty, hormonal axis activation reveals symptoms in predisposed individuals. Insulin resistance, adiposity, and environmental factors, such as lifestyle and endocrine disruptors, further influence the clinical and metabolic manifestations of PCOS.

Overview of adiposity and PCOS

Adiposity, especially visceral adiposity, is critical to developing PCOS. Besides merely representing excess fat accumulation, it influences a range of hormonal, metabolic, and inflammatory processes, contributing to the clinical features of this syndrome.[29] Visceral fat is not just an energy-store organ but also an active endocrine organ, secreting adipokines, cytokines, and free fatty acids that regulate metabolic processes.[30] An excess of this type of fat fosters an environment that promotes IR, inflammation, and hormonal imbalances, which are important metabolic features of PCOS.

Visceral vs. subcutaneous fat

There are two primary types of adipose tissue: subcutaneous fat, located just beneath the skin, and visceral fat, which surrounds internal organs, particularly in the abdominal cavity. Subcutaneous adiposity has a less pronounced impact on metabolic health, while visceral adiposity is directly linked to metabolic dysregulation.[31,32] Visceral fat accumulation drives IR by increasing the flux of free fatty acids to the liver, promoting hepatic IR, and contributing to the development of non-alcoholic fatty liver disease.[33]

Moreover, visceral fat is a significant source of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), which exacerbate IR and further amplify the metabolic disturbances in PCOS.[6] In contrast to normal or increased secretion of adiponectin, an anti-inflammatory adipokine,[34] low adiponectin levels in women with high visceral fat contribute to worsening insulin sensitivity and overall metabolic health.[35,36] Recently, Neuregulin-4 (NRG4), a member of the adipokines family, synthesized and secreted by adipose tissues, was found to be elevated in PCOS and positively correlated with fasting blood glucose, insulin, HOMA-IR, and high-sensitivity C-reactive protein.[37] In this study, the authors observed a higher NRG4 in phenotype A, as described above, compared to the other phenotypes. However, high NRG4 serum concentrations have been independently associated with BMI and obesity.[38] These studies underline the importance of weight management when

addressing metabolic abnormalities and fertility problems in patients with PCOS.

The impact of obesity on PCOS

Obesity plays an important role in the development and exacerbation of PCOS. It is estimated that 40–80% of women with PCOS are overweight or obese.[39] As mentioned earlier, obesity not only worsens the reproductive clinical manifestations of PCOS (anovulation and infertility) but also amplifies the associated metabolic complications. Additionally, new anthropometric indices such as body adiposity index (BAI), visceral adiposity index (VAI), lipid accumulation product (LAP), body roundness index (BRI), and body shape index (ABSI) should be considered in the diagnosis due to their predictive association with obesity and IR, since they may indicate adipose toxicity and increased cardiovascular disease risk in patients with PCOS under the different diagnostic criteria.[40,41]

In PCOS, obesity contributes to a vicious cycle of metabolic and reproductive disturbances. Adiposity, particularly visceral fat, increases IR, which in turn stimulates ovarian androgen production. It is well established that hyperandrogenism contributes to both central obesity and reproductive dysfunction. Androgens influence adipose tissue distribution by promoting adipogenesis and lipid storage in visceral depots while inhibiting fat accumulation in subcutaneous gluteofemoral regions, resulting in a male-pattern fat distribution.[42] Several studies have linked body composition to the different phenotypes of PCOS. Phenotype A, the more androgenic, was associated with the highest visceral fat compared to controls.[43] This observation underscores the bidirectional relationship between obesity and hyperandrogenism, a central issue in PCOS (Fig. 2).

The role of insulin resistance in PCOS

When insulin binds to its receptor (InsR), it triggers tyrosine phosphorylation of the InsR and other downstream substrates, including the insulin receptor substrates IRS-1 and IRS-2. This process activates the phosphatidylinositol 3-kinase (PI3K), leading to the protein kinase B (Akt) cascade, known as the IRS/PI3K/Akt pathway.[44] Ultimately, this process results in the transport of glucose transporter-4 (GLUT-4) to the cell membrane, and subsequently, glucose uptake. Several studies have shown defects in insulin receptor activation in women with PCOS,[45] which might explain why IR affects 65–95% of women with PCOS regardless of whether they are overweight or lean.[46] In IR, cells do not respond appropriately to insulin, particularly in the muscles, fat, and liver. IR and androgens[47] stimulate the pancreas to produce more insulin, leading to hyperinsulinemia, a significant driver of both metabolic and reproductive abnormalities in PCOS.

Hyperinsulinemia directly and indirectly affects the ovaries, primarily by enhancing androgen production in the ovarian theca cells.[48] This process contributes to hyperandrogenism, which manifests as hirsutism, acne, and alopecia, and also disrupts normal follicular development, resulting in anovulation and infertility.[49]

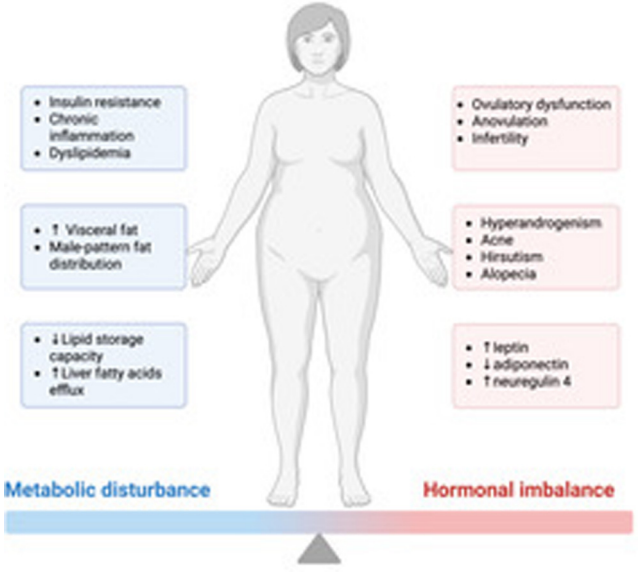

Fig. 2. Metabolic and hormonal interplay in PCOS. PCOS phenotypes result from the interaction between metabolic and hormonal dysfunctions. Visceral fat, insulin resistance, and altered adipokine levels increase cardiometabolic risk and promote inflammation. Hormonal imbalance, mainly due to an excess of ovarian androgens, disrupts the hypothalamic–pituitary–ovarian axis, leading to ovulatory dysfunction and infertility. Hyperandrogenism worsens ovarian function, reinforcing the cycle of metabolic and endocrine disturbances.

Molecular mechanisms linking IR to PCOS

The mechanisms by which IR contributes to PCOS are complex and involve both endocrine and metabolic pathways: 1. *Hyperinsulinemia and ovarian function*: This condition synergizes with LH to stimulate androgen production in the theca cells of the ovaries. Elevated insulin levels increase ovarian androgen production while reducing SHBG levels,[50] thereby increasing the free and bioactive fraction of androgens.[51] Hyperandrogenism affects normal follicular maturation, contributing to the characteristic anovulation seen in PCOS.[21,52] 2. *Insuline resistance and fat distribution*: IR also influences fat distribution by promoting the accumulation of visceral fat. Elevated insulin levels promote the deposition of visceral fat, leading to the central obesity often seen in women with PCOS.[53] Visceral adiposity further contributes to IR by releasing free fatty acids and pro-inflammatory cytokines, such as TNF-α, IL-6, and MCP-1, which impair insulin signaling and exacerbate metabolic dysfunction.[6,54] 3. *Inflammation and IR*: Adipose tissue, particularly visceral fat, functions as an active endocrine organ, secreting a variety of adipokines and pro-inflammatory cytokines.[55–57] These adipokines, including leptin, resistin, and adiponectin, are dysregulated in women with PCOS regardless of weight.[58] Leptin, produced by adipose tissue, is often elevated in obesity and correlates with IR. In contrast, adiponectin, which has anti-inflammatory and insulin-sensitizing properties, is typically reduced in women with PCOS.[59] This condition contributes to chronic inflammation, worsening IR, and promoting androgen excess.[19] 4. *Mitochondrial dysfunction and IR*: Further evidence suggests that mitochondrial dysfunction may also play a role in the IR observed in women with PCOS.[60] Mitochondria are critical for energy production, and their dysfunction can impair insulin signaling and exacerbate metabolic disturbances.[61] Studies have shown that women with PCOS have altered mitochondrial function in their oocytes, which may contribute to poor reproductive outcomes and abnormal folliculogenesis.[62] Mitochondrial dysfunction in adipose tissue, including the effects of androgens,[63] may also impair insulin sensitivity, further perpetuating a metabolic dysfunction.[64]

Fat distribution, insulin resistance, and reproductive outcomes

Fat distribution and IR in PCOS significantly affect phenotype distribution and reproductive health.[65] Increased visceral fat and IR disrupt the hypothalamic–pituitary–ovarian axis, impairing normal follicle development and fertility.[66,67] IR is also associated with lower oocyte quality,[67] negatively affecting outcomes in assisted reproductive technologies (ART), including in vitro fertilization (IVF). Recent evidence shows that weight loss through lifestyle changes or

medications, such as metformin or GLP-1 agonists,[68–70] can restore insulin sensitivity, reduce hyperandrogenism, and improve reproductive function in women with PCOS.[71,72]

Early exposure to androgens

Prenatal androgen exposure may predispose female fetuses to PCOS.[73] In this regard, considerable attention has been focused on the role of fetal androgens as a key factor in the etiology and transgenerational manifestations of the syndrome.[74] The evidence shows that in animal models exposed to dihydrotestosterone during the prenatal stage, metabolic disturbances similar to those seen in PCOS occurred, including the transmission of these traits in a transgenerational manner.[73] Although the placenta plays a crucial role in regulating androgen concentrations in the fetus, both patients and animal models with PCOS exhibited placental dysfunction, creating an intrauterine androgenic environment. This dysfunction manifests as smaller placentas with irregular shapes, reduced villous surface area, and inadequate remodeling of spiral arteries.[75–77] Furthermore, there is evidence of altered placental steroidogenesis, including decreased placental aromatase activity and increased 3 beta-hydroxysteroid dehydrogenase activity, which could result in a greater placental capacity to synthesize androgens,[78] thus contributing to prenatal androgen exposure. At birth, female humans and rodents exposed to high levels of androgens during pregnancy exhibit a longer anogenital distance and, in humans, a lower second-to-fourth digit ratio (D2:D4). These traits are recognized as clinical markers of prenatal androgen exposure at birth.[79–81]

Prenatal exposure to androgens affects extrauterine life, including low birth weight, a higher fat mass percentage, IR, and larger adipocytes, which have been considered indicators of metabolic dysfunction.[82,83] Interestingly, because mitochondria are inherited maternally, this may explain mitochondrial dysfunction in PCOS. Studies in mice examining the effects of prenatal androgen exposure on metaphase II oocyte mitochondria have revealed changes in mitochondrial mRNA content and mitochondrial structure,[84] including increased size, more prominent cristae, and disorganized vacuoles. These findings suggest that fetal androgen exposure from a mother with PCOS may contribute to mitochondrial dysfunction, potentially underlying key aspects of PCOS pathophysiology such as insulin resistance, abnormal follicular development, and oocyte dysfunction.

Likewise, studies in sheep have revealed that exposure to high concentrations of androgens in utero affects the sensitivity of GnRH to estrogen-driven negative feedback. This results in increased LH and an altered follicular development, along with delayed fetal intrauterine growth.[85,86] Some speculate that the disturbed organization of the hypothalamic KISS1 system is one of the mechanisms contributing to the neuroendocrine alterations observed in PCOS.[87,88] In this regard, recent studies have noted morphological changes in kisspeptin/neurokinin B/dynorphin (KNDy) neurons of the arcuate nucleus of the hypothalamus, as well as changes in synaptic inputs in KNDy neurons and kisspeptin neurons of the preoptic area in sheep after exposure to prenatal testosterone.[89]

It is also important to mention that fetal adrenal cortex differentiation in a hyperandrogenic environment may permanently increase the androgenic function of the adrenal cortex, as shown in female rhesus monkey fetuses from mothers exposed to androgens.[90] In this study, fetuses from mothers exposed to serum testosterone during pregnancy exhibited irreversible changes in the function and regulation of adrenal steroidogenic enzymes in the reticular and fascicular zone. Similar observations have been found in hyperandrogenic women.[91]

In general, PCOS is a disease that is also considered to be genetically determined and, as discussed above, has multiple factors playing a role in its development; therefore, the etiology and pathogenesis of PCOS remain unclear. Recent reports examining causality have shown associations between gut microbiota and metabolic abnormalities in patients with PCOS.[92,93] These studies have revealed changes in the diversity of gut microbiota and the relative abundance of related flora in patients with PCOS compared to non-PCOS women, suggesting that this condition may affect intestinal homeostasis and lead to inflammatory conditions. These studies suggest that the gut microbiome in PCOS subjects is associated with IR, hyperandrogenism, chronic inflammation, and metabolic syndrome, which may be linked to short-chain fatty acids, lipopolysaccharides, sex hormones, and the brain-gut axis.[94]

Vitamin D deficiency in PCOS

Evidence suggests an inverse association between serum vitamin D levels and circulating androgens, including IR.[95] A recent randomized, double-blind, two-phase clinical trial demonstrated that high-dose vitamin D3 supplementation (30,000 IU/week) in women with PCOS led to significant improvements in ovarian morphology, menstrual cycle regularity, and ovulation rates.[96] In this study, a subset of hyperandrogenic women receiving vitamin D3 showed a significant decrease in serum testosterone levels, and those with elevated LH/FSH ratios experienced increased serum progesterone levels and regular ovulatory function. There is also evidence suggesting an inverse association between serum vitamin D levels and circulating androgens, including IR.[97] These studies indicate that vitamin D, along with other natural molecules, may serve as valuable adjuvants for managing reproductive and metabolic dysfunctions associated with PCOS.

Genetically determined PCOS

PCOS is recognized as a complex, multifactorial disorder with both genetic and environmental factors contributing to its development. While lifestyle factors such as diet, physical activity, and obesity are critical modifiers of the syndrome's severity, genetic predisposition plays a crucial role in its onset. A growing body of evidence has emerged from genome-wide association studies (GWAS) and Mendelian randomization studies, highlighting the heritable nature of PCOS and uncovering key genetic loci associated with its pathogenesis.

GWAS and PCOS

GWAS have been instrumental in identifying genetic variants that predispose individuals to PCOS.[98,99] Multiple GWAS have identified several loci associated with PCOS, including those involved in obesity, insulin signaling, androgen biosynthesis, and gonadotropin regulation.[100,101] One landmark study identified several loci linked to *FSHB* (follicle-stimulating hormone beta-subunit gene), *THADA* (thyroid adenoma-associated gene), and *DENND1A* (DENN domain-containing protein 1A),[102–104] which are thought to contribute to the hormonal imbalances characteristic of PCOS, such as hyperandrogenism and abnormal follicular development.

Key findings from these studies highlight the involvement of genes that regulate gonadotropin secretion and insulin signaling pathways, which are directly linked to ovarian dysfunction and metabolic alterations. For instance, THADA has been associated with insulin sensitivity, and DENND1A has been shown to play a role in androgen synthesis. These insights underscore the genetic heterogeneity of PCOS and suggest that variations in these genes may contribute to the distinct phenotypes of the syndrome, including hyperandrogenic, ovulatory, and metabolic phenotypes.

Over 20 genetic loci have been identified in various populations, revealing notable differences between East Asian and European

cohorts. These studies illustrate the complex polygenic nature of PCOS and offer potential targets for therapeutic interventions.[105]

Mendelian randomization studies in PCOS

Mendelian randomization is a method that utilizes genetic variants as instrumental variables to investigate causal relationships between risk factors and diseases, including reproductive disorders such as PCOS. In the context of PCOS, Mendelian randomization studies have established a causal relationship between IR, obesity, and reproductive dysfunction. These studies confirm that IR and hyperandrogenism, two central features of PCOS, are not merely correlated but may be causally linked through genetic factors. Furthermore, these studies support the idea that the metabolic aspects of PCOS, such as obesity and IR, may arise from shared genetic susceptibility rather than obesity being a downstream effect of reproductive dysfunction.

For example, Mendelian randomization studies have demonstrated that genetic variants associated with BMI also predispose individuals to develop PCOS, supporting the notion that obesity is a primary driver of metabolic abnormalities and reproductive manifestations.[106,107] Similarly, genetic evidence suggests that hyperinsulinemia exacerbates hyperandrogenism through direct stimulation of the ovaries, thereby linking IR to reproductive dysfunction in PCOS.[108]

Heritability of PCOS and transgenerational transmission

PCOS demonstrates a strong familial aggregation with heritability estimates ranging from 40% to 70%, indicating a significant genetic component.[109,110] Twin studies have also revealed higher concordance rates in monozygotic twins compared to dizygotic twins.[111] Recent studies have identified the transgenerational transmission of PCOS-like traits.[112] Animal studies suggest that hyperandrogenism and metabolic dysfunction can be passed down through multiple generations, implicating the roles of genetic and epigenetic mechanisms in the transgenerational transmission of the syndrome.[73,113] Furthermore, there is a high prevalence of metabolic abnormalities in first-degree male relatives[114] of women with PCOS, particularly in those with obesity. In another study, a cluster of metabolic syndrome, hypertension, and IR was found among brothers of women with PCOS.[115,116] These studies, along with those investigating fetal programming, strongly suggest that prenatal exposure to androgens can induce transgenerational metabolic dysfunction and ovarian abnormalities similar to those seen in PCOS.[89] These findings also support the notion that the genetic and epigenetic contributions to PCOS may result in the persistent transmission of the metabolic syndrome, including growth restriction,[117] across generations, regardless of offspring gender and sex.

Integrating genetic insights into PCOS pathophysiology

The findings from GWAS and Mendelian randomization studies suggest that improving our understanding of the endocrine and metabolic components is important in identifying genetically predisposed individuals. The genetic predisposition to IR, obesity, and hyperandrogenism highlights the importance of early identification of at-risk individuals, particularly those with a family history of PCOS. Furthermore, these insights emphasize the importance of personalized medicine approaches to treating PCOS, given its complex polygenic nature.[118]

By identifying key genetic variants, we can now explore targeted therapies that address the genetics of PCOS. The pharmacogenomic application of genetic information is thought to play a significant role in managing PCOS, especially in individuals with specific genetic profiles that predispose them to severe metabolic or reproductive dysfunction.

Conclusions and future directions

In the etiology of PCOS, visceral fat plays a significant role in perpetuating low-grade chronic inflammation and hormonal and metabolic imbalances. This condition, combined with the reduced secretion of insulin-sensitizing adipokines such as adiponectin, worsens insulin sensitivity, promotes hyperandrogenism, and leads to menstrual irregularities during puberty. In general, the mechanism proposed is that increased visceral fat in PCOS contributes to IR, which plays a central role in reproductive dysfunction. Visceral fat promotes chronic inflammation and the release of free fatty acids, impairing insulin signaling. As a result, the body compensates with elevated insulin levels (hyperinsulinemia), which further exacerbates IR. High insulin levels stimulate ovarian theca cells to produce excess androgens and reduce hepatic production of sex hormone-binding globulin (SHBG), increasing circulating free androgens (Fig. 3). This hormonal imbalance disrupts the hypothalamic–pituitary–ovarian (HPO) axis, leading to abnormal follicular development and ovulatory dysfunction, as recently reviewed.[119] Additionally, the inflammatory and hyperandrogenic environment associated with IR affects oocyte quality, interfering with maturation, mitochondrial function, and chromosomal integrity. These factors contribute to reduced fertility and poor outcomes in assisted reproductive technologies (ART), such as in vitro fertilization (IVF). Overall, fat distribution and IR are key drivers of reproductive impairment in PCOS, significantly affecting both natural and assisted fertility.

Therefore, effective management of visceral adiposity is essential to prevent the progression and severity of the syndrome. Interestingly, differences in 25(OH) vitamin D levels have been observed between women with and without PCOS. Since vitamin D deficiency is linked to metabolic syndrome,[120] and low 25(OH)D levels may exacerbate the clinical manifestations of PCOS, it is worthwhile to consider this when evaluating vitamin D status in these individuals.

Furthermore, identifying specific genetic loci associated with PCOS, combined with insights gained from Mendelian randomization, helps establish a foundation for developing novel therapeutic targets. In this context, drugs that target insulin signaling pathways or androgen production could help address the hormonal, metabolic, and

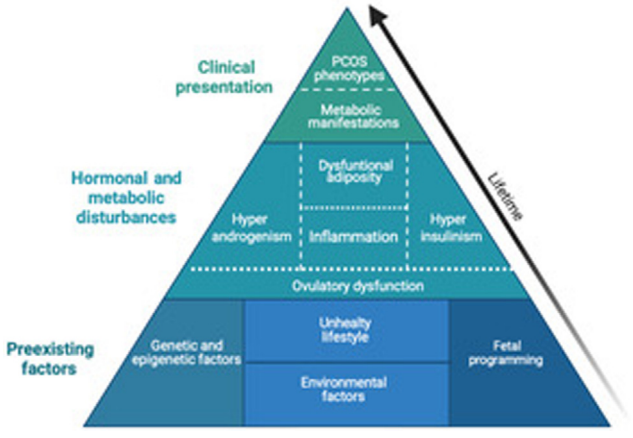

Fig. 3. Pathophysiological aspects of PCOS. PCOS is a complex hormonal and metabolic disorder characterized by hyperandrogenism and insulin resistance. Visceral adiposity contributes to insulin resistance by releasing adipokines and pro-inflammatory cytokines, thereby creating a chronic, low-grade inflammatory state. In the liver, excess free fatty acids from adipose tissue lead to lipid accumulation. Hyperinsulinemia further exacerbates hyperandrogenism by reducing hepatic SHBG production and increasing circulating free androgens.

reproductive disorders in individuals who are genetically and postnatally predisposed. Additionally, genetics may facilitate the early diagnosis of at-risk individuals, preventing the onset of reproductive and metabolic alterations associated with the syndrome, particularly in adolescents, while also identifying ways to prevent or modify prenatal programming. Future research is essential to explore the genetic interactions and epigenetic modifications resulting from the prenatal programming of PCOS. We believe that understanding how environmental factors, both pre- and postnatally, such as diet and stress, interact with genetic susceptibility will be crucial in unraveling the complex etiology of this disorder.

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Conflict of interest

The authors declare no conflict of interest.

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