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Perspective

Polycystic ovary syndrome: A metabolic disorder with therapeutic opportunities

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SUMMARY

Polycystic ovary syndrome (PCOS) is a highly prevalent endocrine disorder characterized by intertwined reproductive and metabolic abnormalities. While its causal origins remain incompletely understood, accumulating evidence suggests metabolic dysfunctions—manifested by insulin resistance, obesity, hyperglycemia, and dyslipidemia—as key contributors to the pathogenesis and progression of PCOS. Emerging interventions targeting these metabolic disturbances, including caloric restriction, GLP-1-based therapies, and bariatric surgery, have shown efficacy in alleviating PCOS symptoms and potentially blocking their inheritance. By addressing the metabolic roots and therapeutic opportunities in PCOS, this perspective highlights a critical shift in fundamentally recognizing PCOS as a metabolic disorder. The future promises more metabolic-focused research to unravel the underlying pathogenesis and develop precise, long-term strategies for managing this complex disease.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common and complex reproductive endocrine disorders in women of reproductive age, affecting an estimated 10%–13% of women worldwide.[1] PCOS poses lifelong health threats for women from adolescence to menopause and beyond, yet it is substantially understudied.[2,3] It is a heterogeneous condition characterized by hallmark signs of hyperandrogenism, ovulatory dysfunction, polycystic ovarian morphology, and/or elevated anti-Müllerian hormone (AMH).[1] Beyond its classic reproductive symptoms, the vast majority of PCOS women concurrently exhibit metabolic disturbances—notably insulin resistance, hyperinsulinemia, overweight/obesity, and dyslipidemia—facing significantly elevated risks for developing type 2 diabetes (T2D) and other metabolic diseases.[2,4,5] To make matters worse, PCOS is known to have strong genetic and epigenetic bases, with evidence of familial clustering and transgenerational transmission to both female and male offspring.[6] This inheritance nature amplifies the syndrome's long-term threats, extending its adverse effects beyond individual women to future generations.

Despite its widespread impacts, the coexistence of reproductive and metabolic abnormalities makes PCOS particularly challenging to study and manage. Over the past decade, research advances have highlighted the crucial roles of metabolic factors—such as adiposity and insulin signaling—in PCOS pathophysiology. While mounting evidence has established strong associations between metabolic dysfunction and PCOS, the field continues to grapple with a basic question: is PCOS fundamentally a metabolic disorder with reproductive consequences, an ovarian disorder with metabolic side effects, a primary endocrine disorder with both metabolic and reproductive consequences, or a combination of these pathways? Disentangling underlying relationships and identifying modifiable characteristics have an important bearing on the development of effective ways to ease long-term sequelae for this prevalent and refractory condition.

In this piece, we integrate recent genetic and experimental achievements to review the pathogenesis of PCOS from the viewpoint of metabolic regulation and discuss promising metabolic intervention strategies identified in both preclinical work and clinical trials of PCOS. Based on emerging evidence detailed in subsequent sections, we propose that metabolic dysfunction is a critical driver of PCOS development. This perspective further highlights metabolic modulation as a promising intervention avenue for managing PCOS and mitigating its inheritance burden. Through an advanced understanding of PCOS as an endocrine-metabolic disorder, we can reframe the narrative around PCOS, transforming how this complex disorder can be prevented and reversed.

METABOLIC FACTORS ASSOCIATED WITH PCOS

The bidirectional interplay between metabolic and reproductive axes in PCOS pathophysiology

Female reproductive function is closely and intricately linked to energy metabolism.[7] Reproduction represents one of the most

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energetically demanding biological processes, requiring substantial investment to support folliculogenesis, ovulation, and pregnancy.[8] Adequate energy availability is essential for maintaining reproductive competence, whereas energy imbalance can disrupt sex hormone homeostasis and impair reproductive function. Physiologically, metabolic factors impose tight control over the hypothalamus-pituitary-ovarian (HPO) axis.[9] Conversely, ovarian-derived androgens also exert important regulatory roles in energy metabolism.[10] This bidirectional interaction is especially important in the pathophysiology of PCOS, a condition characterized by the dual features of reproductive and metabolic dysfunctions.

In the development of PCOS, an increase in the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which is sensitive to energy balance, leads to hypersecretion of luteinizing hormone (LH) relative to follicle-stimulating hormone (FSH) from the pituitary gland.[11,12] Elevated LH level and LH/FSH ratio are observed in the vast majority of women with PCOS.[13] This heightened LH secretion, particularly when coupled with increased insulin levels under obesity or insulin resistance, can independently stimulate androgen production by ovarian theca cells, resulting in hyperandrogenism and follicular maturation arrest.[14,15] Studies further demonstrate that chronic overactivation of GnRH neurons is sufficient to induce key reproductive and endocrine features of PCOS, reinforcing the neuroendocrine contribution to PCOS pathogenesis.[16] Moreover, hyperinsulinemia suppresses hepatic synthesis of sex hormone-binding globulin (SHBG), further increasing the circulating free androgens.[17]

Androgen excess has been well characterized to have detrimental effects on female metabolism.[18] Excessive androgens disrupt adipocyte differentiation and promote adipocyte hypertrophy, leading to adipose tissue dysfunction of PCOS.[19] In addition, androgen excess impairs insulin signaling in key metabolic tissues such as the liver and skeletal muscle.[20,21] These effects contribute to systemic insulin resistance and form a self-reinforcing loop with hyperinsulinemia, further exacerbating the metabolic and reproductive dysfunction in PCOS. Indeed, hyperandrogenism and hyperinsulinemia are now recognized as core pathogenic factors for PCOS. Therefore, PCOS emerges from a complex interplay wherein metabolic derangements and hormonal imbalances perpetuate each other, forming a vicious circuit.

Insulin resistance in PCOS

Insulin resistance is a cornerstone metabolic abnormality in PCOS, present in approximately 60%–90% of women with the syndrome.[22] Although it can be exacerbated by a higher body mass index (BMI), insulin resistance is intrinsic to PCOS and independent of adiposity.[23,24] Non-obese women with PCOS also exhibited a higher prevalence of insulin resistance compared with non-obese healthy controls.[25] It is also noteworthy that PCOS patients with hyperandrogenism tend to have more severe insulin resistance than those with milder or non-hyperandrogenic PCOS phenotypes.[26] Genetic evidence further supports a causal role of elevated testosterone in increasing the risks of T2D and PCOS in women,[27] highlighting the interplay between hyperandrogenism and metabolic dysfunction.

The molecular mechanisms underlying insulin resistance in PCOS are still not fully elucidated, with available data suggesting unique post-receptor signaling abnormalities in insulin-responsive tissues. In skeletal muscle (which accounts for most peripheral glucose uptake), insulin-stimulated glucose disposal is substantially impaired. Myotubes from PCOS women showed decreased insulin receptor substrate-1 (IRS-1)-induced phosphatidylinositol 3-kinase (PI3K) activity and defects in the downstream AKT signaling cascade.[28] These molecular defects blunt GLUT4 translocation and glucose uptake, predisposing PCOS patients to impaired glucose tolerance. Multiple mechanisms likely contribute to this impaired insulin signaling, including reduced AMP-activated protein kinase (AMPK), defective ERK signaling response, mitochondrial dysfunction, and ectopic lipid accumulation.[29–32] Transcriptomic and epigenomic analyses further found abnormal gene expression and DNA methylation profiles in skeletal muscle from PCOS women, potentially contributing to impaired insulin signaling.[33,34]

Insulin resistance in the liver and adipose tissue is also evident in PCOS and can be directly induced by androgen excess.[21,35] Adipocytes in PCOS are often resistant to insulin's anti-lipolysis effects, leading to elevated free fatty acid flux to the liver and muscle.[10] This ectopic fat deposition and lipotoxicity further impair metabolic function and exacerbate insulin resistance. To be noted, insulin resistance in PCOS tends to be "selective"—while metabolic actions of insulin are blunted, insulin's gonadotropic effects on the HPO axis, especially ovarian theca cells, remain intact or even exaggerated. This selective insulin resistance (metabolic insulin resistance with preserved ovarian insulin sensitivity) is a distinctive feature of PCOS pathogenesis, the precise mechanisms of which require further investigation.

Obesity and adipose dysfunction in PCOS

Overweight and obesity are widely prevalent among women with PCOS. Women with PCOS tend to have larger adipocytes and a tendency toward increased visceral fat deposition, even in those with normal weight.[36,37] The presence of obesity amplifies key reproductive features of PCOS: menstrual irregularity and anovulation rates are higher in obese PCOS women, and signs of hyperandrogenism (hirsutism, acne) are often more severe.[38] From a metabolic standpoint, overweight or obese women with PCOS had higher fasting glucose, fasting insulin, insulin resistance index, and worsened lipid profiles than normal-weight PCOS subjects.[39] Obesity per se has adverse impacts on oocyte quality and female fertility, and its combination with PCOS further aggravates the reproductive outcomes in terms of pregnancy and live birth rates.[40,41] Additionally, enzymes involved in steroid metabolism within adipose can generate androgens locally.[42] Studies suggest intra-adipose testosterone production via the enzyme AKR1C3, which is widely expressed in PCOS adipose tissue and can be induced by insulin, might contribute to adipose remodeling and a pro-lipogenic profile in PCOS.[43] This active interaction of insulin and androgen creates a vicious loop where adipose tissue both responds to and produces androgens, exacerbating adverse metabolic performance in PCOS.

Beyond excess adiposity, the dysfunction of adipose tissues plays a critical role in the pathogenesis of PCOS.[44] Adipose tissues in PCOS often show signs of pathologic hypertrophy and endocrine dysfunction, including dysregulation in storage capacity and lipolysis, impaired insulin-mediated glucose transport, and altered adipokine and cytokine secretion.[45,46] Even in

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normal-weight PCOS women, subcutaneous abdominal adipose stem cells demonstrate accelerated adipogenesis and increased lipid accumulation, which correlates with systemic insulin sensitivity and androgen levels, pointing to intrinsic functional defects beyond just excess fat mass.[47] Additionally, white adipose tissues in PCOS secrete an abnormal profile of adipokines. For example, low adiponectin levels are commonly observed in PCOS, which correlates with insulin resistance.[48] Conversely, the levels of leptin, which is synthesized in adipocytes, are often elevated in PCOS in proportion to fat mass; however, high leptin does not exert the expected satiety-promoting effects, hinting at leptin resistance.[49] The imbalance of adipokines fosters an insulin-resistant, pro-inflammatory milieu characteristic of PCOS.[50] This state of low-grade chronic inflammation is closely associated with insulin resistance and hyperandrogenemia in PCOS.[51,52]

Another intriguing aspect of adipose biology in PCOS is the role of brown adipose tissue (BAT), which is responsible for thermogenesis and energy expenditure. Studies have found that BAT activity is reduced in women with PCOS, which may contribute to lower energy expenditure and a weight gain tendency in PCOS.[53] Therefore, obesity and adipose tissue dysfunction are critical features of PCOS metabolic pathologies. Excess adiposity amplifies insulin resistance and hyperandrogenemia, while intrinsic adipose tissue dysfunctions in PCOS, such as adipokine imbalance and impaired energy expenditure via BAT, further compound metabolic risk. Targeting adipose tissue health is thus critical in the management of PCOS.

Dyslipidemia in PCOS

Dyslipidemia is highly prevalent in women with PCOS, with epidemiological studies reporting abnormal lipid levels in roughly 50%–90% of patients.[54,55] The characteristic pattern is an atherogenic lipid profile marked by elevated triglycerides and low-density lipoprotein (LDL) cholesterol, along with reduced high-density lipoprotein (HDL) cholesterol, regardless of BMI.[56] Consistent with an insulin-resistant dyslipidemia, low HDL appears to be the most common lipid derangement in this population. This unfavorable lipid profile of PCOS varies by phenotype. Obesity exacerbates lipid disturbances, but PCOS-related dyslipidemia is not solely explained by excess weight. Notably, even non-obese PCOS patients have higher odds of hypertriglyceridemia and low HDL levels.[25] Androgen excess appears to be a key determinant: hyperandrogenic PCOS phenotypes tend to have higher total cholesterol and lower HDL than those without hyperandrogenism.[57] Mechanistically, insulin resistance and androgen excess act in concert to drive dyslipidemia in PCOS, possibly by increasing triglyceride synthesis, altering adipose lipolysis and muscle fatty acid oxidation, and modulating hepatic lipoprotein processing.[10] These findings reinforce that obesity and androgen status both contribute to the adverse lipid profile in PCOS.

Pancreatic β cell dysfunction and hyperinsulinemia in PCOS

Fasting hyperinsulinemia and an exaggerated insulin release after meals or glucose load are common in PCOS patients. Indeed, pancreatic β cell dysfunction is an intrinsic defect in women with PCOS that is independent of obesity.[58] Both lean and obese PCOS patients showed significantly higher basal insulin levels and greater early-phase insulin secretion after glucose stimulation compared with lean controls,[59,60] contributing to the characteristic hyperinsulinemia in PCOS. On the molecular level, androgen exposure can directly stimulate insulin hypersecretion in mouse and human pancreatic islets in an androgen receptor-dependent manner.[18,61] Over time, this chronic insulin demand on β cells, combined with oxidative injury and peripheral insulin resistance, promoted secondary β cell failure, predisposing to hyperglycemia in females.[18]

There is ongoing debate surrounding the causative relationship between hyperinsulinemia and insulin resistance in PCOS.[62] The traditional view of hyperinsulinemia is that it is the result of compensatory insulin hypersecretion in response to insulin resistance, as insulin resistance, particularly in cases of obese PCOS patients, often concurrently accompanies hyperinsulinemia. However, it should also be noted that hyperinsulinemia can precede insulin resistance in the development of PCOS. Early hyperinsulinemia without insulin resistance has been observed in lean PCOS patients, daughters of women with PCOS, and androgen-programmed animal models,[63–66] suggesting pancreatic β cell dysfunction may represent an early contributor to PCOS pathogenesis rather than a compensatory response to insulin resistance. Therefore, PCOS is characterized by a dynamic interplay of primary hyperinsulinemia and peripheral insulin resistance that eventually gives way to glucose intolerance, at least in a subset of PCOS patients. This evidence leads to the conceptual framework shift recognizing early hyperinsulinemia as a key featured defect in the pathogenesis of PCOS and related metabolic diseases,[67,68] highlighting the necessity to suppress hyperinsulinemia by targeting insulin hypersecretion.

Metabolic diseases associated with PCOS

Women with PCOS face substantially elevated risks of a spectrum of metabolic conditions. Over the last decade, an enhanced understanding of PCOS has led to its recognition as not just a reproductive disorder but also a major metabolic disorder with profound multisystem health implications. Key PCOS-associated metabolic factors are illustrated in Figure 1. This section summarizes main metabolic diseases associated with PCOS (with obesity discussed in the section obesity and adipose dysfunction in PCOS).

Diabetes

PCOS confers an earlier and markedly increased lifetime risk of glucose intolerance and T2D.[69] Longitudinal studies showed that women with PCOS have more than four times the prospective risk of developing T2D compared with age-matched controls.[4,70] They also exhibit a 2-fold higher risk of developing gestational diabetes.[71] Notably, this diabetic risk is not solely explained by obesity. PCOS appears to be an independent risk factor for T2D after adjusting for BMI.[72] Hyperandrogenic PCOS phenotypes are especially vulnerable—PCOS women with hyperandrogenism have an even greater T2D risk than those without hyperandrogenism.[72] The increased risk of T2D in hyperandrogenic PCOS phenotypes may stem from chronic insulin resistance and pancreatic β cell dysfunction. While both androgen and insulin signaling contribute to metabolic deterioration in PCOS, it remains unresolved which factor acts as the

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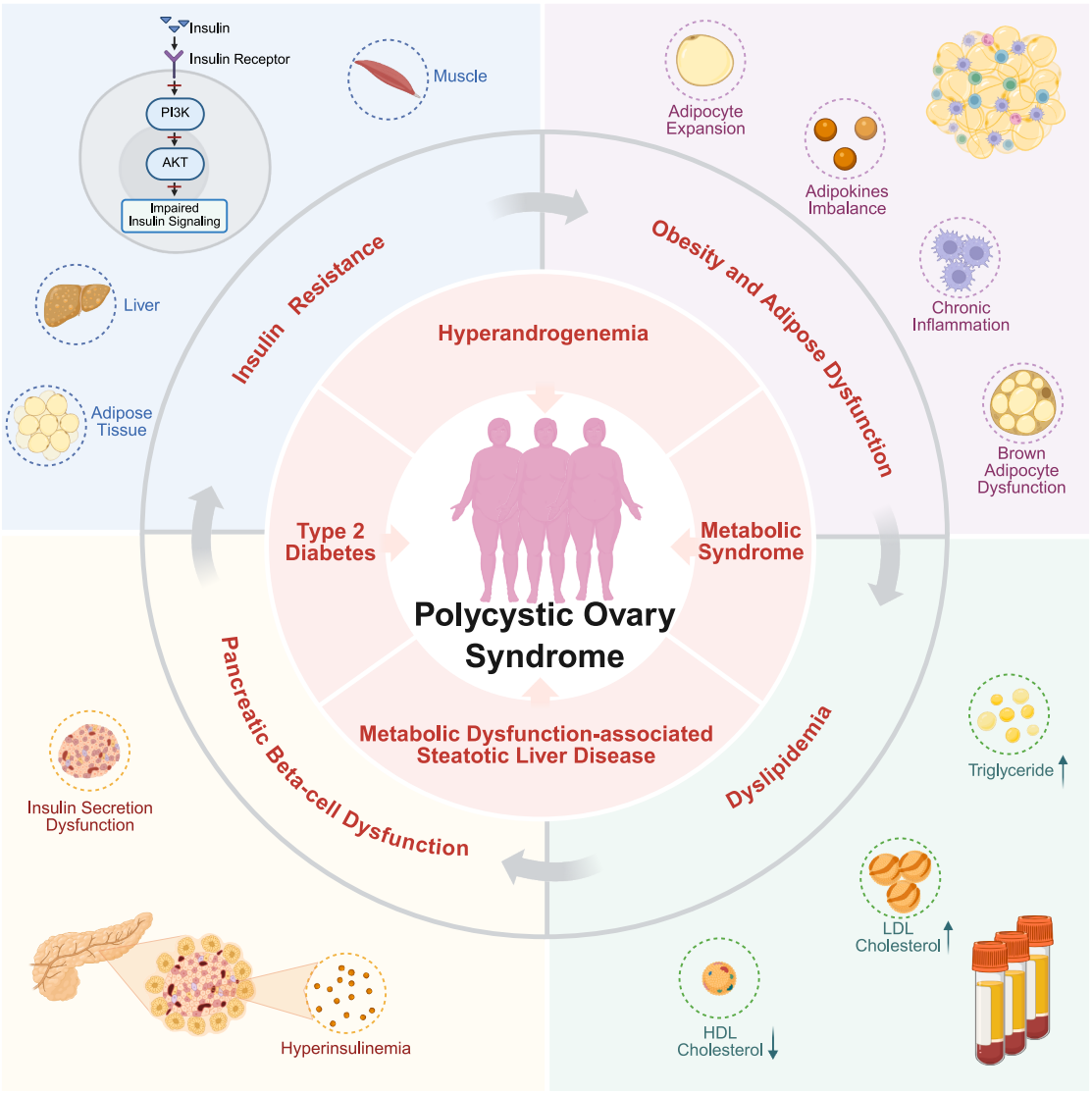

Figure 1. Metabolic factors associated with PCOS

Multiple metabolic factors and metabolic diseases are intricately associated with PCOS. These metabolic factors include insulin resistance in the muscle, liver, and adipose tissue; obesity with adipose dysfunction; dyslipidemia; pancreatic β cell dysfunction; and hyperinsulinemia. In addition, metabolic diseases such as T2D, MetS, and MASLD are closely intertwined with hyperandrogenemia, collectively contributing to the pathogenesis and clinical manifestations of PCOS.

primary driver, and a synergistic interplay between the two is likely. International evidence-based guidelines now recommend routine screening for abnormal glucose metabolism in PCOS, regardless of the patient's age or BMI.[73] Early, targeted screening and intervention are required to prevent the progression to diabetes in women affected by this syndrome.[74]

MetS

Metabolic syndrome (MetS) is diagnosed by the constellation of central obesity, high triglycerides, low HDL cholesterol, hypertension, and impaired fasting glucose. With the high incidence of abdominal obesity, insulin resistance, and dyslipidemia, it is not surprising that MetS is far more prevalent in PCOS patients, as they have common risk factors. Among women with PCOS, one-third to one-half meet these criteria for MetS.[75] The prevalence of MetS in overweight or obese PCOS patients was higher.[5] Moreover, PCOS women with MetS exhibited worse fertility, *in vitro* fertilization, and pregnancy outcomes than those without MetS.[76,77] It is therefore necessary to clinically screen PCOS patients for MetS parameters—measuring blood pressure, fasting lipid profile, and glucose parameters—to mitigate long-term risks.

MASLD

Metabolic dysfunction-associated steatotic liver disease (MASLD) describes a spectrum of liver diseases that is due to hepatic steatosis and is frequently present in women with PCOS.[78] PCOS women showed a 2- to 4-fold higher risk of MASLD, even after adjusting for BMI.[79] The risk of developing metabolic dysfunction-associated steatohepatitis (MASH), which is the advanced stage of MASLD, is also higher in reproductive-age PCOS women,[80] highlighting the large burden of these liver

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diseases in this population. Androgen excess appears to contribute to MASLD development in PCOS. PCOS patients with hyperandrogenemia have significantly higher liver fat content than those without hyperandrogenemia that is independent of obesity and insulin resistance.[81] High androgens may drive hepatic fat accumulation by increasing visceral adiposity and impairing hepatic lipid metabolism. Hyperinsulinemia in PCOS can also promote *de novo* lipogenesis in the liver, leading to hepatic steatosis.[79] Notably, the circulating level of SHBG, as a hepatokine, is decreased in fatty liver and inversely associated with T2D risk.[82] As low SHBG levels predict high androgen bioactivity, this SHBG suppression in MASLD may contribute to hyperandrogenism in PCOS, although its specific role remains understudied. Given that MASLD can progress to cirrhosis and hepatocellular carcinoma, its strong association with PCOS has raised concerns for early screening in this at-risk group.

METABOLIC ABNORMALITIES AS CAUSAL DRIVERS FOR PCOS: GENETIC, EXPERIMENTAL, AND DEVELOPMENTAL EVIDENCE

While the strong associations between PCOS and multiple metabolic factors have been well established, accumulating evidence suggests that metabolic abnormalities are not just correlates but can be causal drivers of PCOS. Studies in genetics and animal models have begun to clarify how perturbations in metabolic regulation might precipitate the reproductive and endocrine features of PCOS. In this section, we integrate key findings from recent genetic, experimental, and developmental advances that support a causal role for metabolic abnormalities in PCOS etiology.

Genetic causality between metabolic factors and PCOS

Mendelian randomization (MR) is a robust genetic approach leveraging genetic variants from genome-wide association studies (GWASs) as instrumental variables to infer causality between exposure and outcome. By targeting genetically proxied metabolic risk factors, the MR approach minimizes confounding and reverse causality, mimicking randomized controlled trials and providing reliable evidence to determine causal links between metabolic traits and PCOS. A growing body of MR-based research supports the notion that metabolic dysfunctions are not the consequences but critical contributors to PCOS etiology. These studies revealed significant causal roles for BMI, body fat, waist-to-hip ratio, T2D, MASLD, triglyceride, LDL, and HDL cholesterol in the risk of PCOS.[83–86] For example, BMI and HDL cholesterol emerged as top-ranked risk factors for PCOS in female-specific MR analyses.[83] Furthermore, genetically predicted fasting insulin—indicative of insulin resistance—was causally associated with PCOS that is independent of BMI.[84] In addition to these glucose and lipid metabolic dysregulations, excess branched-chain amino acids have also been implicated in PCOS development.[87] Importantly, these findings are unidirectional, as no significant effects of genetically predicted PCOS on the aforementioned metabolic traits were observed,[83] thereby supporting the possibility that metabolic dysfunction may act as an upstream contributor to PCOS development—at least in genetically predisposed individuals.

To be noted, excessive adiposity during childhood or adolescence significantly contributes to the risk of PCOS. Genetically determined childhood body size showed an independent effect on PCOS risk after adjusting for adult body size,[86] pinpointing an early causative role of adiposity on PCOS pathogenesis. Genetic predisposition to PCOS was also associated with higher childhood BMI and adiposity, which persisted through late adolescence.[88] Additionally, genome-wide cross-trait analysis identified positive genetic correlations between adulthood BMI, childhood BMI, and PCOS.[89] A positive overall genetic correlation between T2D and PCOS was also observed,[84] suggesting a shared genetic basis underlying obesity, T2D, and PCOS.

Another important line of evidence comes from the male phenotype of PCOS. Accumulating studies suggest that a male equivalent of PCOS exists, especially among those with a family history of PCOS.[2] A confirmative study explored the genetic risk factors for PCOS in men, showing phenotypic consequences including obesity, T2D, dyslipidemia, and marked androgenic alopecia.[90] This study suggests that ovarian function is not required for PCOS features, pointing to PCOS as a metabolic condition with manifestations in both men and women.[91] The above genetic studies provide compelling evidence to consider metabolic dysfunctions, specifically obesity, dysglycemia, and dyslipidemia, as contributing etiological factors in PCOS pathogenesis, at least in a subset of PCOS cases. These insights lay the groundwork for understanding PCOS as a metabolic disorder. Further studies are warranted to identify additional metabolic risk factors that may contribute to PCOS, allowing for a more comprehensive understanding of its metabolic underpinnings.

Functional roles of PCOS genetic susceptibility genes in metabolic regulation

PCOS is characterized by familial clustering and has a strong heritability.[92] Large-scale GWASs conducted in Han Chinese and European ancestries have identified numerous loci associated with PCOS that are extensively replicated and shared between populations,[93–97] suggesting a common genetic architecture for this condition. The susceptibility genes identified by PCOS GWAS were revealed to be important regulators for gonadotropin and androgen levels as well as ovarian function.[94,95] Intriguingly, many of these genes also play essential roles in metabolic regulation and are also implicated in metabolic diseases such as T2D and obesity (Table 1),[98–104] highlighting the metabolic etiologies of PCOS. Among these, variants in the *INSR* gene, which encodes the insulin receptor and serves as a key molecule in classic insulin signaling, are significantly associated with PCOS,[94] suggesting a genetic predisposition to insulin resistance in PCOS. Variants in *INSR* are strongly linked to hyperandrogenemia and anovulation,[105,106] two clinical diagnostic features of PCOS. Consistently, reduced expression levels of *INSR* were observed in adipose tissue and skeletal muscle of obese PCOS patients.[107] These findings provide strong support for the role of genetically programmed insulin resistance in the pathogenesis of PCOS.

Among PCOS-associated susceptibility genes, *THADA* and *TOX3* have been found to be associated with hyperglycemia and insulin resistance. PCOS-GWAS susceptibility variants in *THADA* and *TOX3* confer significant risks for MetS and insulin resistance in women with PCOS.[111] Interestingly, a risk variant for T2D had already been identified in the *THADA* gene.[108]

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Table 1. PCOS-GWAS susceptibility genes in metabolic regulation

Locus	Implicated genes	First GWAS report	Clinical associations with metabolic trait	Functional roles in metabolic regulation	References
2p21	*THADA*	Chen et al.[93]	type 2 diabetes	insulin secretion, thermogenesis	Chen et al.,[93] Zeggini et al.,[108] Zhang et al.,[109] and Moraru et al.[110]
2q34	*ERBB4*	Day et al.[95]	BMI	obesity, metabolic syndrome, hepatic lipogenesis	Day et al.,[95] Burns et al.,[97] Zhang et al.,[98] Zeng et al.,[99] and Wang et al.[100]
9q33.3	*DENND1A*	Chen et al.[93]	insulin levels, insulin resistance	–	Chen et al.,[93] Tian et al.,[111] and Li et al.[112]
12q13.2	*ERBB3*	Shi et al.[94]	type 1 diabetes, type 2 diabetes, MASLD	hepatic lipogenesis, pancreatic β cell hyperplasia in insulin resistance	Shi et al.,[94] Wang et al.,[100] Arai et al.,[101] and Törn et al.[102]
12q14.3	*HMGA2*	Shi et al.[94]	obesity, type 2 diabetes	adipogenesis	Shi et al.,[94] Ng et al.,[103] and Anand and Chada[113]
16q12.2	*FTO*	Moolhuijsen et al.[114]	obesity, BMI	adiposity, brown fat thermogenesis	Moolhuijsen et al.,[114] Wojciechowski et al.,[115] and Zhang et al.[116]
16q12.1	*TOX3*	Shi et al.[94]	insulin resistance	hepatic gluconeogenesis	Shi et al.,[94] Tian et al.,[111] and Liu et al.[117]
19p13.3	*INSR*	Shi et al.[94]	metabolic syndrome, insulin resistance	insulin signaling	Shi et al.,[94] Tian et al.,[111] and Jones et al.[107]
22q12	*CHEK2*	Tyrmi et al.[96]	type 2 diabetes	insulin secretion	Tyrmi et al.[96] and Chong et al.[104]

The implicated genes listed are those reported from PCOS GWAS and are associated with energy metabolism.

Functional studies further identified that THADA maintains insulin secretion and functional β cell mass through regulating β cell calcium homeostasis and endoplasmic reticulum stress-induced apoptosis.[109] The dysregulation of THADA could thus lead to impaired β cell function and hyperglycemia. Additionally, the PCOS susceptibility gene *TOX3* has been shown to control hepatic gluconeogenesis and insulin sensitivity via activating hepatic transcriptional programs.[117] Dysregulation of TOX3 exacerbates insulin resistance and glucose intolerance, mechanisms central to both T2D and PCOS pathogenesis. The functional roles of these susceptibility genes connect glucose metabolic pathways to PCOS pathogenesis.

The PCOS susceptibility gene *THADA* has also been found to modulate energy storage and thermogenesis balance in *Drosophila*,[110] linking it to obesity and adipose metabolic dysfunction. Another PCOS susceptibility gene, *HMGA2*, plays a crucial role in adipogenesis and diet-induced obesity.[113] More recent GWAS meta-analyses have expanded the list of PCOS loci and reinforced their influence on both reproductive and metabolic pathways. For example, one study has identified *FTO* as a novel PCOS susceptibility gene,[114] the genotype of which was strongly associated with obesity in PCOS.[115] *FTO* is a key regulator of brown adipocyte thermogenesis and energy expenditure, and its dysfunction contributes to diet-induced obesity.[116] Interestingly, *FTO* also plays regulatory roles in mouse oocyte and embryonic development as well as granulosa cell function,[118,119] bridging metabolic and reproductive phenotypes. The pleiotropic roles of these PCOS susceptibility genes in glucose and lipid metabolism further support the idea that metabolic disturbances confer risks for PCOS in susceptible individuals, corroborating their contribution to the development of PCOS from a genetic perspective.

As PCOS phenotypes are heterogeneous, refined clinical clustering of PCOS has allowed for its classification into metabolic and reproductive subtypes.[120] Genetic studies revealed that the metabolic subtype of PCOS exhibits a distinct genetic architecture, characterized by loci associated with insulin resistance, lipid dysregulation, and obesity.[121] This genetic distinction provides additional evidence supporting the hypothesis that metabolic abnormalities represent a pivotal etiological driver in PCOS. In summary, human genetic evidence strongly links metabolic dysfunction to PCOS predisposition.

Metabolic animal models of PCOS

PCOS-like animal models induced by androgen excess at prenatal, peripubertal, and adult stages have been extensively characterized, each exhibiting varying degrees of reproductive and metabolic features.[122,123] Beyond these hyperandrogenic models, elevated AMH exposure has also been shown to recapitulate hallmark neuroendocrine and metabolic features of PCOS, including increased adiposity, hyperinsulinemia, impaired glucose tolerance, and insulin resistance.[124,125] While these models support the pathogenic roles of androgen and AMH excess, animal models that directly induce metabolic disturbances have further enabled testing of whether metabolic dysfunction alone is sufficient to trigger PCOS-like phenotypes. A variety of such metabolic models have been developed, and they reinforce the causal role of metabolic aberrations in the pathogenesis of PCOS. Studies in mice demonstrate that chronic administration of a high-fat and high-sucrose diet

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induced PCOS-like reproductive phenotypes in females, including hyperandrogenism and impaired folliculogenesis, as well as led to adiposity and insulin resistance.[126] The female Goto-Kakizaki (GK) rat, which is a typical spontaneous T2D model marked by hyperglycemia and insulin resistance, also exhibited hallmark PCOS traits such as anovulation, hyperandrogenism, and polycystic morphology.[127] Comparisons between the above rodent models and clinical parameters of women with PCOS revealed consistent reproductive signatures.[126,127] Moreover, chronic obesogenic western-style diet administration initiating at puberty induced PCOS-like polycystic morphology in rhesus macaque females, which further worsened the reproductive dysfunction and infertility in the presence of hyperandrogenemia.[128–130] The metabolic and reproductive abnormalities in these animals closely replicate the main characteristics in human PCOS, further validating that diet-induced energy excesses are critical pathogenic drivers for PCOS.

Studies in knockout mouse models provide compelling evidence for the role of metabolic dysfunction in the pathogenesis of PCOS. Deletion of the insulin receptor in ovarian theca cells was effective to correct the hyperandrogenism and infertility in female mice, corroborating the pathogenic role of insulin signaling on ovarian function.[15] The hypothalamic kisspeptin neurons, which control GnRH release and serve as the central governor for reproductive function, are also subjected to the regulation of metabolic factors.[131] Female mice with neuron-specific insulin receptor deletion exhibited impaired ovarian follicle maturation due to dysregulated LH release.[132] Moreover, combined disruption of insulin and leptin signaling in hypothalamic neurons can induce a PCOS-like phenotype,[133] illustrating the role of central metabolic sensing in reproductive homeostasis. In addition to insulin-related pathways, androgen signaling is also a critical regulator of reproductive and metabolic features in PCOS. Notably, knockout of the androgen receptor specifically in the brain or adipose tissue reverses PCOS-like phenotypes in androgen-exposed mice, restoring ovulatory function, improving insulin sensitivity, and reducing adiposity.[134,135] These findings support the view that disturbances in metabolic signaling—whether through insulin or androgen pathways—can perturb reproductive and systemic homeostasis, tipping the balance toward a PCOS-like state. Insulin and androgen pathways appear to engage in a tightly coupled feedback loop, contributing collectively to the heterogeneous clinical manifestations observed in women with PCOS. Further dissecting the molecular and temporal interactions between these pathways will be essential to fully understand PCOS etiology.

Developmental programming of PCOS

During the last decade, strong clinical associations have been established between childhood obesity and the predisposition to PCOS, with those mothers having obesity exhibiting a higher risk of later PCOS.[86,136–138] Evidence from GK rats suggests that metabolic dysregulation during fetal life, especially maternal intrauterine hyperglycemia and hyperandrogenism, programs reproductive and metabolic impairments that manifest in puberty and adulthood.[127] These observations align well with the concept of developmental origins of health and disease (DOHaD), suggesting that adverse maternal environments during the early developmental stage prime later onset of PCOS.

Accumulating evidence from studies on PCOS offspring strongly supports the theory that PCOS susceptibility is shaped by developmental and transgenerational metabolic programming, as illustrated in Figure 2. A breakthrough study by Risal et al. in 2019 provided the first evidence for transgenerational inheritance of PCOS.[139] They found that daughters born to mothers with PCOS display a 5-fold-increased risk of developing the syndrome. More importantly, in mouse models prenatally exposed to androgen and obesity, PCOS-like reproductive and metabolic features can be transmitted across three generations (from F1 to F3) in female offspring, which exhibited impaired energy balance, including adiposity and liver lipid accumulation.[139] A pioneering study by Tata et al. demonstrated that prenatal exposure to high AMH was sufficient to reprogram the fetus and induce PCOS-like phenotypes in female offspring.[124] This prenatal AMH model provided further transgenerational evidence that PCOS reproductive and metabolic traits can be passed down to the third generation via epigenetic modifications.[125] Building on this, Cotellessa et al. introduced the mini-AMH model, showing that exposure to high AMH during minipuberty—a critical postnatal window for HPO axis maturation—can similarly lead to long-term reproductive and metabolic abnormalities in female mice.[140] These studies provide robust evidence that both prenatal and early postnatal hormonal milieus contribute to the developmental programming of PCOS. By employing *in vitro* fertilization-embryo transfer and surrogacy, the most recent progress from our team substantiated that this transgenerational inheritance of PCOS was mediated by oocytes that were independent of intrauterine exposure.[141] These findings are in agreement with previous studies showing transmission of PCOS traits through altered DNA methylation landscape.[125,139] Specifically, DNA methylation changes in PCOS oocytes and embryos predominantly affect genes involved in metabolic pathways,[139,141] thus establishing a clear mechanistic link between epigenetic inheritance and transgenerational PCOS transmission. This compelling evidence echoes the DOHaD theory and supports the developmental origins of PCOS, where an adverse maternal environment—excess androgen, AMH, obesity, or diabetes—can rewire the metabolic and reproductive axis toward PCOS in offspring.

The adverse metabolic programming associated with maternal PCOS is not confined to female offspring. Recent data have expanded the understanding of PCOS, demonstrating transgenerational inheritance of reproductive and metabolic dysfunctions in the male lineage. Sons born to mothers with PCOS display elevated risks for obesity, dyslipidemia, and pancreatic β cell dysfunction.[112,142,143] Mouse models replicating maternal hyperandrogenism as well as high AMH during minipuberty revealed that metabolic dysfunctions, including glucose intolerance, abnormal insulin release, and insulin resistance, were also observed in males,[140,143] supporting the existence of a male metabolic phenotype of PCOS. Consistent alterations of small non-coding RNAs and DNA methylation were observed in sperm from offspring mice and blood from sons with PCOS mothers, suggesting conserved epigenetic mechanisms underlying male germline transmission of PCOS-associated metabolic dysfunction.[142,143] The observations from both female and male offspring lineages collectively demonstrate that PCOS exhibits transgenerational developmental origins that are mediated by germ cell epigenetic inheritance. These

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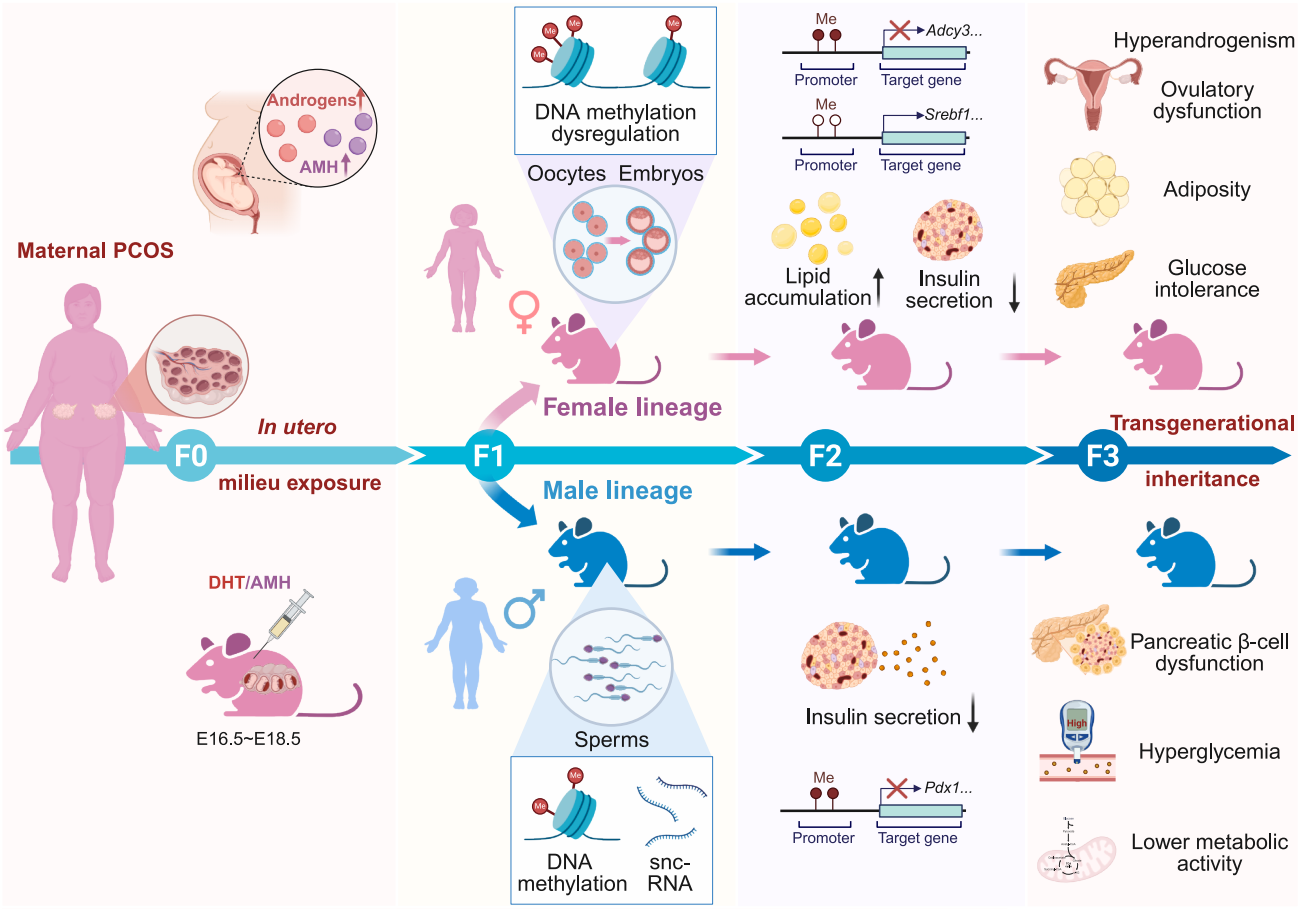

Figure 2. Transgenerational epigenetic inheritance of PCOS in female and male offspring

PCOS exhibits developmental origins and transgenerational inheritance, with metabolic and reproductive dysfunctions transmitted through both female and male lineages. In mouse models exposed to androgen or AMH excess *in utero*, metabolic phenotypes—including adiposity, hyperglycemia, glucose intolerance, and impaired insulin secretion—persist across three generations (F1–F3) via maternal and paternal germlines independently. This inheritance is mediated through epigenetic alterations, specifically DNA methylation dysregulation in oocytes and DNA methylation/small non-coding RNA (sncRNA) changes in sperm. Abnormal methylation of insulin secretion-related genes appears conserved across offspring sexes. These epigenetic abnormalities impair offspring metabolic functions and predispose them to future disease risks.

"epigenetic memories" in the metabolic pathway are responsible for transmitting PCOS-like traits to future generations and shaping disease susceptibility in both sexes. The sustained metabolic traits across multiple generations further suggest that metabolic disturbances may play a fundamental role in PCOS onset from an early stage.

Taken together, evidence from genetic studies, clinical observations, and experimental animal models collectively indicates that metabolic dysfunction—characterized by obesity, insulin resistance, hyperglycemia, and dyslipidemia—plays a pivotal role in the development and progression of PCOS (Figure 3). Notably, altered sex steroids, particularly androgen and AMH excess, also contribute to these metabolic disturbances. Both metabolic and endocrine derangements are tightly interconnected and synergistically drive the heterogeneous clinical features of PCOS, although their causal hierarchy remains incompletely resolved. The multi-generational transmission of the syndrome further highlights the urgency for early interventions, which may reset developmental programming and break the transgenerational cycle of PCOS.

METABOLIC INTERVENTIONS FOR PCOS: A PROMISING FRONTIER

Given the critical role of metabolic dysfunction in PCOS, therapies targeting metabolic disturbances have gained prominence as strategies to prevent and even reverse aspects of the syndrome. Traditional treatments for PCOS have often focused on managing reproductive symptoms, yet they do not address the underlying metabolic issues. In recent years, a "metabolic approach" to PCOS has been recognized as a promising frontier, spanning lifestyle dietary modifications, metabolic-targeting medications, and even metabolic surgery. Here we summarize key metabolic intervention strategies and the evidence supporting their efficacy in PCOS management (Figure 3).

CR

Dietary interventions targeting impaired energy metabolism have shown remarkable potential in mitigating key PCOS reproductive symptoms.[144] Recent studies further highlight caloric restriction (CR) as an effective dietary intervention strategy not only for

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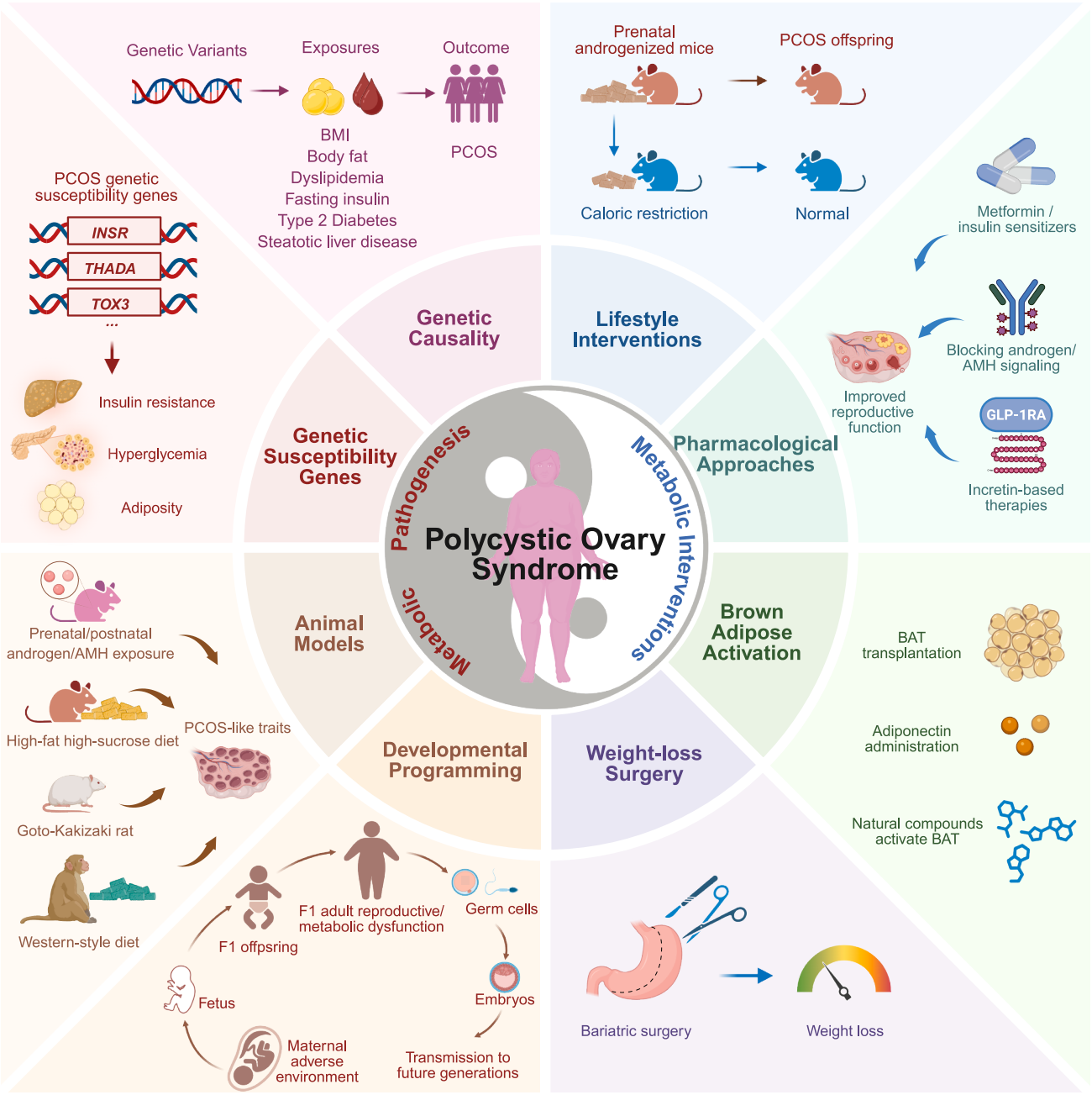

Figure 3. Metabolic dysfunctions as contributing factors and intervention targets for PCOS

Evidence from genetic causality analyses, functional roles of genetic susceptibility genes, animal models, and developmental programming studies collectively suggests that metabolic dysfunctions contribute to the development of PCOS. Targeted metabolic interventions—including CR, pharmacological approaches (e.g., metformin and GLP-1RA), brown adipose activation, and weight-loss surgery—show therapeutic promise in alleviating PCOS symptoms and blocking its inheritance. BMI, body mass index; BAT, brown adipose tissue; GLP-1RA, GLP-1 receptor agonist.

alleviating PCOS symptoms but also for preventing their inheritance to offspring.[141] In mouse models of PCOS induced by prenatal androgen exposure, maternal CR showed the potential to restore the aberrant DNA methylation in oocytes and offspring metabolic tissues, specifically targeting genes involved in insulin secretion and AMPK signaling pathways,[141] both of which play central roles in maintaining glucose homeostasis and energy balance. The restored DNA methylation by maternal CR effectively prevented metabolic and reproductive dysfunctions passing on to female offspring. Moreover, these benefits of CR were further validated in embryos from women with PCOS. These findings underscore the epigenetic plasticity of PCOS and suggest that preconception metabolic modification can prevent the transmission of PCOS in successive generations.

Interestingly, CR's impacts extend beyond maternal inheritance of PCOS. Male offspring from androgen-exposed mothers

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also demonstrated improved glucose metabolism following CR intervention, which further blocked the male-lineage inheritance of metabolic abnormalities.[143] These improvements were attributed to restored DNA methylation in sperm of prenatal androgenized mice, leading to corrected expression of genes critical for pancreatic β cell function. The normalization of these aberrant DNA methylations prevented the transmission of hyperglycemia and impaired insulin secretion to subsequent generations, highlighting the potential of CR to block inheritance of PCOS-related traits in both female and male offspring. A particularly intriguing discovery is that CR targets the shared insulin secretion pathway to correct DNA methylation aberrations in germ cells from both maternal and paternal lineages.[141,143] This suggests that insulin secretion dysfunction is critical for the pathogenesis and inheritance of PCOS. By restoring normal insulin signaling, CR offers a mechanism to mitigate energy surplus and reset metabolic programming, thus preventing the transmission of PCOS-related traits to future generations. These findings highlight the tremendous potential of CR in reversing PCOS features and breaking its cycle of inheritance.

The ability of CR to remodel DNA methylation patterns in both oocytes and sperm provides compelling evidence that preconception metabolic modulations can reset the developmental programming of PCOS, establishing a strong scientific foundation for translating CR-based metabolic interventions into clinical applications. In line with these animal model findings, clinical randomized controlled trials have shown that weight loss of 5%–10% was able to restore spontaneous ovulation and menstrual regularity in women with PCOS, along with reduced serum testosterone and free androgen index, improved insulin sensitivity, and improved lipid profiles.[145–147] These clinical benefits have informed international guidelines to recommend lifestyle interventions (diet plus exercise) as first-line therapy for overweight or obese PCOS.[1] Future studies should explore whether similar effects can be achieved through tailored dietary regimens or pharmacological approaches that mimic the beneficial effects of CR.

Other metabolic-modifying dietary strategies

Ketogenic diets, which are very low in carbohydrates and high in fats, have garnered interest as a metabolic therapy for PCOS. By drastically reducing dietary carbohydrates and shifting metabolism toward ketone production, ketogenic diets often produce rapid weight loss and robustly lower insulin levels, which can be particularly advantageous in PCOS. Several clinical trials have shown the beneficial effects of ketogenic diets on overweight/obese women with PCOS. An 8- to 12-week ketogenic diet significantly reduced blood androgen and LH levels and decreased body weight and fat mass, as well as improved insulin resistance in PCOS subjects.[148,149] A randomized controlled trial compared a 16-week very-low-calorie ketogenic diet to a standard low-calorie diet in obese PCOS women. The ketogenic approach yielded greater visceral fat loss and significantly better improvements in hyperandrogenemia and ovulatory function.[150] This suggests that beyond equal-calorie dieting, a ketogenic diet may confer added endocrine benefits. Despite these promising outcomes, ketogenic diets must be approached carefully. More research is needed on long-term adherence and safety (e.g., effects on lipid profiles or nutrient status).

Intermittent fasting

Intermittent fasting approaches aim to leverage metabolic benefits of fasting, such as increased fat oxidation, which could counteract PCOS-related metabolic disturbances. Time-restricted eating—confining food intake to a limited window each day without necessarily reducing calorie intake—has emerged as a promising strategy to improve insulin sensitivity and combat obesity.[151] Clinical trials suggested women with PCOS could also benefit from time-restricted eating, which showed significant improvements in menstrual cycle regularity and hyperandrogenemia, alongside a comprehensively improved metabolic profile.[152] While larger clinical trials are needed, time-restricted eating could be a feasible lifestyle intervention for PCOS women who find continuous calorie counting challenging. Other intermittent fasting paradigms (e.g., 5:2 diets or alternate-day fasting) warrant further study in PCOS, as broadly improved insulin sensitivity and weight loss in MetS populations have been observed.

Pharmacological approaches

Metformin and other insulin sensitizers

Insulin-sensitizing therapies form a cornerstone of pharmacological management in PCOS. Metformin represents the most widely used drug due to its efficacy in improving metabolic and reproductive outcomes and its favorable safety and cost profile, which has been extensively studied in PCOS patients.[153] A meta-analysis of randomized controlled trials showed that metformin exerted superior effects on testosterone, free androgen index, and SHBG levels when combined with oral contraceptive pills in women with PCOS.[154] Recent studies further identify the efficacy of metformin in restoring endometrial health in PCOS patients and further blocking inheritance of PCOS-related traits, fueling the role of its long-term beneficial effects.[143,155] Beyond metformin, other thiazolidinediones, such as pioglitazone and rosiglitazone, working on enhancing insulin sensitivity, also conferred clinical benefits for PCOS.[156] Although due to their side effects, thiazolidinediones are not routinely used in PCOS, these clinical trials are still instructive in highlighting insulin resistance as a key druggable pathway. Additionally, other agents with insulin-sensitizing or metabolic actions, such as orlistat (a lipase inhibitor reducing lipid absorption), berberine (an AMPK activator), and resveratrol (sirtuins and mitochondrial function activator), have also shown promise in PCOS.

Incretin-based therapies

The cutting-edge incretin-based therapies have been used beyond glucose control and weight loss and are emerging as powerful pharmacological approaches for managing PCOS. A landmark randomized trial revealed that the GLP-1 receptor agonist liraglutide exerted beneficial roles in reducing body weight and ameliorating ovarian dysfunction in PCOS women with obesity.[157] Further clinical trials reported substantially superior weight loss with GLP-1 agonists compared with metformin or diet, along with additional metabolic and reproductive benefits for PCOS.[158,159] It is noteworthy that the reproductive benefits of GLP-1 agonists in PCOS appear largely secondary to weight loss, as the improvement in menstrual regularity of PCOS women was proportional to the weight lost.[160] This suggests that losing fat—especially visceral fat—rather than a direct action of GLP-1 on ovaries may be the key mediator. Beyond GLP-1 analogs, the newer dual incretin agonists (such as tirzepatide, a GLP-1/GIP

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dual agonist) produce even greater weight loss in obesity clinical trials.[161] Although formal studies in PCOS are pending, these agents hold great potential to reverse the obesity-insulin resistance axis in PCOS to a remarkable degree. Therefore, incretin-based drugs provide a powerful tool to tackle the obesity and insulin resistance of PCOS.[162] Their role in PCOS management is expanding, and ongoing clinical studies may solidify their place. The weight loss achievable with GLP-1 drugs opens a new avenue in PCOS management, offering a unique opportunity to improve both fertility and metabolic health.

Androgen and AMH pathway blockade therapies

Hormonal signaling pathways have emerged as promising targets for the prevention and treatment of PCOS. Anti-androgen therapy, such as the use of androgen receptor antagonists (e.g., flutamide), has demonstrated efficacy in improving PCOS-like phenotypes in animal models by reversing the reproductive and metabolic dysfunctions.[163] In parallel, the AMH pathway has garnered attention as both a biomarker and a potential driver of PCOS pathophysiology. A recent study developed a monoclonal antibody that selectively targets AMH receptor 2 (AMHR2), enabling precise blockade of AMH signaling.[140] Administration of this AMHR2-neutralizing antibody during mini-puberty effectively prevented the development of PCOS-like reproductive and metabolic cardinal defects in adult mice. Therapeutic administration of this AMHR2 antibody in adulthood also alleviated established PCOS phenotypes.[140] While the optimal timing and clinical applicability of these endocrine interventions remain to be defined, these findings highlight the translational promise of targeting androgen and AMH signaling pathways for the prevention and treatment of PCOS.

BAT activation

Emerging evidence suggests that BAT activation may serve as a promising metabolic intervention for PCOS. Studies in rodent models have demonstrated that BAT transplantation can effectively reverse PCOS phenotypes, including hyperandrogenism, anovulation, and polycystic ovarian morphology.[164] Interestingly, BAT transplantation led to increased circulating levels of adiponectin, a key regulator of ovarian physiology and whole-body energy metabolism. Consistent with this finding, direct administration of adiponectin similarly rescued PCOS traits, suggesting that BAT-mediated adiponectin signaling may play a crucial role in alleviating PCOS symptoms.[164] Further supporting the role of BAT in PCOS treatment, pharmacological activators of BAT, including ginsenoside compound K and rutin, both are natural bioactive compounds, significantly activated BAT and ameliorated PCOS symptoms.[165,166] Ginsenoside compound K treatment restored estrous cyclicity, normalized ovarian steroidogenic enzyme expression, and reduced the number of cystic follicles.[165] Given these benefits, BAT activation represents a promising metabolic intervention that targets both systemic energy expenditure and ovarian function. Strategies to enhance BAT activity—whether through transplantation, pharmacological activators, or lifestyle interventions—warrant further investigation as potential therapeutic approaches for PCOS.

Weight-loss surgery

Bariatric surgery, a proven weight-loss treatment for severe obesity, holds great promise for PCOS management. In a prospective trial comparing the efficacy between drugs and bariatric surgery for women with PCOS and obesity, bariatric surgery yielded a higher complete remission rate in these patients, with the endpoint BMI being the major contributing factor.[167] The BAMBINI trial is the first randomized controlled trial demonstrating that vertical sleeve gastrectomy increased spontaneous ovulation rates and improved metabolic profiles in women with PCOS and obesity, outperforming lifestyle and pharmacological (metformin and/or orlistat) interventions.[168] Despite higher complication rates, the profound benefits in improving reproductive and metabolic outcomes position bariatric surgery as a prioritized option for severe obesity and refractory PCOS. Given the highly effective and sustained weight reduction after bariatric procedures, it directly addresses the driving factor of obesity in PCOS. The magnitude of these changes often exceeds what is achievable with medication alone. Future research should continue to follow post-bariatric PCOS patients to confirm long-term benefits. As the epidemic of obesity intersects with PCOS, metabolic surgery may play an increasing role in the therapeutic landscape.

OPENING QUESTIONS AND DIRECTIONS FOR FUTURE RESEARCH

The advances in metabolic underpinnings and interventions for PCOS highlight how far we have come in addressing this complex condition. These findings substantiate that PCOS is not only a reproductive disease but is indeed a metabolic disorder, offering a transformative lens through which this disorder can be understood and treated. By targeting the metabolic roots of PCOS, we have an unprecedented opportunity to tailor interventions that not only alleviate its symptoms but also disrupt the cycle of its inheritance. Therefore, metabolic dysfunction in PCOS acts analogously to the Yin-Yang duality of Tai Chi, serving both as a fundamental factor driving its pathogenesis and as a targetable pathway for effective prevention and therapies (Figure 3). At present, PCOS research stands at the crossroads of pressing challenges and promising opportunities. As we look ahead, several opening questions emerge regarding how we define and manage this syndrome.

The fundamental etiological question—is PCOS initiated by reproductive/ovarian defects or metabolic dysfunction (or varying combinations in different patients)?—remains open. As reviewed, existing evidence suggests a plethora of metabolic factors, such as obesity and insulin resistance, can cause PCOS features, yet PCOS also occurs in lean women with seemingly primary ovarian or neuroendocrine abnormalities. This phenotypic and biological heterogeneity indicates the need to shift away from considering it as merely a reproductive disease to raising awareness of its broader implications. It is likely that PCOS in nature is an umbrella diagnosis for reproductive and metabolic derangements. Future research needs to disentangle distinct PCOS subtypes, identify specific causal pathways, and follow up their respective long-term outcomes. Advanced multi-omics (e.g., genomics, proteomics, and metabolomics) in large PCOS cohorts could help define distinct molecular signatures and biomarkers, which will facilitate the development of precision therapeutic strategies.

A deeper understanding of PCOS pathogenesis from genetic, environmental, mechanistic, and clinical avenues is urgently

needed. Although results from PCOS genetic studies have yielded important insights into its reproductive and metabolic pathways, the genetic basis of PCOS remains largely unresolved given its high heritability. It also remains unclear whether PCOS's origins lie in specific pathways, tissues, or cell types in genetically predisposed individuals. Moreover, identifying the specific genes involved and elucidating their functional significance are still crucial challenges for decoding the biological mechanisms of PCOS and translating these findings into clinical application. Additionally, certain environmental contributions, such as how *in utero* exposure leads to germ cell epigenetic reprogramming in PCOS, warrant further study. In view of the transgenerational effects and developmental programming of PCOS, future research should explore early-life determinants that set the stage for later PCOS-related risk. Such mechanistic insights will lay the groundwork to inform PCOS management. Advancing our understanding of how genetic, environmental, and epigenetic factors intersect in metabolism and reproduction will pave the way for more precise preventive and therapeutic strategies for women with PCOS.

While CR has demonstrated potential as a promising strategy for reversing PCOS and preventing its transmission to offspring, rigorous clinical studies are needed to bridge these findings from animal models to clinical patients. Future research should explore whether other lifestyle metabolic adjustments, such as intermittent fasting, tailored macronutrient compositions, or structured exercise programs, can achieve similar benefits. These lifestyle intervention strategies could expand current therapeutic avenues and address the unmet needs in PCOS first-line treatment. Furthermore, building on the transgenerational epigenetic discoveries, medication therapies targeting at reversing key epigenetic marks may loom on the horizon for PCOS management.

Looking forward, we anticipate new classes of medications (e.g., dual/triple incretin agonists, advanced insulin sensitizers, and natural Chinese medicine products) will be tested in PCOS. The roles of innovative pharmacotherapies and metabolic surgeries in managing PCOS traits and their inheritance should be a priority for investigation, especially assessing their long-term reproductive and metabolic outcomes. Currently, dramatic weight loss by bariatric surgery confers substantial benefits for obese PCOS, but the challenge lies in combating weight regain. How this affects PCOS in the long run is still unknown. Addressing the sustainability of metabolic therapy outcomes is critical for PCOS, given its lifelong burden from adolescence to post-menopause. Large-scale and well-designed clinical trials are essential to translate these insights into evidence-based guidelines, ensuring that metabolic interventions become integral to PCOS management.

Despite the current gaps in our knowledge, recognizing metabolic dysfunction as a cornerstone in PCOS pathogenesis represents a significant leap forward. Targeting these metabolic pathways offers a strategic opportunity to advance precision prevention and treatment for this prevalent complex disorder, providing hope for women affected by this condition and safeguarding the health of future generations. While our understanding of PCOS remains in its infancy, the strides made thus far lay a solid foundation for transforming PCOS management through the lens of metabolic regulation.

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AUTHOR CONTRIBUTIONS

Y.Z., Z.-J.C., and H.Z. conceptualized the work. Y.Z. wrote the manuscript and drafted figures. Z.-J.C. and H.Z. supervised the work, provided guidance during the writing process, and revised the manuscript. All authors read and approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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