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REVIEW ARTICLE

Revisiting metformin in polycystic ovary syndrome: A multifaceted therapeutic approach beyond glycemic control

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is a multifaceted endocrine condition that impacts women of reproductive age, distinguished by hyperandrogenism, anovulation, insulin resistance, and persistent low-grade inflammation. Current treatments largely address individual symptoms without modifying the disease's underlying pathophysiology, leading to suboptimal long-term outcomes. This comprehensive review highlights the evolving role of metformin a traditional insulin sensitizer in PCOS management, beyond its established glycemic effects. Recent studies reveal metformin's multifaceted actions, including modulation of ovarian steroidogenesis, improvement of mitochondrial function, reduction of oxidative stress, enhancement of adipose browning, correction of dyslipidemia via the adenosine monophosphate-activated protein kinase (AMPK)–sterol regulatory element-binding protein-1c (SREBP-1c) pathway, and anti-inflammatory effects through the gut–ovary–immune axis. Additionally, metformin demonstrates promising synergy with agents like glucagon-like peptide-1 (GLP-1) receptor agonists, offering superior metabolic and reproductive outcomes. By integrating clinical evidence with emerging molecular insights, this review positions metformin as a cornerstone therapy capable of addressing both metabolic and reproductive disturbances in PCOS. It also underscores the need for future personalized strategies combining metformin with novel targeted therapies to achieve more sustainable disease control.

KEYWORDS

Polycystic Ovary Syndrome (PCOS); Metformin; Insulin resistance; Hyperandrogenism; Mitochondrial function

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women and remains a complex condition for both clinicians and researchers [1]. The WHO estimates that 6–13% of women of reproductive age are affected, while up to 70% may remain undiagnosed. The prevalence and severity of associated metabolic complications can also differ among ethnic populations [2]. Symptoms usually develop during the reproductive years and may include irregular menstrual cycles, excessive hair growth, acne, hyperinsulinemia, and other manifestations of hyperandrogenism. Metabolic abnormalities, particularly insulin resistance and obesity, are reported in a substantial proportion of women with PCOS. The condition is also an important contributor to female reproductive difficulties. Early recognition and appropriate management are therefore important for reducing both reproductive and metabolic complications. Although the precise cause of PCOS has not been fully established, genetic predisposition and environmental influences are thought to contribute to its development. Evidence of familial susceptibility has also been reported among first-degree relatives of affected individuals. Despite extensive research, the underlying mechanisms and diagnostic aspects of PCOS continue to be investigated [3].

Treatment of PCOS focuses on managing hyperandrogenism, regulating menstrual cycles, preventing endometrial hyperplasia and carcinoma, restoring ovulation when pregnancy is desired, and reducing long-term metabolic risks [4]. Lifestyle modification, including a balanced diet, regular physical activity, and appropriate weight management, remains an important part of treatment. Combined oral contraceptives are commonly used to manage menstrual irregularities and hyperandrogenic symptoms, while antiandrogens may be added when required. For women planning pregnancy, ovulation induction may be achieved using agents such as clomiphene citrate, letrozole, or gonadotropins. In vitro fertilization may be considered when other treatment approaches are unsuccessful [5].

Despite the range of available therapies, effective long-term management of PCOS remains difficult because many treatments primarily target individual symptoms rather than the interconnected metabolic and reproductive abnormalities of the disorder. As a result, treatment responses may be incomplete or may diminish after discontinuation. Long-term adherence to lifestyle interventions can also be challenging, which may reduce their overall effectiveness [6]. Pharmacological treatments, including oral contraceptives, antiandrogens, and ovulation-inducing agents, may also be associated with limitations and adverse effects. Ovulation induction can require careful monitoring and may involve invasive procedures, while conventional treatments may not fully address the broader metabolic and psychological burden of PCOS. Insulin resistance, dyslipidemia, obesity, and increased cardiovascular risk remain important concerns, while anxiety, depression, and reduced quality of life are also frequently associated with the condition [7]. In addition, long-term evidence regarding the effectiveness and safety of available treatments and their ability to influence disease progression remains limited.

These challenges highlight the need for treatment strategies that address the broader metabolic and reproductive abnormalities associated with PCOS rather than focusing only on individual symptoms. An effective approach should consider metabolic health, reproductive function, and psychological well-being while also supporting long-term adherence and improved clinical outcomes.

Metformin is an insulin-sensitizing drug widely used in the treatment of type 2 diabetes and has been extensively studied as a therapeutic option for PCOS. Evidence indicates that it can provide benefits across several clinical features of the

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disorder [8]. By improving insulin sensitivity, metformin may reduce circulating androgen levels and support the restoration of menstrual regularity. It may be particularly useful in women with insulin resistance or other metabolic abnormalities and is often used in combination with other treatment approaches [9]. Although metformin has been used in PCOS for many years, recent research has increased interest in its combination with newer therapeutic agents. For example, treatment combining metformin with GLP-1 receptor agonists such as liraglutide has shown greater improvements in weight reduction, insulin sensitivity, and ovulatory function than either treatment alone in selected patient groups. These findings support the use of metformin as part of a broader and more individualized approach to PCOS management. Therefore, this review examines the evolving therapeutic role of metformin, including its potential combination with newer pharmacological approaches, in the management of PCOS [10].

Methodology

A literature search was conducted using Web of Science, Scopus, PubMed, PubMed Prime, Cochrane Library, ScienceDirect, and Google Scholar. The review focused on recent studies examining the therapeutic role of metformin in PCOS, particularly its potential effects beyond insulin sensitization. The initial search yielded 350 publications, of which 190 studies were selected for inclusion after screening and assessment.

Inclusion criteria

1. Studies evaluating the therapeutic use of metformin in PCOS, including metabolic, reproductive, and combination therapies.

2. Studies investigating the molecular mechanisms of metformin in PCOS through in vitro, in vivo, or clinical research.

3. Peer-reviewed research articles and clinical trials reporting experimental, molecular, or pharmacological findings.

4. Studies published in English.

5. Research published within the previous 10–15 years to reflect recent developments in metformin therapy for PCOS.

6. Studies assessing the safety, efficacy, or therapeutic potential of metformin as monotherapy or in combination with other drugs for PCOS.

Exclusion criteria

1. Studies investigating metformin for conditions unrelated to PCOS or outside the reproductive and metabolic aspects of the disorder.

2. Non-peer-reviewed publications, including conference abstracts, editorials, and opinion articles, unless they contained substantial original data.

3. Articles published in languages other than English without a reliable translation.

4. Studies with major methodological limitations or insufficient data that could affect the reliability of the findings.

5. Duplicate publications and studies whose findings were already extensively represented in previous systematic reviews or meta-analyses.

Novelty and Mechanism

This review examines recent advances in the therapeutic use of metformin for the management of polycystic ovary syndrome (PCOS). It focuses on the effects of metformin on endocrine, metabolic, inflammatory, and reproductive pathways beyond its established role as an insulin sensitizer [11]. Metformin may reduce hyperandrogenism by inhibiting androgen production and androgen receptor expression. It may also improve ovulatory function and influence the hypothalamic–pituitary–ovarian axis [12].

Metformin may improve oocyte quality and endometrial receptivity by regulating mitochondrial dynamics and oxidative stress. Its metabolic effects are partly mediated through AMPK activation and subsequent suppression of the mechanistic target of rapamycin (mTOR) pathway [13]. Metformin also has immunomodulatory and anti-inflammatory effects, including promotion of M2 macrophage polarization and reduction of pro-inflammatory cytokines. These effects may help reduce ovarian stromal inflammation and improve insulin sensitivity and systemic metabolic parameters [14].

Metformin may influence epigenetic mechanisms through changes in DNA methylation and histone acetylation. These changes can affect genes involved in insulin signaling and follicular development and may contribute to longer-term metabolic and reproductive effects [15]. Metformin may also influence the gut–ovary axis by altering gut microbiota composition and bile acid signaling. These changes may affect hormonal balance and systemic metabolism, while increased short-chain fatty acid production and improved intestinal barrier function may further contribute to its metabolic effects [16].

The therapeutic potential of metformin is particularly relevant because of its established clinical use, affordability, and potential application across different PCOS phenotypes [17]. Unlike studies that focus on individual molecular pathways, this review combines evidence from clinical trials, cellular studies, and translational research to provide a broader understanding of metformin in PCOS management. The findings suggest that metformin may have therapeutic effects beyond insulin resistance and symptom control, supporting its potential role as part of a broader approach to PCOS treatment. The integration of molecular mechanisms with clinical evidence may also help guide the development of more individualized treatment strategies for women with PCOS.

Characteristics-Specific Efficacy of Metformin in PCOS

Metformin provides therapeutic benefits across several clinical and metabolic features of PCOS. It reduces hyperandrogenism by decreasing insulin-mediated ovarian androgen production, improves insulin sensitivity, supports menstrual regularity and ovulation, and may improve dyslipidemia and adipose tissue dysfunction [18]. Its effects can vary according to PCOS phenotype and disease severity, but current evidence supports its role as a multi-targeted treatment with benefits in both reproductive and metabolic aspects of the condition [19]. The following sections discuss its effects on the major features of PCOS, as summarized in Figure 1.

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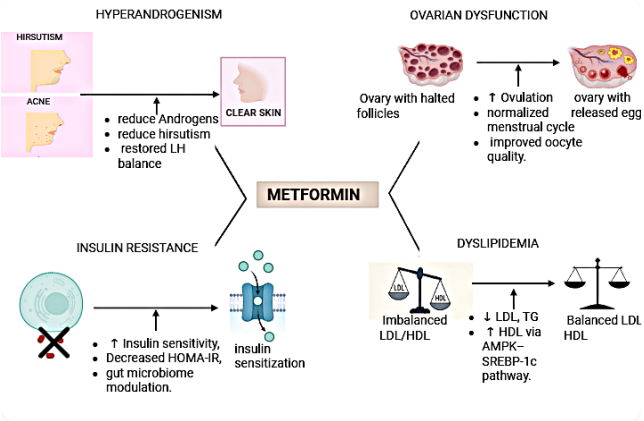

Figure 1. Metformin exerts multifaceted therapeutic effects in PCOS by targeting core metabolic and hormonal abnormalities. It reduces hyperandrogenism, leading to clearer skin and decreased hirsutism. It restores ovarian function by promoting ovulation and improving oocyte quality. Metformin enhances insulin sensitivity and regulates gut microbiota, aiding in glucose homeostasis. Additionally, it corrects dyslipidemia by lowering LDL and triglycerides and increasing HDL via the AMPK–SREBP-1c pathway.

Hyperandrogenism

Metformin, through its insulin-sensitizing action, can reduce androgen levels and improve hyperandrogenic symptoms in women with PCOS [20]. Meta-analyses indicate that metformin may improve ovulation rates and reduce hirsutism severity, although its effect on ovulation may be lower than that of clomiphene citrate when used alone [21]. Metformin treatment has also been associated with reductions in serum testosterone, with some studies reporting decreases of approximately 25–50% after treatment for up to six months [22]. Early treatment may be particularly useful in

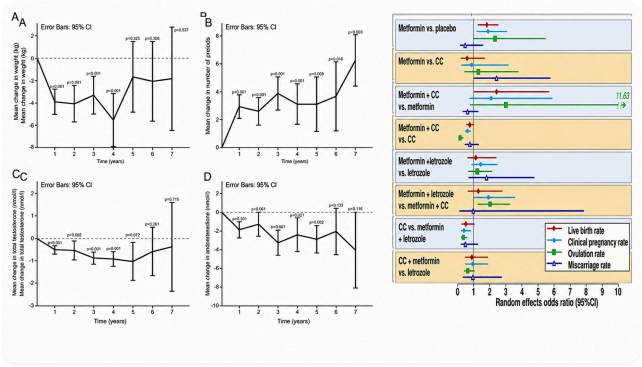

Figure 2. Illustrates the trends in body weight (A), number of menstrual cycles per year (B), total plasma testosterone (C), and plasma androstenedione levels (D) over the course of treatment. Data are presented as means with 95% confidence intervals indicated by vertical bars. Statistical comparisons to baseline values were conducted using the Wilcoxon paired sample test. Note: Data beyond 7 years are not shown, as fewer than 10% of participants continued metformin therapy beyond this period. It compares the impact of metformin-based treatment regimens with other commonly used therapies for PCOS on key fertility outcomes, based on a meta-analysis conducted for the 2023 internal clinical guidelines on PCOS management. Odds ratios (ORs) greater than 1 indicate a favorable outcome for the metformin-containing regimen in each respective comparison. Miscarriage rates are reported per patient, except in the metformin versus placebo comparison, where only the miscarriage rate per pregnancy was available in the source study. Abbreviations: CC – clomiphene citrate; PCOS – polycystic ovary syndrome.

obese adolescents with hyperandrogenism, as elevated insulin levels are associated with altered hypothalamic–pituitary–ovarian axis function and increased androgen production. Short-term metformin therapy in obese adolescents has been shown to reduce hyperinsulinemia and testosterone levels and to attenuate adrenal androgen responses to ACTH stimulation [23]. These findings suggest that early metformin treatment may help control hyperandrogenism and reduce related metabolic complications in PCOS (Figure 2).

Metformin and ovarian androgen synthesis

Metformin indirectly reduces androgen synthesis by lowering circulating insulin levels and improving insulin sensitivity, particularly in hepatic and peripheral tissues. It also directly suppresses ovarian steroidogenesis through activation of AMP-activated protein kinase (AMPK), which acts as a central energy sensor and downregulates steroidogenic acute regulatory protein (StAR) and Cytochrome P450 family 17 subfamily A member 1 (CYP17A1), along with other enzymes involved in androgen synthesis [24–26]. AMPK activation reduces androgen production and luteinizing hormone (LH) responsiveness and may help restore normal follicular development [27].

Metformin may also influence follicular morphology and development. Chronic androgen excess in hyperandrogenic ovaries can interfere with normal follicular maturation, contributing to anovulation and the characteristic polycystic ovarian morphology [28,29]. By reducing local androgen levels, metformin may help restore intraovarian paracrine signaling and support antral follicle development and ovulation [30].

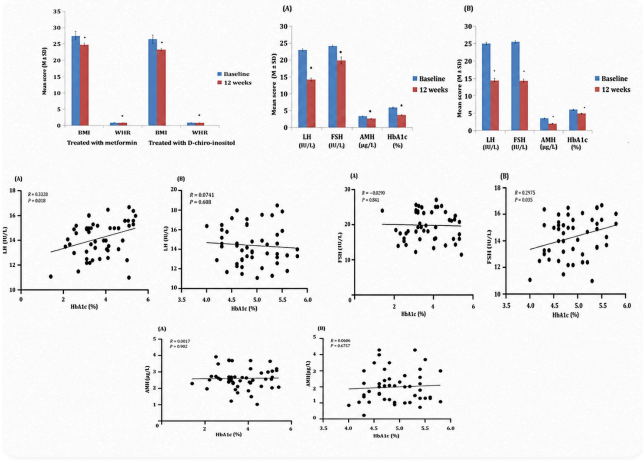

Figure 3. Displays the average Body Mass Index (BMI) and Waist-to-Hip Ratio (WHR) among women receiving metformin or D-chiro-inositol therapy. Displays the average concentrations of essential biochemical markers in patients administered metformin (Panel A) and D-chiro-inositol (Panel B).Parameters include Anti-Müllerian Hormone (AMH), Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), and Glycated Haemoglobin (HbA1c). Presents the correlation between HbA1c and LH levels in patients administered metformin (A) versus D-chiro-inositol (B). Illustrates the relationship between HbA1c and FSH levels in the metformin group (A) compared to the D-chiro-inositol group (B). Depicts the correlation between HbA1c and AMH levels in individuals treated with metformin (A) and those receiving D-chiro-inositol (B).

Metformin may also reduce LH-stimulated androgen production, which can influence estradiol levels, estrone conversion, and endometrial receptivity [31]. These hormonal changes may improve reproductive outcomes, including

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implantation and pregnancy outcomes, when metformin is used alongside fertility treatments. Recent meta-analyses comparing metformin-based regimens with standard PCOS treatments have reported improvements in ovulation and clinical pregnancy rates, with some evidence of reduced miscarriage risk, particularly when metformin is combined with clomiphene citrate [32]. The findings presented in Figures further illustrate these fertility-related outcomes (Figure 3). Overall, metformin affects ovarian androgen production through both metabolic and direct ovarian mechanisms, making it an important therapeutic option in PCOS management [33].

Ethel Codner et al. evaluated the effects of metformin on hyperandrogenism and ovarian function in adolescent females with type 1 diabetes (T1D) [34]. The randomized, double-blind, placebo-controlled study included 24 females with T1D, hyperandrogenism, and poor metabolic control. Metformin treatment reduced testosterone, free androgen index, androstenedione, 17-OH progesterone, and estradiol levels. Steroid hormones, gonadotropins, and sex hormone-binding globulin remained stable in the metformin group. However, no significant differences were observed in Ferriman–Gallwey scores, ovulation rates, Glycated hemoglobin (HbA1c) levels, or daily insulin requirements compared with placebo. The study concluded that metformin reduced circulating androgen levels in hyperandrogenic adolescents with T1D but had limited effects on clinical hyperandrogenism, ovulation, and metabolic control [35]. Huamin Zeng conducted a meta-analysis evaluating the efficacy and safety of metformin combined with spironolactone in women with PCOS [36]. The analysis included randomized controlled trials comparing metformin plus spironolactone with metformin alone and assessed body mass index (BMI), hirsutism score, luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, fasting blood glucose, homeostatic model assessment of insulin resistance (HOMA-IR), and adverse effects. The combination significantly reduced BMI and total testosterone but did not significantly affect hirsutism scores, FSH, or LH levels. When treatment continued for more than six months, the combination also improved fasting blood glucose and insulin resistance measured by HOMA-IR. The incidence of adverse effects was not higher than with metformin alone. Overall, metformin combined with spironolactone may provide greater benefits for reducing BMI and serum androgen levels in women with PCOS [36].

T. Kazerooni conducted a study involving 40 women with PCOS who received metformin 500 mg three times daily for eight weeks. Clinical features including acne, hirsutism, and BMI were assessed before and after treatment. Metformin significantly reduced total testosterone, fasting blood glucose, BMI, menstrual cycle duration, acne, and hirsutism scores. However, no significant changes were observed in DHEAS, prolactin, FSH, LH, or the LH/FSH ratio. The response to metformin also differed between women with elevated dehydroepiandrosterone sulfate (DHEAS) levels and those with normal DHEAS levels. Overall, metformin reduced fasting blood glucose and testosterone levels and improved clinical features of hyperandrogenism in women with PCOS [37].

Insulin resistance

Polycystic ovarian morphology, ovulatory dysfunction, and hyperandrogenism are the main features of polycystic ovary syndrome (PCOS). Insulin resistance (IR) is an important metabolic abnormality that contributes to both metabolic and reproductive complications [38]. IR occurs in up to 70% of women with PCOS, including those with normal body weight, suggesting that factors other than obesity contribute to impaired insulin action. Compensatory hyperinsulinemia can further increase hyperandrogenism through several mechanism [39]. Insulin stimulates ovarian androgen production by increasing the activity of steroidogenic enzymes such as CYP17A1 in theca cells, together with LH. Hyperinsulinemia also reduces hepatic production of sex hormone-binding globulin (SHBG), increasing the availability of circulating androgens. Increased androgen levels can interfere with follicular development, ovulation, and normal ovarian morphology [40]. At the cellular level, PCOS is associated with impaired insulin receptor autophosphorylation and abnormalities in post-receptor signaling, particularly the PI3K-Akt pathway, which reduces glucose uptake in muscle and adipose tissue. Chronic low-grade inflammation and altered adipokine levels, including increased TNF-α, IL-6, and chemerin, may further contribute to insulin resistance [41].

Recent studies have provided further insight into the relationship between insulin resistance and PCOS. In a polycystic ovary (PCO) rat model, PCO development increased insulin resistance, testosterone levels, and chemerin mRNA and protein expression. Treatment with metformin and pioglitazone reduced chemerin expression and improved metabolic and endocrine parameters, suggesting a potential role for chemerin in PCOS pathophysiology [42]. Metformin remains an important treatment for insulin resistance in PCOS. Through activation of AMP-activated protein kinase (AMPK), it reduces hepatic gluconeogenesis and circulating insulin levels, thereby improving insulin sensitivity [43]. In a study of 113 women with PCOS classified into insulin-resistant (IR) and non-insulin-resistant (NIR) groups according to HOMA-IR, metformin reduced LH and free androgen index (FAI) levels and improved ovulatory function. Metformin also produced beneficial anthropometric and endocrine effects in women with normal insulin levels, suggesting that its actions may extend beyond glucose regulation (Figure 4) [44].

Gut microbiota modulation by metformin: A novel insulin-sensitizing mechanism in PCOS

Metformin is traditionally used in PCOS to improve insulin sensitivity by reducing hepatic gluconeogenesis and increasing peripheral glucose uptake. Recent evidence suggests that metformin may also act through the gut microbiota, providing another mechanism for its effects in insulin-resistant PCOS. This mechanism adds to the understanding of metformin's broader therapeutic effects and may be particularly relevant in women with insulin resistance [45]. This mechanism adds to the understanding of metformin's broader therapeutic effects and may be particularly relevant in women with insulin resistance [46]. Women with PCOS commonly show gut dysbiosis, including reduced microbial diversity and changes in the Firmicutes/Bacteroidetes ratio. These alterations may contribute to low-grade inflammation and insulin resistance through increased intestinal permeability and metabolic endotoxemia [47]. Therefore, the gut microbiota may have an important role in the interaction between endocrine and metabolic abnormalities in PCOS [48].

Metformin may influence insulin sensitivity not only through systemic metabolic pathways but also through changes in the gut microbiota [49]. Treatment can modify

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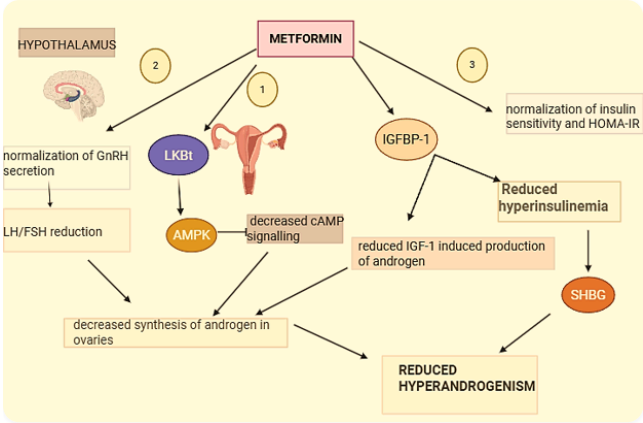

Figure 4. Figure outlining the molecular mechanisms by which metformin alleviates hyperandrogenism in PCOS. Metformin acts through three main pathways: (1) It activates the LKB1–AMPK pathway in the ovaries, reducing cAMP signaling and androgen synthesis. (2) In the hypothalamus, it normalizes GnRH secretion, leading to reduced LH/FSH and androgen production. (3) It increases IGFBP-1 and improves insulin sensitivity, reducing hyperinsulinemia and IGF-1–induced androgen production. This also enhances SHBG levels.

microbial composition soon after administration, potentially before measurable systemic glucose-lowering effects. These changes may increase bacteria that produce short-chain fatty acids (SCFAs), including butyrate, which can activate AMP-activated protein kinase (AMPK) [50].

Wu et al. reported that metformin treatment increased Akkermansia muciniphila and other SCFA-producing bacteria in patients with type 2 diabetes, with improvements in insulin sensitivity and systemic inflammation [51]. Zhang et al. reported that metformin treatment in women with PCOS reduced serum endotoxin levels and improved gut microbial diversity, including an increase in Bifidobacterium abundance [52]. These findings suggest that the gut microbiota may contribute to the insulin-sensitizing effects of metformin and support the potential use of probiotics, prebiotics, or dietary interventions alongside metformin [53]. Gut microbial profiles may also help identify differences in treatment response or gastrointestinal tolerance among patients. Overall, gut microbiota modulation represents a potential mechanism through which metformin improves insulin resistance in PCOS and may support more individualized treatment strategies [54].

Johanna Melin conducted a systematic review and meta-analysis evaluating metformin and lifestyle modification compared with placebo in adults with PCOS. The review searched MEDLINE, EMBASE, PsycINFO, All EBM, and CINAHL. Metformin produced greater reductions in BMI, HOMA-IR, and fasting glucose than placebo, although mild gastrointestinal adverse effects were more common. Low-certainty evidence also indicated greater reductions in waist-to-hip ratio, total cholesterol, low-density lipoprotein, and triglycerides with metformin [55].

Wan-Wan Liu et al. studied 113 women with PCOS who were classified into insulin-resistant (IR) and non-insulin-resistant (NIR) groups according to HOMA-IR. Metformin improved ovulatory function and menstrual regularity in both groups. In the NIR group, it also reduced LH, free androgen index (FAI), BMI, and waist circumference, without significant changes in fasting glucose, insulin, or lipid levels. These findings suggest that the effects of metformin may extend beyond its role in improving insulin resistance [56]. Arslanian and colleagues reported that three months of metformin treatment in obese adolescents with PCOS improved glucose tolerance and insulin sensitivity, reduced insulin levels, and decreased total and free testosterone concentrations. A modest reduction in abdominal adipose tissue and improvement in menstrual cyclicity were also observed. The hormonal response to ACTH stimulation was reduced after treatment, while adverse effects were generally mild and temporary. The authors suggested that metformin may improve metabolic abnormalities and reduce androgen excess in obese adolescents with PCOS, although further double-blind, placebo-controlled studies are needed [57]. Nahid Kabiri and colleagues investigated the effects of metformin in a rat model of polycystic ovary (PCO). PCO induction in 30 female rats increased chemerin mRNA and protein expression, insulin resistance, and androgen and progesterone levels. Treatment with metformin and pioglitazone reduced chemerin expression, improved insulin sensitivity, and partially corrected abnormal steroidogenesis. These findings identify chemerin, a pro-inflammatory adipokine associated with metabolic and reproductive dysfunction, as a potential therapeutic target in PCOS. Metformin-mediated reduction of chemerin may contribute to its metabolic, anti-inflammatory, and endocrine effects[58]. This has been outlined in Figure 3.

Ovarian dysfunction and anovulation

Ovarian dysfunction, mainly characterized by chronic anovulation, is a major feature of PCOS and an important cause of infertility. Approximately 70–80% of women with PCOS experience anovulatory cycles, while more than 90% of women with chronic anovulation are diagnosed with PCOS [59]. Impaired follicular maturation is associated with increased intraovarian androgen levels and altered gonadotropin secretion, which interfere with dominant follicle selection and ovulation [60]. These changes contribute to irregular menstruation and infertility. Increased LH:FSH ratios, often in PCOS, may further contribute to follicular arrest. Metformin can improve ovulation through its insulin-lowering and endocrine effects. Clinical studies have reported ovulation rates of approximately 40–60% with metformin alone, particularly in women with elevated fasting insulin or insulin resistance. In women resistant to clomiphene, metformin has resulted in ovulation in approximately 35–45% of cases [61]. Menstrual regularity may also improve in up to 50–70% of women within 3–6 months of treatment, particularly when metformin is combined with lifestyle modification [62]. Treatment may reduce LH and free testosterone levels and increase SHBG, thereby improving the hormonal environment required for ovulation. Metformin may also support mono-follicular development and therefore has a lower risk of multiple pregnancy than gonadotropin therapy [63]. Overall, metformin is a useful option for managing ovarian dysfunction in women with PCOS, particularly when anovulation is associated with metabolic abnormalities.

Metformin and mitochondrial function: A novel mechanism in restoring ovarian activity in PCOS

Recent research on PCOS has identified mitochondrial dysfunction in ovarian cells, particularly granulosa and theca cells, as a potential contributor to ovarian dysfunction [64]. These cells are involved in steroidogenesis and follicular development, and mitochondrial abnormalities may impair follicular maturation and oocyte quality. Increased oxidative

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stress, altered mitochondrial dynamics, and reduced energy production can contribute to follicular arrest and chronic anovulation [65]. In addition to its effects on insulin resistance and hyperandrogenism, metformin may directly improve mitochondrial function in the ovary. Metformin activates AMP-activated protein kinase (AMPK), which supports mitochondrial biogenesis and energy metabolism [66]. It may also increase mitochondrial membrane potential, reduce reactive oxygen species (ROS), and improve ATP production, thereby supporting follicular growth and ovulation [67]. Metformin may further improve ovarian mitochondrial function by increasing SIRT3 and GPX4, reducing oxidative stress, activating AMPK, inhibiting mTOR, and increasing Beclin-1 expression, which promotes autophagy and cellular repair, as shown in Figure 5 [32].

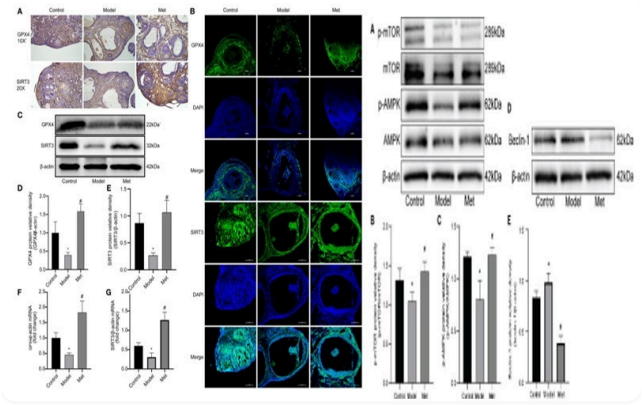

Figure 5. Metformin enhances the expression of GPX4 and SIRT3 in the ovaries of PCOS mice, as demonstrated by immunohistochemistry, immunofluorescence, Western blotting, and qPCR. Increased protein and mRNA levels indicate improved mitochondrial function and antioxidant activity. ($P < 0.05$ vs control; #$P < 0.05$ vs PCOS group; Mean ± SEM, n = 3). It demonstrates that metformin modulates the expression of AMPK and mTOR signaling components in the ovaries of PCOS mice. Western blot analysis (A) revealed changes in total and phosphorylated levels of mTOR and AMPK, with quantitative comparisons shown for phosphorylated mTOR (B) and phosphorylated AMPK (C). Additionally, Beclin-1 expression, an autophagy-related protein, was assessed by Western blot (D), with relative protein levels shown in panel (E). The results indicate that metformin activates AMPK while suppressing mTOR signaling and upregulates Beclin-1 expression. Data are presented as mean ± SEM (n = 3), with significance denoted by *$P < 0.05$ vs control and #$P < 0.05$ vs PCOS group.

Wang et al. used a letrozole-induced PCOS rat model and found that metformin improved mitochondrial morphology and function in granulosa cells. Treatment also normalized estrous cycles and increased the number of antral follicles, suggesting improved follicular maturation [68]. Li et al. reported that metformin reduced ovarian oxidative stress by decreasing mitochondrial fission proteins such as Drp1 and increasing fusion-related proteins such as Mfn1, thereby improving mitochondrial dynamics. These effects occurred without major changes in systemic insulin levels, suggesting that metformin may have a direct effect on ovarian mitochondrial function and may partly explain its benefits in lean or norm insulinemic women with PCOS [69]. This mechanism also supports the potential use of metformin with mitochondrial-targeted therapies, including antioxidants and coenzyme Q10, to further improve ovarian function and oocyte quality [70]. Overall, the effects of metformin on ovarian mitochondria provide a possible cellular mechanism for improving anovulation and expand its potential role in reproductive management beyond insulin resistance [71]. Tang et al. evaluated more than 30 randomized controlled trials in a meta-analysis of metformin for ovulation in women with PCOS. Metformin significantly improved ovulation and menstrual regularity compared with placebo, while the combination of metformin and clomiphene citrate was particularly beneficial in women who were resistant to clomiphene, with improvements in ovulation and pregnancy rates.

Palomba et al. conducted a randomized trial in women with clomiphene-resistant PCOS and reported that metformin induced ovulation in approximately 60% of participants. Pregnancy outcomes also improved without an increased risk of multiple gestations, supporting the use of metformin when conventional ovulation induction is unsuccessful [72]. Morin-Papunen et al. treated women with PCOS with metformin for six months and reported restoration of regular menstrual cycles in 68% and ovulation in 46% of participants. The benefits were observed even in women without substantial weight loss, suggesting that the effects of metformin on ovulation may involve hormonal and insulin-sensitizing mechanisms in addition to weight reduction [73]. Neveu et al. reported that three months of metformin treatment restored ovulatory cycles in 75% of previously anovulatory women with PCOS [73]. Improved follicular growth was also observed, suggesting that metformin may influence the ovarian environment and follicular maturation [74]. Nestler et al. provided early evidence of the effect of metformin on ovulation in hyperinsulinemic women with PCOS. Ovulation occurred in 84% of women receiving metformin compared with 38% in the placebo group. The study supported a link between reduced insulin levels and improved reproductive function and contributed to the subsequent use of metformin in the management of PCOS-related anovulation. [75].

Chronic low-grade inflammation

These inflammatory mediators are associated with insulin resistance, endothelial dysfunction, hyperandrogenism, and ovarian abnormalities in PCOS [59]. Women with PCOS commonly have elevated high-sensitivity C-reactive protein (hs-CRP) levels and increased macrophage infiltration in adipose and ovarian tissues, contributing to a pro-inflammatory ovarian environment [76]. This inflammatory state can interfere with follicular development, increase androgen production, and worsen insulin resistance, further contributing to metabolic and reproductive abnormalities [77]. Metformin has also shown anti-inflammatory effects in PCOS. It may reduce inflammation by inhibiting nuclear factor-kappa B (NF-κB) signaling, decreasing pro-inflammatory cytokine expression, and activating AMP-activated protein kinase (AMPK) [78]. Studies have reported reductions in serum CRP, IL-6, and TNF-α following 8–12 weeks of metformin treatment, including effects that were independent of weight loss [79]. Mohlig et al. reported reductions in CRP and IL-6 after three months of metformin treatment in insulin-resistant women with PCOS [79]. González et al. also found that metformin reduced oxidative stress markers and inflammatory cytokines, with improvements in insulin sensitivity and menstrual regularity [80]. These findings suggest that the anti-inflammatory effects of metformin may contribute to both metabolic improvement and restoration of ovarian function [81]. By influencing inflammatory pathways and improving insulin sensitivity, metformin may provide additional benefits in

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PCOS beyond its conventional metabolic effects [82].

Metformin and the gut–ovary–immune axis: A novel therapeutic mechanism in PCOS

Chronic low-grade inflammation in PCOS is associated with adipose tissue dysfunction and changes in gut microbiota. The gut–ovary–immune axis describes the interaction between intestinal microbiota, immune responses, and ovarian function [83]. Gut dysbiosis in PCOS is characterized by reduced microbial diversity, fewer short-chain fatty acid (SCFA)-producing bacteria, and increased endotoxin-producing Gram-negative bacteria. These changes can increase intestinal permeability and allow bacterial products such as lipopolysaccharide (LPS) to enter the circulation and promote inflammation [84].

Circulating LPS activates Toll-like receptor 4 (TLR4) signaling and increases pro-inflammatory mediators such as TNF-α, IL-6, and CRP. This inflammatory response can impair insulin signaling, increase androgen production, and interfere with follicular development and ovulation [85]. Metformin may modify gut microbiota in addition to its glucose-lowering and insulin-sensitizing effects. It can increase beneficial bacteria such as Akkermansia muciniphila, which supports intestinal barrier function, while reducing pro-inflammatory bacteria such as Desulfovibrio. These changes may reduce systemic inflammation and improve hormonal parameters in PCOS [86]. Zhang et al. reported that 12 weeks of metformin treatment increased gut microbial diversity and reduced serum LPS and TNF-α levels in women with PCOS, with these changes associated with improved menstrual regularity and insulin resistance [87]. Wu et al. further showed that fecal transplantation from metformin-treated mice improved PCOS-like metabolic and reproductive abnormalities in recipient animals, supporting a role for the gut microbiota in metformin-mediated effects [88]. These findings suggest that microbiota-targeted approaches, including probiotics, prebiotics, and dietary interventions, may complement metformin therapy in PCOS [89]. Further studies have examined the relationship between gut microbiota, inflammation, and ovarian function in PCOS. Zhang et al. reported that 12 weeks of metformin treatment increased Akkermansia muciniphila and reduced LPS levels in women with PCOS. These changes were accompanied by lower serum TNF-α and IL-6 levels, improved insulin sensitivity, and greater menstrual regularity [90].

Wu et al. demonstrated in a PCOS rat model that microbiota changes induced by metformin could be transferred through fecal transplantation. Rats receiving fecal material from metformin-treated animals showed improved estrous cycles, reduced ovarian cyst formation, and lower inflammatory marker levels, supporting a possible causal role of the microbiome in ovarian recovery [91]. Shin et al. reported that metformin-associated microbiota changes increased SCFA production and improved intestinal barrier integrity in insulin-resistant subjects. Although the study was not specific to PCOS, the findings support a possible role for metformin in reducing metabolic endotoxemia and inflammation [92]. Liu et al. found that metformin treatment in women with PCOS increased SCFA-producing bacteria and reduced serum endotoxin and CRP levels. These microbiota changes were also associated with lower total testosterone levels and improved ovulatory function [93]. Kushugulova et al. reported increased gut microbial diversity following metformin treatment in women with PCOS, together with improved ovulatory outcomes and reduced IL-6 levels. These findings support the potential contribution of the gut–immune axis to the therapeutic effects of metformin in PCOS [94].

Dysregulated lipid metabolism

PCOS is often associated with an atherogenic lipid profile, which may contribute to insulin resistance and increase the long-term risk of cardiovascular disease[95,96]. The lipid abnormalities in PCOS are influenced by several factors. Hyperinsulinemia caused by insulin resistance increases hepatic very-low-density lipoprotein (VLDL) production and reduces hepatic lipase activity, resulting in higher circulating triglyceride levels [97]. Hyperandrogenism may also affect lipid metabolism by altering adipocyte function and lipolysis, further contributing to insulin resistance and ovarian dysfunction [98]. Metformin may help improve dyslipidemia by increasing insulin sensitivity in hepatic and peripheral tissues in addition to reducing hepatic glucose production [99]. It may reduce VLDL secretion and enhance lipid oxidation, while improvements in body weight and visceral adiposity can further benefit lipid metabolism. Mohan et al. reported that 3–6 months of metformin treatment reduced serum triglycerides by approximately 10–15%, along with total cholesterol and LDL-C levels in women with PCOS [100]. Harborne et al. also observed improvements in lipid profiles with metformin treatment despite the absence of significant weight loss, suggesting a possible direct effect on hepatic lipid metabolism [101]. Overall, metformin may provide additional metabolic benefits by improving lipid abnormalities and reducing cardiovascular risk while supporting the management of reproductive and metabolic complications associated with PCOS.

AMPK–SREBP-1c axis: A novel mechanism in metformin's lipid-modulating effect in PCOS

One emerging mechanism through which metformin may improve PCOS-related metabolic abnormalities is the regulation of hepatic lipid metabolism through the AMP-activated protein kinase (AMPK)–SREBP-1c signaling pathway [102]. SREBP-1c is a transcription factor that regulates lipogenic enzymes such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC). In PCOS, hyperinsulinemia and androgen excess can increase SREBP-1c activity, promoting hepatic triglyceride synthesis, VLDL production, and lipid accumulation in the liver [103]. Metformin activates AMPK, which suppresses SREBP-1c activity and reduces the expression of enzymes involved in de novo lipogenesis. This can decrease hepatic triglyceride production and improve the lipid profile [104]. Zhou et al. demonstrated that metformin activates AMPK and inhibits SREBP-1c in hepatocytes, resulting in reduced lipid synthesis [103]. Benrick et al. further reported that metformin treatment in DHEA-induced PCOS mice reduced hepatic fat accumulation and SREBP-1c expression, together with improvements in insulin sensitivity and lipid parameters [105]. These findings position the AMPK–SREBP-1c axis as a novel therapeutic target that contributes to metformin's broader metabolic benefits in PCOS management [106].

Supporting evidence

Mohan et al. conducted a meta-analysis involving more than 700 women with PCOS and reported that metformin significantly improved lipid parameters. After 12–24 weeks of treatment, serum triglycerides decreased by approximately

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15%, LDL cholesterol by 9%, and HDL cholesterol showed a modest increase. These changes were accompanied by improved insulin sensitivity and were not dependent on major weight loss, supporting the metabolic benefits of metformin [107]. Harborne et al. evaluated the effects of metformin on lipid profiles in women with PCOS and found reductions in triglycerides and LDL cholesterol, along with an improvement in HDL cholesterol after three months of treatment. The lipid benefits were also observed in women without significant weight loss, suggesting a direct effect of metformin on hepatic lipid metabolism [108]. Cakir et al. studied adolescents with PCOS and reported that three months of metformin treatment significantly reduced total cholesterol and triglyceride levels. Treatment was also associated with improved menstrual regularity and reduced androgen levels, indicating potential benefits of early metabolic intervention in reducing future cardiovascular risk [109]. Ehrmann et al. investigated the metabolic effects of metformin in obese women with PCOS and found significant reductions in triglyceride and total cholesterol levels. These changes were associated with improved insulin sensitivity and lower fasting insulin concentrations, highlighting the relationship between glucose and lipid metabolism in PCOS [110]. Talaat et al. reported that six months of metformin treatment reduced serum VLDL and triglyceride levels in women with PCOS. Improvements in liver function markers were also observed, suggesting that metformin may have beneficial effects on hepatic lipid metabolism and may help reduce the risk of hepatic steatosis in PCOS [111].

Obesity and adipose tissue dysfunction

Obesity, particularly visceral or central obesity, is common in women with PCOS and affects approximately 50–70% of patients. However, adipose tissue dysfunction can also occur in lean women with PCOS and is characterized by altered adipokine secretion, increased inflammatory cytokines, and impaired lipid storage [112]. These abnormalities contribute to insulin resistance, systemic inflammation, and hyperandrogenism and may worsen the metabolic and reproductive features of PCOS [113]. Visceral adiposity also increases lipolysis and circulating free fatty acids, which can impair insulin signaling and increase hepatic glucose and androgen production, further aggravating metabolic dysfunction [114].

Metformin may help reduce visceral fat, increase adiponectin levels, and decrease inflammatory cytokine production [115]. It also improves insulin sensitivity in adipose tissue and reduces free fatty acid release, which may help limit lipotoxicity and insulin resistance. In a PCOS mouse model, metformin treatment reduced body weight and adiposity compared with untreated PCOS animals and improved glucose tolerance and insulin sensitivity, as shown by improved OGTT and ITT responses and reduced area under the curve values in Figure 3. Metformin also activates AMP-activated protein kinase (AMPK) in adipocytes, which may reduce inflammatory signaling and improve adipocyte insulin sensitivity. These effects suggest that metformin may be useful in managing obesity and adipose tissue dysfunction associated with PCOS.

Metformin and adipose tissue browning: A novel mechanism in PCOS management

Browning refers to the conversion of energy-storing white adipose tissue into energy-expending beige adipose tissue, characterized by increased expression of thermogenic proteins such as uncoupling protein 1 (UCP1) and enhan mitochondrial activity. This process increases energy expenditure, limits lipid accumulation, and improves insulin sensitivity, which may be beneficial in obesity-associated metabolic dysfunction in PCOS (Figure 6) [116,117].

Women with PCOS commonly exhibit visceral obesity and adipose tissue dysfunction, including reduced thermogenic activity and impaired mitochondrial function. These abnormalities contribute to insulin resistance and inflammation, which may further aggravate hyperandrogenism and anovulation [118]. Metformin may promote adipose tissue browning through activation of AMP-activated protein kinase (AMPK), which supports mitochondrial biogenesis and increases the expression of thermogenic genes such as PRDM16, PGC-1α, and UCP1. Chen et al. reported that metformin increased UCP1 and PRDM16 expression in inguinal white adipose tissue of high-fat diet-induced obese mice, indicating enhanced browning and thermogenesis [119]. Zhao et al. similarly demonstrated that metformin-induced AMPK activation promoted beige adipocyte differentiation in vitro and in vivo, accompanied by improved insulin sensitivity and reduced weight gain in mice [120].

Clinical evidence is also emerging. Barzilai et al. reported increased markers of beige adipose tissue in adipose biopsies from women with insulin-resistant PCOS after six months of metformin treatment, together with reductions in waist circumference, visceral fat mass, and HOMA-IR [121]. These findings suggest that adipose tissue browning may contribute to the metabolic effects of metformin and provide an additional mechanism beyond glucose regulation. Combining metformin with other approaches that promote adipose browning may therefore represent a potential strategy for improving adipose tissue function in PCOS (Table 1).

Chen et al. investigated the effects of metformin on adipose tissue metabolism in high-fat diet-induced obese mice. Metformin increased UCP1, PRDM16, and PGC-1α expression in inguinal white adipose tissue and improved mitochondrial function and thermogenesis, supporting an AMPK-mediated role in white adipose tissue browning [122]. Zhao et al. evaluated the effects of metformin on adipocyte development in vitro and in vivo. Metformin increased browning-related genes through AMPK–PGC-1α signaling in cultured preadipocytes. In high-fat diet-fed mice, treatment reduced weight gain, increased beige adipose markers, and enhanced oxygen consumption, suggesting that metformin promotes beige adipogenesis and metabolic improvement. Yadav et al. investigated metformin combined with caloric restriction in obese female rats and found that metformin independently increased brown-fat-associated genes, including UCP1 and TMEM26, in white adipose tissue [123,124]. Metformin treatment also produced greater improvements in HOMA-IR, insulin sensitivity, and inflammatory markers compared with caloric restriction alone, suggesting an additional contribution of adipose tissue browning to its metabolic effects [125]. Wang et al. examined mitochondrial biogenesis and thermogenic activity in adipose tissue from insulin-resistant individuals and reported increased mitochondrial DNA content and thermogenic gene expression following metformin treatment [85]. These effects were associated with reduced adipose inflammation and improved metabolic flexibility and appeared to involve AMPK signaling. Although the study was not specific to PCOS, the findings provide mechanistic support

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for considering adipose tissue browning as a potential component of metformin-mediated metabolic improvement in PCOS [126].

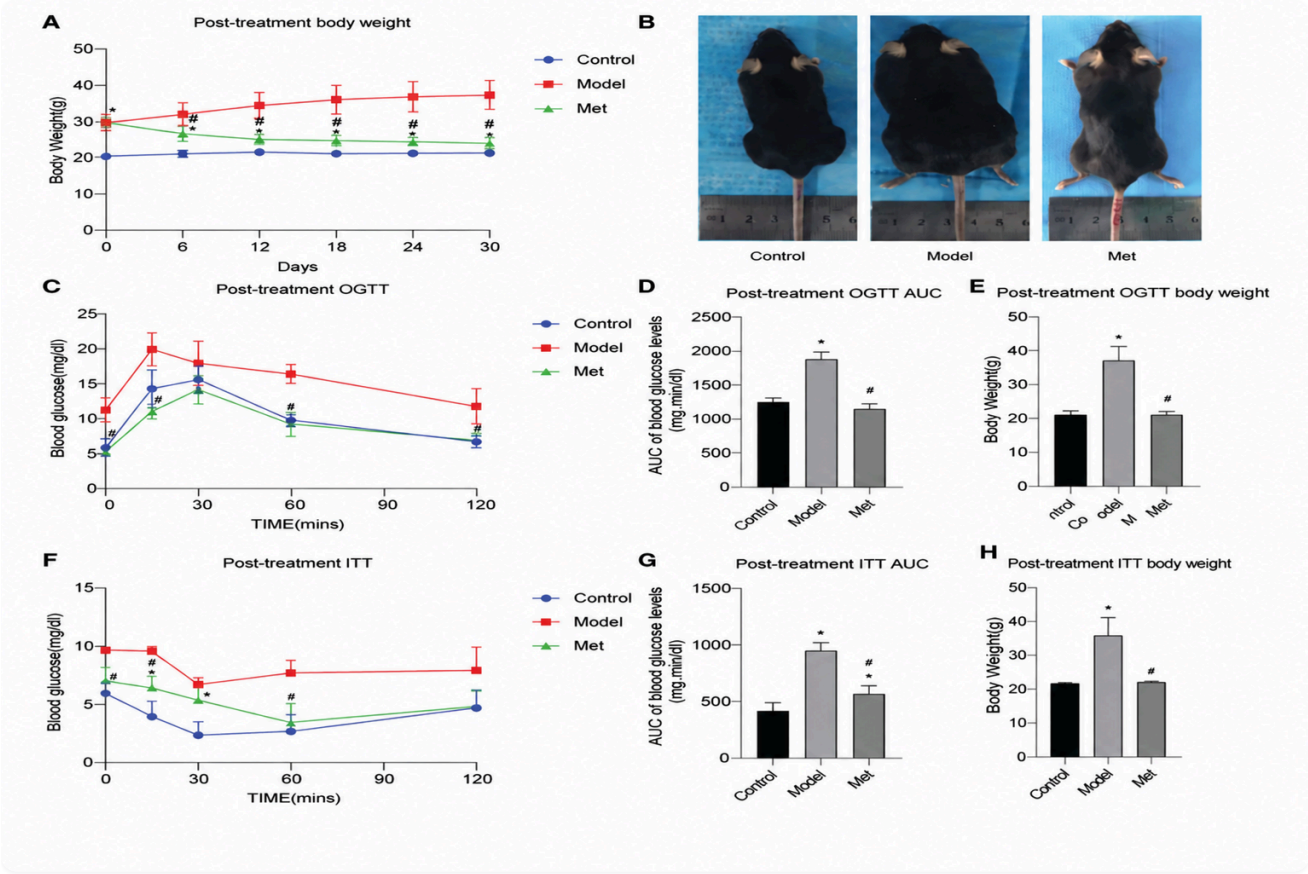

Figure 6. Illustrates that metformin treatment significantly improves obesity, glucose intolerance, and insulin resistance in a PCOS mouse model. The results show reduced body weight (A, E, H) and smaller body size (B) in metformin-treated mice compared to the untreated PCOS group. Glucose metabolism improved, as indicated by better OGTT performance (C), lower area under the OGTT curve (D), and enhanced insulin sensitivity observed through ITT results and reduced ITT AUC (F, G). Statistically significant differences were noted (*P < 0.05 vs control; #P < 0.05 vs PCOS), with all values expressed as mean ± SEM (n = 6).

Table 1. Recent novel roles of metformin in PCOS (2023–2025).

Sl no	Model / Population	Metformin use	Novel mechanism / Outcome	Key findings	Significance	Reference
1	168 adolescent girls with PCOS	500 mg BID + COCs for 6 months	↓ Insulin AUC, ↓ HOMA-IR, ↓ ovarian volume	Effects sustained for 2 years post-treatment	Metformin with COCs has long-term metabolic benefits in adolescents	[127]
2	PCOS rat model (Letrozole + HFD)	Oral metformin for 4 weeks	↑ Intestinal AMPK, ↑ beneficial gut bacteria, restored estrous cycle	Reversed ovulatory and metabolic features	Suggests gut–reproductive axis modulation by metformin	[128]
3	Adult women with PCOS	1500 mg/day for 12 weeks	↓ Serum irisin (a novel myokine), improved insulin sensitivity	Significant metabolic improvement	Irisin may serve as a novel biomarker of metformin response	[129]
94	PCOS mice	200 mg/kg for 6 weeks	Inhibited ovarian ferroptosis, ↓ ROS, restored folliculogenesis	Improved ovarian morphology	Proposes ferroptosis as a new metformin target in PCOS	[32]
5	Pregnant women with PCOS	Continued metformin into 1st trimester	↓ Miscarriage rate, ↑ clinical pregnancy rate	OR for miscarriage: 0.64	Validates metformin's role in early pregnancy outcomes	[130]
6	Obese PCOS women	1500 mg/day for 6 months	↓ LH-driven CYP19 expression via ERK1/2 inhibition	↓ Testosterone, ↑ SHBG, ↓ fasting insulin	Shows hormonal and metabolic modulation	[131]
7	PCOS women (resistant cases)	Metformin + Liraglutide	↓ BMI, ↓ AMH, ↑ ovulation & pregnancy	Superior to metformin alone	Supports dual therapy for better reproductive outcomes	[132]

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Table 1 (continued)

Sl no	Model / Population	Metformin use	Novel mechanism / Outcome	Key findings	Significance	Reference
8	PCOS with NAFLD	2000 mg/day for 3 months	↓ ALT/AST, improved hepatic insulin sensitivity	Improved liver and metabolic function	Dual-targeted benefit in PCOS with liver involvement	[133]
9	Granulosa cells (in vitro)	Metformin pre-treatment	↓ TNF-α-induced apoptosis, ↓ caspase-3	Preserved cell viability	Anti-inflammatory action improves follicular survival	[134]
10	Infertile PCOS women (Clomiphene-resistant)	Metformin + Clomiphene for 3 cycles	↑ Endometrial thickness, ↑ LIF gene expression	↑ Implantation, ↑ pregnancy rate	Enhances endometrial receptivity via PI3K-AKT pathway	[37]

Future Perspective

Future research on metformin in PCOS should extend beyond its established role in improving insulin sensitivity and focus on its emerging effects at the cellular and molecular levels. Particular attention should be given to mitochondrial function, oxidative stress, the AMPK/mTOR pathway, and autophagy, as these mechanisms may contribute to the effects of metformin on ovarian function. However, the precise pathways involved and their tissue-specific effects are not yet fully understood. Further studies are therefore needed to determine how metformin influences mitochondrial activity, oxidative stress, and granulosa cell function, especially in women with metabolically severe forms of PCOS.

The use of potential biomarkers, including irisin, AMH, and endometrial markers such as leukemia inhibitory factor (LIF), may help identify women who are more likely to respond to metformin and support a more individualized treatment approach. Combination therapy with agents that target mitochondrial function or hormonal abnormalities may also be useful, particularly in women who show an inadequate response to metformin alone. Long-term clinical studies should further assess ovulation, fertility, pregnancy, and live birth outcomes to determine whether the benefits of treatment are sustained over time. In addition, studies incorporating genomics, transcriptomics, and epigenetic approaches may help clarify the molecular actions of metformin and identify new therapeutic targets. Such research could contribute to the development of more precise and individualized treatment strategies for PCOS.

Conclusion

Metformin remains an important therapeutic option in polycystic ovary syndrome, with effects extending beyond glycemic control. Its potential benefits include improving insulin sensitivity, regulating ovarian steroidogenesis, supporting follicular function, improving lipid metabolism, and reducing inflammation. These diverse effects highlight its potential to address both metabolic and reproductive abnormalities associated with polycystic ovary syndrome.

Emerging evidence suggests that metformin may act through multiple molecular pathways, including AMPK–SREBP-1c signaling, mitochondrial function, oxidative stress, adipose tissue browning, and inflammatory pathways. Its effects on ovarian function and steroid hormone production may also contribute to improved reproductive outcomes, particularly in women with metabolic abnormalities or suboptimal responses to conventional approaches.

However, differences in treatment response among polycystic ovary syndrome phenotypes highlight the need for individualized therapeutic strategies. Further well-designed clinical studies are required to clarify the mechanisms underlying the broader effects of metformin and to evaluate its potential combination with newer targeted therapies. A better understanding of these mechanisms may help optimize metformin-based treatment and support more personalized management of polycystic ovary syndrome.

Authors Contribution

All the authors have read and approved the final version of the manuscript.

Ethics Statement

None.

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