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**Review Article**

# Therapeutic Role of Metformin in Polycystic Ovary Syndrome: A Comprehensive Review

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## ABSTRACT

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder among women of reproductive age, affecting an estimated 8% - 13% of this population worldwide, and carrying substantial reproductive, metabolic, and psychological consequences. Metformin, a Biguanide insulin sensitizer originally developed for the management of type 2 diabetes mellitus, has emerged over the past three decades as one of the most studied pharmacological agents in PCOS. Its therapeutic relevance extends well beyond glycemic control, encompassing the modulation of hyperandrogenism, restoration of menstrual cyclicity, improvement of ovulation rates, attenuation of systemic inflammation, and favourable modification of the gut microbiome. This comprehensive review critically examines the molecular mechanisms underlying metformin's action in PCOS, synthesizes clinical evidence from randomized controlled trials, systematic reviews, and meta-analyses, and evaluates its role across key clinical domains including metabolic outcomes, reproductive function, pregnancy management, and long-term cardiometabolic risk reduction. Current guideline recommendations, safety considerations, and the evolving landscape of combination therapy are also discussed. While the evidence supporting metformin's use in PCOS is robust in several domains, important nuances remain regarding patient selection, dosing strategies, and pregnancy use. This review aims to provide clinicians and researchers with a current, evidence-based understanding of metformin's comprehensive therapeutic profile in PCOS.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) stands as the most common endocrine disorder affecting women of reproductive age globally, with a prevalence estimated between 8% and 13% depending on the diagnostic criteria applied and the population studied [1]. Originally described by

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Stein and Leventhal in 1935 as a clinical entity characterized by bilateral polycystic ovaries, oligomenorrhea, and signs of virilization, our understanding of PCOS has since expanded dramatically to encompass a multisystem disorder involving metabolic, reproductive, psychological, and cardiovascular dimensions [2].

The 2003 Rotterdam consensus, developed jointly by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), remains the most widely applied diagnostic framework [3]. According to these criteria, a diagnosis of PCOS requires the presence of at least two of the following three features: oligo- or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology (PCOM) on ultrasound, following the exclusion of other secondary causes. This expanded definition gave rise to four recognized phenotypic subtypes, reflecting the considerable clinical heterogeneity of the syndrome and underlining the complexity of its therapeutic management.

Beyond the reproductive sphere, PCOS carries substantial metabolic burden. Insulin resistance (IR) is present in approximately 50 - 70% of women with PCOS, irrespective of body mass index (BMI), and is now regarded as a central pathophysiological driver of the syndrome [4,41]. Compensatory hyperinsulinemia arising from insulin resistance amplifies ovarian androgen production, suppresses sex hormone-binding globulin (SHBG) synthesis in the liver, and disrupts the pulsatile release of gonadotropins from the pituitary, collectively perpetuating the hormonal dysregulation that defines PCOS [5]. Furthermore, women with PCOS carry a substantially elevated risk of type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, non-alcoholic fatty liver disease, and cardiovascular disease, all of which have profound long-term implications for health and quality of life [6,44].

Given the central role of insulin resistance in PCOS pathophysiology, insulin sensitizers have attracted considerable clinical interest. Among these, metformin, a synthetic biguanide that has been the first-line pharmacological treatment for type 2 diabetes for several decades, has become the most extensively studied agent in PCOS [7]. Its introduction into PCOS management in the early 1990s, first documented to alleviate hyperandrogenism and improve menstrual cyclicity, represented a paradigm shift in understanding and treating the metabolic underpinnings of the syndrome [2]. The present review aims to provide a comprehensive and current synthesis of the therapeutic role of metformin in PCOS, spanning its molecular mechanisms of action through to its clinical applications and safety profile, drawing upon randomized controlled trials, meta-analyses, systematic reviews, and landmark international guidelines [8,9].

## PATHOPHYSIOLOGY OF PCOS: THE FOUNDATION FOR METFORMIN'S ROLE

### *Insulin Resistance and Hyperinsulinemia*

Insulin resistance in PCOS is not merely a consequence of obesity; it represents a primary, intrinsic defect in insulin signal transduction. The molecular basis of this defect is well characterized: excessive serine phosphorylation of insulin receptor substrate-1 (IRS-1) impairs downstream phosphatidylinositol 3-kinase (PI3K)/Akt signalling, which is responsible for the metabolic actions of insulin including glucose uptake and glycogen synthesis. Critically, the mitogen-activated protein kinase (MAPK) arm of insulin signalling, which governs cell proliferation and

steroidogenesis, remains functionally intact or even upregulated in PCOS, a divergence termed "pathway-selective insulin resistance." This selective resistance explains how the ovary continues to respond to insulin's steroidogenic actions even while peripheral metabolic tissues become refractory to its glucose-lowering effects [10]. The resulting compensatory hyperinsulinemia synergizes with luteinizing hormone (LH) to stimulate androgen production in theca cells and suppresses hepatic synthesis of SHBG, thereby increasing circulating free androgen levels [10,9].

### *Hyperandrogenism and Its Consequences*

Hyperandrogenism, whether clinical (hirsutism, acne, androgenic alopecia) or biochemical (elevated serum testosterone, androstenedione, or free androgen index), is the most defining feature of PCOS [11]. At the molecular level, hyperandrogenism arises primarily from dysregulated ovarian steroidogenesis, characterized by upregulation of cytochrome P450 enzymes, particularly CYP17A1, which encodes 17α-hydroxylase/17,20-lyase, the rate-limiting enzymatic complex in androgen biosynthesis in theca cells. In women with PCOS, both the expression and activity of CYP17A1 are elevated in ovarian theca cells, driven in part by excess LH stimulation and hyperinsulinemia, resulting in the overproduction of 17α-hydroxyprogesterone, androstenedione, and testosterone [11,12,13].

### *Chronic Low-Grade Inflammation*

Emerging evidence has firmly established that PCOS is characterized by a state of chronic low-grade inflammation, independent of obesity. Elevated circulating levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-1β (IL-1β), tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), have been consistently documented in women with PCOS compared with matched healthy controls [14]. This chronic inflammatory milieu amplifies insulin resistance, impairs ovarian follicular development, and contributes to endothelial dysfunction, collectively worsening both the reproductive and cardiometabolic phenotype of the syndrome [14,15].

### *Gut Microbiome Dysbiosis*

In recent years, the gut microbiome has emerged as an important contributor to PCOS pathophysiology. Women with PCOS exhibit characteristic patterns of gut microbial dysbiosis, including reduced alpha diversity, decreased abundance of beneficial genera such as *Akkermansia* and *Ruminococcaceae*, and increased representation of potentially detrimental species such as *Bacteroides* and *Escherichia/Shigella* [15,16,28]. This dysbiosis impairs the intestinal production of short-chain fatty acids (SCFAs) such as butyrate and propionate, promotes intestinal permeability, and triggers systemic endotoxemia, all of which exacerbate insulin resistance and systemic inflammation. The gut microbiome thus constitutes both a target and a mediator of metabolic dysfunction in PCOS, and its modulation by pharmacological agents such as metformin has become an area of active scientific investigation [15].

## METFORMIN: PHARMACOLOGY AND MECHANISM OF ACTION

### *Chemical Properties and Pharmacokinetics*

Metformin (1,1-dimethylbiguanide hydrochloride) is a small, hydrophilic molecule derived from guanidine compounds found in the French lilac plant (*Galega officinalis*) [17]. It is orally bioavailable, with absorption occurring primarily in the small intestine via organic cation

transporters (OCTs) [18]. It is not bound to plasma proteins, is not metabolized hepatically, and is excreted unchanged in the urine, making renal function a critical determinant of its safe use. Standard dosing in PCOS typically ranges from 1,000 to 2,550 mg per day, administered in divided doses with meals to minimize gastrointestinal side effects. Extended-release formulations have been developed and are increasingly preferred due to their substantially improved gastrointestinal tolerability profile [19,20].

### *Activation of AMP-Activated Protein Kinase (AMPK)*

The best-characterized mechanism through which metformin exerts its metabolic effects is the activation of AMP-activated protein kinase (AMPK), a master regulator of cellular energy homeostasis [19,20]. Metformin inhibits Complex I of the mitochondrial electron transport chain, thereby reducing ATP synthesis and raising the intracellular AMP: ATP ratio. This energy-sensing change activates AMPK, which subsequently initiates a cascade of metabolic reprogramming: stimulation of glucose uptake via GLUT4 translocation in skeletal muscle, inhibition of hepatic gluconeogenesis and lipogenesis via suppression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) enzymes, and reduction of fatty acid synthesis [21,22]. In the context of PCOS, AMPK activation in ovarian theca cells has been shown to reduce androgen biosynthesis by downregulating the expression and activity of steroidogenic enzymes, including CYP17A1 and HSD3B2 [21].

### *Suppression of Hepatic Glucose Production*

A central pharmacological action of metformin is the suppression of hepatic gluconeogenesis, which is chronically elevated in states of insulin resistance [23]. By inhibiting mitochondrial Complex I and reducing the hepatic energy state, metformin decreases the availability of gluconeogenic substrates and inhibits key rate-limiting gluconeogenic enzymes, leading to a reduction in fasting blood glucose [22,23]. In PCOS, where chronic hyperinsulinemia fails to adequately suppress hepatic glucose output, this action is particularly relevant to restoring metabolic homeostasis and reducing the systemic consequences of hyperinsulinemia [24].

### *Direct Anti-Androgenic Effects on Ovarian Steroidogenesis*

Beyond its insulin-sensitizing actions, metformin exerts direct anti-androgenic effects on ovarian steroidogenesis that are independent of its effects on peripheral insulin sensitivity. Hirsch and colleagues demonstrated in a well-designed in vitro study using NCI-H295R cells, an established model of steroidogenesis, that metformin directly inhibits androgen production by downregulating the expression and activity of HSD3B2 and CYP17A1, as well as by reducing mitochondrial Complex I activity, which limits the supply of cholesterol precursors for steroidogenesis [21]. Clinical studies have corroborated these findings: Kurzthaler and colleagues documented that short-term metformin administration produces measurable reductions in LH-stimulated testosterone levels within days of initiation, preceding any detectable changes in insulin sensitivity or body weight, confirming the direct ovarian mechanism [25].

### *Modulation of Inflammatory Pathways*

Metformin possesses significant immunomodulatory properties that are increasingly recognized as important contributors to its beneficial effects in PCOS. Through AMPK activation, metformin suppresses the NF-κB

signalling pathway, a master regulator of pro-inflammatory gene expression, thereby reducing the transcription and secretion of pro-inflammatory cytokines including IL-6, TNF-α, IL-1β, and IL-17 [27]. Simultaneously, metformin upregulates anti-inflammatory mediators including IL-10 and attenuates oxidative stress by reducing reactive oxygen species (ROS) production. In the ovarian microenvironment, metformin also modulates TGF-β signalling, mitigating ovarian fibrosis while promoting follicular development and oocyte maturation through increased expression of growth differentiation factor-9 (GDF-9) and bone morphogenetic protein-15 (BMP-15). These immunomodulatory properties position metformin as a drug that addresses not just the metabolic but also the inflammatory dimension of PCOS pathophysiology [26,27].

### *Gut Microbiome Modulation*

A growing body of evidence suggests that a substantial proportion of metformin's metabolic benefits are mediated through its effects on the gut microbiome. Metformin accumulates at high concentrations in the intestinal lumen, where it modulates microbial composition by selectively enriching beneficial bacteria, most notably *Akkermansia muciniphila*, which is associated with improved gut barrier function and systemic metabolic health [28]. Metformin-induced changes in the gut microbiome promote the production of SCFAs such as butyrate and propionate, which activate intestinal AMPK, improve insulin sensitivity, reduce intestinal permeability, and attenuate systemic endotoxemia and inflammation [29]. A 2025 mechanistic study in a PCOS rat model demonstrated that metformin-mediated intestinal AMPK activation significantly restored ovulatory function and improved metabolic parameters in parallel with favorable shifts in gut microbial composition, identifying indole-3-carboxaldehyde (I3A), a gut microbiome-derived metabolite involved in the regulation of inflammation and apoptosis, as a key downstream mediator of these effects [30].

## METFORMIN AND METABOLIC OUTCOMES IN PCOS

### *Insulin Resistance and Glycemic Parameters*

The evidence base for metformin's ability to improve insulin sensitivity in PCOS is among the most robust of any therapeutic intervention in this condition. A systematic review and meta-analysis of 32 randomized controlled trials (RCTs), specifically commissioned to directly inform the 2023 International Evidence-Based Guideline for PCOS, demonstrated that metformin significantly reduces fasting insulin levels, homeostatic model assessment of insulin resistance (HOMA-IR), and fasting blood glucose in women with PCOS compared with placebo, with or without concomitant lifestyle modification [31]. The same comprehensive meta-analysis also found reductions in C-reactive protein (CRP) and plasminogen activator inhibitor-1 (PAI-1), markers of inflammation and thrombotic risk respectively, suggesting that metformin's glycemic benefits extend to the broader cardiometabolic risk profile of women with PCOS [31,32].

### *Body Weight and BMI*

The effect of metformin on body weight in PCOS is modest but clinically meaningful, particularly in overweight and obese individuals. The 2023 meta-analysis referenced above provided moderate-certainty evidence that metformin reduces BMI in adult women with PCOS who have a BMI of ≥25 kg/m², with or without concomitant lifestyle modification [31,33,34]. Importantly, this BMI-

reducing effect was not observed in women with a BMI below 25 kg/m² or in adolescents, suggesting that the weight-reducing properties of metformin are most applicable to the overweight or obese PCOS phenotype. The mechanism behind metformin-induced weight loss appears to be multifactorial, involving central appetite suppression through hypothalamic AMPK modulation, reduced caloric absorption in the gut, and alterations in gut hormone profiles, particularly increases in glucagon-like peptide-1 (GLP-1) secretion [31,34,35].

### *Lipid Profile*

Dyslipidemia, characterized by elevated triglycerides, low HDL-cholesterol, and elevated small dense LDL particles, is a frequent metabolic complication of PCOS and contributes substantially to the elevated cardiovascular risk observed in this population [36]. Metformin has been reported to produce favorable changes in lipid profiles, including reductions in triglycerides and total cholesterol [31,37]. Notably, in a systematic review comparing various antidiabetic agents as add-on therapy to metformin in PCOS, patients receiving metformin as the core treatment showed greater increases in HDL-C levels compared with those receiving dipeptidyl peptidase-4 inhibitors or thiazolidinediones [38].

### *Metformin versus Combined Oral Contraceptive Pills (COCPs)*

An important evidence synthesis commissioned as part of the 2023 International PCOS Guideline update compared metformin against COCPs and their combination across 36 RCTs. This meta-analysis found that metformin was superior to COCPs for lowering fasting insulin, HOMA-IR, and triglycerides, while COCPs were superior for managing clinical hyperandrogenism and menstrual irregularity. The combination of metformin and COCPs outperformed either agent alone for most hormonal outcomes, supporting the rationale for combination use in women with both metabolic and hyperandrogenic features [39].

### *Long-Term Metabolic Protection*

Given the elevated cardiometabolic risk profile of women with PCOS, long-term prevention of type 2 diabetes and cardiovascular disease represents an important therapeutic goal [72]. Metformin's well-established role in reducing the incidence of type 2 diabetes in high-risk populations is directly relevant to PCOS management [6,31]. Longitudinal observational data suggest that sustained metformin use, extending up to 10 years in some cohort studies, is associated with maintained improvements in menstrual regularity and sustained metabolic benefits over the long term [34].

## METFORMIN AND HORMONAL OUTCOMES

### *Reduction of Circulating Androgens*

One of the most clinically impactful actions of metformin in PCOS is its ability to reduce circulating androgen levels. Multiple randomized trials and meta-analyses have documented significant reductions in total testosterone, free testosterone, androstenedione, and the free androgen index (FAI) following metformin therapy [25,42]. A longitudinal observational cohort study found that metformin lowered total testosterone and androstenedione levels progressively over the first year of treatment, with further reductions observed in subsequent years, demonstrating durable androgenic benefit [34]. The anti-androgenic effect arises through both indirect pathways, reduction of compensatory hyperinsulinemia, and through direct inhibition of

steroidogenic enzymes within the ovary, as described in the preceding section [21,42].

A study using artificial neural network modeling identified baseline hyperandrogenemia and menstrual irregularity as the strongest clinical predictors of metformin treatment response in women with PCOS, suggesting that the subset with pronounced hormonal dysregulation derives the greatest anti-androgenic benefit from therapy. Importantly, lower serum testosterone levels at baseline were identified in this analysis as a predictor of treatment discontinuation, offering a clinically actionable insight for monitoring adherence [69].

### *Improvement in SHBG*

Metformin consistently raises serum SHBG concentrations in women with PCOS, thereby reducing the bioavailable fraction of circulating androgens. This effect is primarily mediated through reduction of hyperinsulinemia, since insulin is a potent suppressor of hepatic SHBG synthesis. Increases in SHBG contribute directly to the clinical improvement of hyperandrogenic features such as hirsutism and acne, and serve as a useful biomarker of metformin's overall therapeutic response [9,42].

### *Attenuating Clinical Hyperandrogenism*

The reduction in biochemical hyperandrogenism with metformin translates into measurable improvement in clinical manifestations, though the degree varies among patients. For dermatological manifestations such as hirsutism, metformin alone is generally inferior to anti-androgen agents such as spironolactone or combined oral contraceptives, though it contributes meaningfully to overall hormonal normalization and is particularly relevant in patients who cannot or prefer not to use COCPs [44]. The evidence base specifically for metformin's effect on acne in PCOS has been systematically reviewed, with multiple studies demonstrating clinically significant improvements in modified Ferriman-Gallwey scores following treatment [73].

## METFORMIN AND REPRODUCTIVE OUTCOMES

### *Restoration of Menstrual Cyclicity*

Anovulation and oligomenorrhea are hallmark features of PCOS, arising from arrested follicular development due to the combined effects of hyperandrogenism, excess insulin, and elevated intraovarian androgen concentrations. Metformin has been shown to restore ovulatory menstrual cycles in a meaningful proportion of women with PCOS [44,43]. Observational data suggest improvement in menstrual regularity in approximately 50% of women with oligomenorrhea following metformin treatment [44]. The mechanism is multifactorial: reduced insulin levels lower tonic LH hypersecretion, decreased ovarian androgen production alleviates follicular arrest, and improved ovarian sensitivity to follicle-stimulating hormone (FSH) promotes physiological follicular maturation [44,43].

### *Ovulation Induction: Metformin as Monotherapy*

For women with PCOS seeking fertility, metformin has demonstrated efficacy as a sole ovulation-induction agent, particularly in lean women where insulin resistance may be less pronounced. A meta-analysis of RCTs concluded that metformin is a reasonable first-line treatment option for non-obese women with anovulatory PCOS-related infertility, based on its capacity to restore spontaneous ovulation and achieve pregnancy rates comparable to clomiphene citrate in this subgroup [43]. However, metformin

monotherapy is generally less effective than pharmacological ovulation inducers in obese women with PCOS, where insulin resistance is more severe and requires more aggressive intervention or combination therapy [43,44].

### *Metformin in Combination with Ovulation Inducers*

The most extensively studied and clinically adopted strategy for metformin in PCOS-related infertility is its use in combination with ovulation-inducing agents. The landmark multicenter RCT by Legro and colleagues (2007), involving 626 infertile women with PCOS, demonstrated that clomiphene citrate alone was superior to metformin alone for live birth rates, but this study highlighted important subgroup effects and helped define the complementary role of combination approaches [52]. When combined with clomiphene citrate, metformin has been shown in subsequent meta-analyses to improve ovulation and pregnancy rates beyond what either agent achieves alone, by sensitizing ovarian follicles and the pituitary to clomiphene's anti-estrogenic action. The 2023 International Evidence-Based Guideline for PCOS recognizes letrozole as the preferred first-line pharmacological infertility therapy, while recommending clomiphene in combination with metformin as an alternative approach [44,52].

### *Metformin in IVF and ART Cycles*

Women with PCOS undergoing assisted reproductive technology (ART) face specific challenges, most notably a high risk of ovarian hyperstimulation syndrome (OHSS). Pre-treatment with metformin before and during controlled ovarian stimulation has been shown in meta-analyses to significantly reduce the risk of OHSS, improve clinical pregnancy rates, and increase the live birth rate in PCOS patients undergoing IVF, making it a valuable adjunct to ART protocols in this population [45]. These benefits likely reflect metformin's ability to reduce insulin-driven ovarian sensitivity to gonadotropin stimulation and to lower the pro-inflammatory and pro-angiogenic factors that contribute to OHSS pathogenesis [45,66].

## METFORMIN AND PREGNANCY OUTCOMES IN PCOS

### *Miscarriage and Early Pregnancy Loss*

Women with PCOS carry a significantly elevated risk of first-trimester miscarriage, estimated to be two to three times higher than in the general population, driven in part by hyperandrogenism, insulin resistance, and impaired endometrial receptivity [46]. A systematic review and meta-analysis of 17 randomized and non-randomized controlled studies found that metformin treatment was associated with a significantly lower rate of early miscarriage in women with PCOS compared with placebo (cumulative rate 6.58% versus 18.35%; relative risk 0.40, 95% CI 0.20–0.78). The mechanistic basis for this protective effect is thought to involve metformin's ability to reduce hyperinsulinemia and androgens, both of which impair endometrial function, and to improve the systemic inflammatory milieu that governs early placental development [47].

### *Gestational Diabetes Mellitus (GDM)*

GDM is one of the most common obstetric complications in PCOS, occurring at a significantly higher rate than in the general obstetric population [48]. Evidence from randomized trials and meta-analyses indicates that metformin administration during pregnancy may reduce the risk of developing GDM in women with PCOS [74]. A 2024 study specifically examining metformin during pregnancy in previously infertile PCOS patients confirmed that metformin

may reduce GDM risk, miscarriage, and preterm delivery without adverse effects on fetal outcomes [49]. However, the timing and duration of metformin treatment appear to be critical determinants of these protective effects; evidence suggests that discontinuing metformin upon pregnancy confirmation may increase miscarriage risk, while continuation through at least the first trimester may confer greater benefit, underscoring the need for individualized clinical judgment [75].

### *Fetal Safety and Teratogenicity*

A major clinical concern regarding metformin use during pregnancy is the possibility of fetal exposure, since metformin crosses the placenta through organic cation transporters [50]. A meta-analysis examining metformin use during early pregnancy in the setting of diabetes mellitus combined with PCOS found that early exposure to metformin does not increase the risk of fetal birth defects [51]. Nonetheless, the 2023 International PCOS Guideline does not routinely recommend metformin use during pregnancy in women with PCOS, acknowledging that further long-term data on offspring outcomes, particularly regarding metabolic and neurodevelopmental health, are still needed [44].

### *Preeclampsia and Hypertensive Disorders*

Preliminary evidence from observational studies and small trials suggests that metformin may confer protection against pregnancy-induced hypertension and preeclampsia in women with PCOS, consistent with its anti-inflammatory and endothelial-protective properties. However, the evidence base in this specific domain remains limited and primarily observational, and adequately powered RCTs are needed before firm clinical recommendations can be made [44,53].

## METFORMIN AND THE GUT MICROBIOME IN PCOS

The emerging intersection between gut microbiome research and PCOS therapeutics has generated considerable scientific interest. Women with PCOS exhibit significant gut microbial dysbiosis, including impaired secretion of β-glucuronidase, an enzyme that deconjugates estrogens and enables their binding to estrogen receptors, thereby reducing circulating estrogen and contributing to reproductive dysfunction [54]. Metformin addresses this dysbiosis through several mechanisms: it enriches beneficial SCFA-producing bacteria, enhances gut barrier integrity, reduces bacterial lipopolysaccharide (LPS) translocation into the systemic circulation, and favorably modulates immune cell differentiation in the gut-associated lymphoid tissue [2829,30].

A 2024 study published in the *International Journal of Molecular Sciences* documented significant changes in gut microbiota composition and SCFA profiles in women with PCOS compared with healthy controls, and found that metformin therapy was associated with partial restoration of dysbiotic microbial patterns, particularly improvements in *Akkermansia* abundance and SCFA production [55]. A subsequent 2025 mechanistic study demonstrated that metformin-mediated intestinal AMPK activation in a letrozole-plus-high-fat-diet PCOS rat model significantly reversed metabolic disorders and restored ovulatory functions, with notable improvements in gut microbiota composition and serum indole-3-carboxaldehyde (I3A) levels, a gut microbiome-derived metabolite shown to mitigate inflammation [30]. These findings collectively position the gut microbiome as both a therapeutic target and a mediator of metformin's systemic effects in PCOS [30,55].

## METFORMIN IN SPECIAL POPULATIONS

### *Adolescents with PCOS*

Diagnosing and treating PCOS in adolescence is inherently challenging, as many features of normal pubertal development, including oligomenorrhea and mild acne, overlap with PCOS features, requiring careful clinical judgment. The 2023 International PCOS Guideline recommends that metformin may be considered in adolescents with PCOS or those at risk for metabolic features and cycle regulation, particularly when COCPs are contraindicated or not preferred [44]. The metabolic and hormonal benefits of metformin in adolescents are supported by evidence, though the magnitude of BMI reduction observed in overweight adults is not consistently replicated in adolescent cohorts [31,44].

### *PCOS Across Different Phenotypes*

The four recognized phenotypic subtypes of PCOS differ substantially in their metabolic burden, with Phenotype A (the classic full combination of hyperandrogenism, anovulation, and PCOM) carrying the greatest insulin resistance and cardiometabolic risk, while Phenotype D (PCOM with anovulation, without biochemical hyperandrogenism) typically exhibits a milder metabolic profile [67]. Metformin's therapeutic utility is greatest in phenotypes with pronounced insulin resistance and metabolic dysfunction, and clinicians should individualize treatment decisions based on the patient's phenotypic profile and metabolic risk burden [44,67].

### *PCOS and Long-Term Risk Beyond Reproductive Age*

While PCOS is primarily recognized as a condition of reproductive age, its metabolic consequences persist beyond the menopause transition, with women with a history of PCOS carrying elevated long-term risks for type 2 diabetes and cardiovascular disease [68]. The potential role of metformin in attenuating these long-term risks in post-reproductive women with PCOS is an area that merits continued investigation, though high-quality evidence in this specific population remains limited at present [68,73].

## SAFETY PROFILE AND ADVERSE EFFECTS OF METFORMIN

### *Gastrointestinal Side Effects*

Gastrointestinal adverse effects are by far the most common side effects associated with metformin, occurring in approximately 20 - 30% of treated patients and comprising nausea, vomiting, diarrhea, abdominal cramping, and bloating [56]. These effects are typically dose-dependent and most pronounced during the initiation phase of therapy. They can be significantly mitigated by starting at a low dose (e.g., 500 mg once daily) and increasing gradually over two to four weeks, and by always administering the medication with or after meals. The extended-release (ER) formulation is associated with fewer GI adverse effects, with studies reporting GI side effects in 5 - 20% of patients on ER preparations compared with up to 30% on immediate-release formulations [57,58,59].

### *Lactic Acidosis*

Lactic acidosis is the most serious potential adverse effect associated with metformin and carries a black box warning from the US Food and Drug Administration (FDA). However, it is exceedingly rare in clinical practice, with an estimated incidence of less than 0.03 cases per 1,000 patient-years [60]. Risk is confined almost exclusively to patients with predisposing

conditions including significant renal impairment, severe hepatic disease, decompensated heart failure, excessive alcohol use, or acute hemodynamic compromise. Standard clinical practice requires assessment of renal function (eGFR) before initiation and at regular intervals during treatment [61].

### *Vitamin B12 Deficiency*

Long-term metformin use is associated with reduced absorption of vitamin B12 in the terminal ileum, which can lead to subclinical or overt B12 deficiency in a proportion of patients on chronic therapy. The clinical consequences of B12 deficiency, including peripheral neuropathy, megaloblastic anemia, and cognitive decline, may be insidious in onset and are potentially serious if undetected. A randomized controlled trial by de Jager and colleagues *(BMJ*, 2010) provided robust evidence that long-term metformin treatment is associated with a significant reduction in serum B12 levels [62]. Clinicians managing PCOS patients on long-term metformin should therefore monitor serum vitamin B12 levels periodically, with a suggested interval of annually or biannually [44,62].

### *Hypoglycemia*

Unlike sulfonylureas, metformin does not stimulate insulin secretion and therefore does not cause hypoglycemia when used as monotherapy. This is a particularly important safety advantage in the PCOS population, where treatment is often continued long-term in non-diabetic women. The risk of hypoglycemia is relevant only in the context of combination therapy with insulin or insulin secretagogues, or in unusual circumstances of extreme caloric restriction or prolonged strenuous exercise [63].

## CURRENT GUIDELINES AND CLINICAL RECOMMENDATIONS

The 2023 International Evidence-Based Guideline for the Assessment and Management of PCOS, developed under the leadership of Helena Teede and colleagues on behalf of a large international consortium including ESHRE and ASRM, represents the most current and authoritative clinical guidance for PCOS management [44]. Key recommendations pertaining to metformin include: (i) metformin is recommended primarily for the management of metabolic features in PCOS, including insulin resistance and associated glycemic and lipid abnormalities, with evidence supporting greater efficacy than inositol supplementation in this domain; (ii) for the management of menstrual irregularity and hyperandrogenism, COCPs remain the first-line pharmacological treatment, though metformin may be preferred or used concurrently when metabolic comorbidities are prominent or when COCPs are contraindicated; (iii) in the context of infertility treatment, letrozole is recognized as the preferred first-line pharmacological ovulation induction agent, with clomiphene in combination with metformin as an alternative; and (iv) metformin is not routinely recommended for use during pregnancy in women with PCOS, reflecting ongoing uncertainties about optimal timing and long-term offspring outcomes. These recommendations align closely with those of the American College of Obstetricians and Gynecologists (ACOG) and the Endocrine Society [44].

## EMERGING STRATEGIES: METFORMIN IN COMBINATION THERAPY

### *Metformin and GLP-1 Receptor Agonists*

The advent of glucagon-like peptide-1 (GLP-1) receptor agonists, including liraglutide,

semaglutide, and exenatide, as potent metabolic agents has generated substantial interest in their combination with metformin in PCOS. A prospective study by Jensterle and colleagues demonstrated that the combination of metformin and liraglutide achieved superior weight loss, BMI reduction, and waist circumference reduction compared with either agent alone in obese PCOS women who had previously shown poor response to metformin monotherapy [64]. A 2025 clinical and preclinical study reported that the combination of metformin and liraglutide produced more pronounced improvements in gut microbiota composition and metabolic metabolite profiles in PCOS models compared with either drug alone, suggesting complementary mechanisms of action [65].

### *Metformin and Inositols*

Inositols, particularly myo-inositol (MI) and D-chiro-inositol (DCI), are naturally occurring molecules that act as insulin second messengers and have been evaluated as insulin sensitizers in PCOS. While some trials have reported modest improvements in metabolic and reproductive outcomes with inositol supplementation, the 2023 International PCOS Guideline concluded that metformin has greater efficacy than inositol and that inositol offers only limited clinical benefits in PCOS. The combination of metformin with myo-inositol has been explored in several small trials with promising early results related to insulin sensitivity and ovarian function, but the evidence base remains insufficient to recommend this combination in routine clinical practice [44].

### *Metformin and Other Antidiabetic Agents*

Thiazolidinediones (TZDs), such as pioglitazone, are PPAR-γ agonists with potent insulin-sensitizing effects that, when combined with metformin, have demonstrated greater improvements in lipid profiles compared with metformin alone [38,66]. However, TZDs carry significant safety concerns including fluid retention, weight gain, bone loss, and potential cardiovascular risk, which limit their routine use in the PCOS population, particularly in reproductive-aged women [66]. Dipeptidyl peptidase-4 (DPP-4) inhibitors combined with metformin show particular promise for glycemic profile optimization in PCOS, though the evidence base specific to PCOS reproductive and hormonal outcomes is still maturing [38,66].

## LIMITATIONS OF CURRENT EVIDENCE AND FUTURE DIRECTIONS

Despite the substantial body of evidence reviewed above, several important limitations and knowledge gaps persist in the metformin-in-PCOS literature. Many RCTs have been conducted in small and heterogeneous patient populations, limiting the generalizability of their findings [70]. Variability in diagnostic criteria (NIH 1990 versus Rotterdam 2003 versus AE-PCOS 2006), dosing regimens, treatment duration, and outcome measures across studies further complicates cross-study comparisons and meta-analytic synthesis [31,70]. The precise degree to which metformin's benefits in PCOS are driven by insulin sensitization versus its direct anti-androgenic, anti-inflammatory, and microbiome-modulatory effects remains to be fully elucidated.

Future research priorities should include adequately powered RCTs stratified by PCOS phenotype, BMI category, and degree of insulin resistance, to better define the patient populations most likely to benefit from metformin. The long-term offspring outcomes of metformin-exposed pregnancies in PCOS require continued follow-up in well-designed prospective cohorts. The integration of gut microbiome analysis into clinical trials of metformin in PCOS represents a

promising mechanistic frontier that may yield actionable biomarkers of treatment response. Finally, the development and validation of pharmacogenomic predictors of metformin response in PCOS, including variants in the organic cation transporter genes *OCT1* and *OCT2*, which govern metformin's intestinal absorption and renal excretion, offers an exciting pathway toward precision medicine approaches in this heterogeneous condition [71].

## CONCLUSION

Metformin occupies a well-established and irreplaceable role in the therapeutic landscape of PCOS, underpinned by more than three decades of accumulating clinical evidence and a progressively deepening mechanistic understanding. Its pleiotropic actions, encompassing AMPK-mediated metabolic reprogramming, direct ovarian anti-androgenic effects through CYP17A1 and HSD3B2 regulation, suppression of systemic inflammation via NF-κB inhibition, and favorable modulation of the gut microbiome, make it uniquely well-suited to address the multifaceted pathophysiology of this syndrome. In clinical practice, metformin has demonstrated meaningful efficacy across a range of outcomes central to PCOS management, including improvement of insulin resistance and glycemic parameters, reduction of circulating androgens and SHBG normalization, restoration of menstrual cyclicity and ovulatory function, enhancement of fertility outcomes in combination with ovulation inducers, reduction of early pregnancy loss, and attenuation of long-term cardiometabolic risk.

The most current international guidelines recognize metformin as the preferred pharmacological agent for the metabolic features of PCOS and an important adjunct in infertility management, while cautioning against its routine use in pregnancy pending further long-term safety data on offspring health. Its tolerability profile is well-characterized, with gastrointestinal adverse effects being common but manageable, serious adverse effects including lactic acidosis exceedingly rare in the appropriately selected patient, and vitamin B12 deficiency the most important long-term monitoring concern. As research continues to illuminate the molecular intricacies of PCOS pathophysiology, including the emerging roles of the gut microbiome and pathway-selective insulin resistance, metformin's role is likely to evolve rather than diminish, either as a precisely targeted monotherapy or as a foundational component of rational combination strategies with newer metabolic agents. For the millions of women worldwide living with PCOS and its far-reaching consequences, metformin remains not merely a treatment for insulin resistance, but a cornerstone of comprehensive, evidence-driven, and person-centred care.

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