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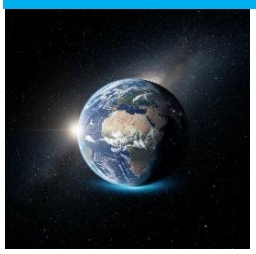

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Impact of Insulin-Sensitizing Agents on Reproductive Function in Women with Polycystic Ovary Syndrome

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Abstract

Background. Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age, which collectively impair fertility. Insulin-sensitizing agents have emerged as a key therapeutic strategy to improve metabolic, hormonal, and reproductive outcomes in this population.

Aim. This review critically evaluates current evidence on insulin-sensitizing agents in women with PCOS, addressing both their mechanisms of action at the metabolic and ovarian levels and their effects on reproductive outcomes.

Material and Methods. A review of randomized controlled trials, meta-analyses, and high-quality observational studies published up to 2025 evaluated the effects of metformin, myo-inositol, and berberine on reproductive outcomes in women with PCOS.

Results. Insulin-sensitizing agents improve metabolic dysfunction and ovulatory outcomes in PCOS. Metformin increases ovulation and clinical pregnancy rates, particularly in women with insulin resistance or higher BMI, though its effect on live birth is inconsistent. Myo-inositol and berberine show beneficial effects on metabolic parameters and ovulatory function, but evidence for live birth and miscarriage remains limited.

Conclusions. Insulin-sensitizing therapies support reproductive function in women with PCOS, particularly in metabolically compromised phenotypes. Metformin has the strongest evidence base, whereas myo-inositol and berberine are promising adjunctive or alternative options. Future high-quality randomized trials focusing on live birth and miscarriage outcomes, standardized reporting, and precise patient stratification are needed to optimize the clinical use of these agents in PCOS-related infertility.

Keywords: Polycystic Ovary Syndrome (PCOS), Insulin resistance, Insulin sensitizers, Myo-inositol, Metformin, Fertility, Reproductive outcomes, Ovulation induction, Hyperandrogenism

1 Introduction

PCOS is the most common endocrine disorder in reproductive aged women, with a prevalence between 5% and 15%, depending on the diagnostic criteria applied [1]. Reproductive and metabolic disorders represent a major clinical challenge in women of reproductive age, with significant implications for both fertility and long-term health. In women with PCOS, insulin resistance and compensatory hyperinsulinemia have been closely associated with impaired reproductive outcomes, including ovulatory dysfunction and reduced fertility [2], underscoring the importance of addressing metabolic dysregulation in infertility management. Given the central role of insulin resistance and compensatory hyperinsulinemia in the pathophysiology of PCOS, therapeutic strategies aimed at reducing insulin levels have gained increasing attention. This review focuses on pharmacological agents and dietary supplements with insulin-lowering or insulin-sensitizing properties that are commonly used in the management of PCOS, with particular emphasis on their potential benefits for ovulatory function and reproductive outcomes.

1.1 Endocrine Alterations in PCOS

PCOS is characterized by a broad spectrum of interrelated hormonal disturbances that disrupt normal reproductive endocrine function. Hyperandrogenism and hyperinsulinemia have been demonstrated as the two predominant interrelated mechanisms involved in the development of PCOS [3]. A prospective cohort study observed significantly higher levels of serum testosterone, dehydroepiandrosterone sulfate (DHEAS), fasting blood glucose, and fasting insulin, as well as lower insulin sensitivity, in the PCOS population with recurrent pregnancy loss (RPL) compared to the PCOS population without RPL [4]. This complex hormonal milieu not only underlies the clinical manifestations of PCOS, such as hirsutism, oligo/anovulation, and menstrual irregularities, but also contributes to impaired folliculogenesis and subfertility in affected women.

1.1.1 Hypothalamic–pituitary–ovarian (HPO) axis disorder

A defining feature of PCOS is dysregulation of the HPO axis, typically manifested as an increased frequency of gonadotropin-releasing hormone (GnRH) pulses and enhanced luteinizing hormone (LH) secretion relative to follicle-stimulating hormone (FSH). This altered gonadotropin profile promotes excessive androgen synthesis in the ovarian theca cells while impairing follicular maturation, contributing to chronic anovulation and an elevated LH/FSH ratio [5].

1.1.2 Elevated AMH

In women with PCOS, serum anti-Müllerian hormone (AMH) concentrations are markedly elevated compared with healthy counterparts, reflecting both the increased number of small antral follicles and altered folliculogenesis [6]. Elevated AMH has been shown to reduce follicular sensitivity to FSH by decreasing FSH receptor expression and inhibiting FSH-induced aromatase activity in granulosa cells, which impairs estradiol production and prevents the selection and maturation of a dominant follicle. This mechanism contributes to the accumulation of small antral follicles and follicular arrest, thereby perpetuating anovulation in PCOS [7].

1.1.3 Insulin Dysregulation

Insulin resistance in PCOS arises from post-receptor defects in insulin signaling pathways in peripheral tissues, particularly skeletal muscle and adipose tissue. As a compensatory response, pancreatic β-cells secrete higher amounts of insulin, leading to hyperinsulinemia [8]. Both lean and obese women with PCOS exhibit this dysregulation, although obesity exacerbates the severity of insulin resistance [9].

1.1.4 Hyperandrogenism

Insulin resistance with compensatory hyperinsulinemia exacerbates hyperandrogenism by stimulating ovarian androgen production and suppressing hepatic sex hormone-binding globulin (SHBG) synthesis, thereby increasing the bioavailability of free androgens [10].

1.2 Infertility

Hyperinsulinemia acts synergistically with luteinizing hormone to enhance ovarian androgen production and suppress hepatic SHBG synthesis, thereby increasing circulating free androgen levels. These alterations disrupt folliculogenesis, impair HPO axis signaling, and adversely affect granulosa cell function, leading to ovulatory dysfunction, compromised oocyte quality, impaired endometrial receptivity, and ultimately reduced fertility [11–15]. The impact of hormonal disturbances associated with PCOS on reproductive outcomes is summarized in Table 1.

Table 1. Causes of infertility and early pregnancy loss in PCOS [16].

Disorder	Effect
LH hypersecretion	Adverse effect on the developing oocyte • inhibition of the oocyte maturation inhibitor • premature oocyte maturation anovulation Premature follicular differentiation, premature luteinization: follicular arrest Adverse effect on the developing endometrium • increased endometrial advancement Hyperandrogenism Hyperestrogenism
Hyperandrogenism	Impaired folliculogenesis and granulosa cell function Detrimental effect on endometrial function
Insulin resistance	Hyperandrogenism Independent risk factor for recurrent pregnancy loss
Hyperinsulinemia	LH hypersecretion Hyperandrogenism Adverse affects on endometrial function by • potentiation of LH and androgen effects • influencing PAI activity
Obesity	Menstrual disorders Increased risk of miscarriage after spontaneous or assisted conception by • predisposition to insulin resistance • induced reduction in SHBG thus, hyperandrogenemia
Increased inhibin levels	Anovulation
Increased plasminogen activator inhibitor (PAI), (fibrinolysis inhibitor)	Early recurrent unexplained/spontaneous miscarriage by • provoking thrombotic placental insufficiency abnormality • impaired trophoblastic development and poor placentation in early pregnancy
Reduced/delayed GDF-9 expression	Follicular arrest before granulosa cells gain competence to initiate apoptosis Decreased long-term developmental potential of the oocytes
Hyperexpression of antiapoptotic factors (EGF and TGF-α)	Blocking of apoptosis and atresia
Expression of insulin-like growth factor (IGF) and its intrafollicular receptors	Inhibitory effect on IGF and FSH actions: follicular arrest
Increased TNF-α	Modulation of theca cell steroidogenesis Decreased estradiol levels

2 Metformin

Metformin also called dimethyl biguanide is a classic insulin sensitizer, that enhances insulin responsiveness in peripheral tissues and suppresses hepatic gluconeogenesis, leading to reduced circulating glucose levels and improved metabolic control [17]. It has been widely used in women with PCOS for its reproductive benefits, and it may also have a preventive effect against long-term cardiovascular diseases [18].

2.1 Mechanisms of Action in the Context of Fertility

Obesity impairs natural and assisted conception and reduces the likelihood of a healthy pregnancy, in part due to increased insulin resistance [19]. Metformin improves systemic insulin sensitivity and lowers serum androgen levels in women with PCOS, while also exerting direct effects on ovarian function. It modulates ovarian steroidogenesis, reduces intra-ovarian hyperandrogenism [20], and alleviates intra-ovarian insulin resistance [21] by interfering with autocrine and paracrine insulin signaling pathways [22]. These ovarian actions occur partly independently of systemic metabolic improvements or ovulatory function [23].

Additionally, metformin may enhance endometrial receptivity, potentially contributing to better reproductive outcomes in this population. In women with PCOS, baseline uterine, sub-endometrial, and endometrial blood flows are reduced compared to controls. Metformin treatment significantly improves these indices of uterine vascularization, restoring them to levels comparable with healthy controls, without affecting endometrial thickness or pattern [24,25].

Furthermore, evidence suggests that metformin use is associated with improved menstrual regularity and increased fertility in patients with PCOS [26,27]. Observational studies indicate that metformin therapy for 3–6 months can restore regular menstrual cycles and ovulation in approximately 60% of women with PCOS, although data on pregnancy outcomes remain limited [28].

2.2 Metformin as an Adjunctive Therapy for Ovulation Induction

2.2.1 Metformin with Clomiphene Citrate

By inducing ovulation in women with polycystic ovary syndrome (PCOS), clomiphene citrate is widely used as a first-line treatment. Adjunctive therapy with metformin, an insulin-sensitizing agent, has been shown in some studies to enhance the ovulation-

inducing effects of clomiphene citrate. A meta-analysis results indicate that using metformin alone is less effective than using metformin with clomiphene citrate (CC) for live birth rate but CC with metformin may increase ovulation and pregnancy rates - relevant for infertile women trying to conceive [29]. The combination of metformin with CC over 8–9 months further increases ovulation rates to around 66% and results in an estimated 34% pregnancy rate. In CC-resistant patients, ovulation and pregnancy rates are reduced to roughly 40% and 25%, respectively [28]. This combination has therefore gained attention as a strategy to optimize fertility treatment in this patient population.

2.2.2 Sequential metformin + letrozole

There is growing evidence supporting the efficacy of letrozole for ovulation induction in women with PCOS, with some studies suggesting that it may be even more effective than clomiphene [30–32]. In clomiphene-resistant patients with polycystic ovary syndrome (PCOS), preliminary treatment with metformin has been shown to favorably modulate the metabolic and hormonal milieu, thereby optimizing conditions for subsequent ovulation induction [33]. Prospective studies have shown that this drug combination can result in high ovulation and pregnancy rates in patients with PCOS who are resistant to clomiphene [34,35]. While results are mixed regarding the statistical superiority of combination therapy with metformin over letrozole monotherapy, many studies report favorable trends, including higher ovulation and pregnancy rates [36]. In one of the largest prospective studies, ovulation occurred in approximately 91% of patients who were initially treated with metformin for 6–8 weeks and subsequently received 2.5 mg of letrozole daily on days 3–7 of the menstrual cycle, with a pregnancy rate of 57% [34]. These findings suggest that metformin-letrozole combinations may offer a valuable therapeutic option, particularly for patients who are resistant to clomiphene or have additional metabolic concerns.

2.2.3 Metformin as Gonadotropin Therapy Enhancement

In cases where first-line ovulation induction agents such as clomiphene citrate or letrozole fail to induce ovulation, gonadotropins are commonly employed [37]. These exogenous FSH and LH preparations directly stimulate ovarian folliculogenesis, promoting the development and maturation of multiple follicles[38].

The current systematic review with meta-analysis demonstrated that metformin administration significantly increases the live birth and pregnancy rates of about two-fold, and reduces the cancellation rate of about 60% in PCOS patients who receive gonadotropins for ovulation induction [39]. The cancellation rate refers to cycles that are discontinued before embryo transfer or an attempt to achieve pregnancy, for example due to insufficient ovarian response, poor oocyte quality, or risk of ovarian hyperstimulation syndrome (OHSS).

2.2.4 Impact on Metformin use on ART Cycles outcomes

Metformin treatment in patients with polycystic ovary syndrome (PCOS) undergoing in vitro fertilization (IVF) has been shown to improve outcomes and is associated with modulation of insulin-like growth factors (IGF). Increased free IGFs may be acting in conjunction with FSH in improving the ovarian stimulation, oocyte maturation, and total number of advanced embryos obtained per cycle.

In a retrospective analysis of clomiphene-resistant women with PCOS, administration of metformin prior to gonadotropin stimulation improved fertilization rates, and increased pregnancy rates compared to cycles without metformin [40]. However, more recent meta-analyses suggest that while metformin administration before and during ART cycles increases pregnancy rates, the evidence regarding live birth rates remains inconclusive [41].

It is worth noting that metformin treatment has been shown to be associated with increased clinical pregnancy rates in women with a Body Mass Index (BMI) of 26 or greater. Therefore, metformin should be carefully considered in women with PCOS undergoing IVF or Intracytoplasmic Sperm Injection – Embryo Transfer (ICSI-ET) and may be particularly beneficial in those with higher BMI[42].

2.3 Lower risk of OHSS

Additional benefits of metformin co-treatment during IVF or ICSI in women with PCOS include a reduced risk of ovarian hyperstimulation syndrome (OHSS). OHSS is primarily caused by excessive angiogenesis and increased vascular permeability induced by Vascular Endothelial Growth Factor (VEGF) released from ovarian follicular cells during gonadotropin stimulation [41]. However, the data from studies on humans are limited, an experimental study in an animal model has shown that metformin reduces the risk of OHSS through various mechanisms. It decreases ovarian VEGF levels or its induction, thereby limiting the vascular permeability responsible for fluid shifts and severe OHSS symptoms.

In addition, metformin normalizes the expression of proteins involved in inflammation and angiogenesis, such as Cyclooxygenase-2 (COX-2) and Nitric Oxide Synthase (NOS), which may restrict the formation of pathological vasculature [43]. Furthermore, it has been shown that by lowering estradiol levels on the trigger day, metformin reduces the risk of an excessive ovarian response to gonadotropins [44].

2.4 Patient Characteristics Associated with Reproductive Response to Metformin in PCOS

Metformin's reproductive effects in women with PCOS appear to vary across patient subgroups, with metabolic phenotype and baseline insulin resistance among the most consistent predictors of benefit. Evidence suggests that metformin's capacity to improve ovulation, menstrual regularity, and pregnancy outcomes is more pronounced in women with insulin resistance or obesity, likely due to its ability to enhance insulin sensitivity and reduce hyperinsulinemia, which are central to PCOS pathophysiology and anovulatory infertility. In studies of PCOS populations, those with demonstrable insulin resistance experienced greater improvements in ovulation and reproductive endocrine parameters with metformin treatment compared with less insulin-resistant counterparts, although data remain heterogeneous [45].

Additionally, although some analyses have reported improved reproductive outcomes with metformin in women with higher BMI, other evidence indicates that the effects may be attenuated in severely obese individuals (e.g., BMI >35 kg/m²), suggesting a complex interaction between body composition and treatment response [46]. In lean PCOS phenotypes, metformin has also been shown to restore menstrual cyclicity and ovulation in some cases, particularly when insulin resistance is present, although the magnitude of reproductive benefit may be less consistent than in those with overt metabolic dysfunction [47].

Collectively, these findings support the notion that metabolic characteristics, including baseline insulin resistance and BMI, may help identify PCOS patients who are most likely to derive reproductive benefit from metformin, but they also underscore the need for individualized assessment and further targeted research.

3 Myo-inositol (MI)

MI is another insulin-sensitizing agent used in women with PCOS. It has been shown to improve insulin sensitivity, normalize ovarian function, and restore spontaneous ovulation [48],

representing a promising alternative to conventional treatments for managing infertility associated with the PCOS.

3.1 Mechanisms of action

MI plays a key role in the intracellular insulin signaling pathway. It serves as a precursor of inositol phosphoglycans (IPGs), which function as second messengers of insulin signaling [49]. At the molecular level, myo-inositol has been shown to modulate multiple pathways that enhance insulin sensitivity. Notably, it promotes the activation of 5′-adenosine monophosphate–activated protein kinase (AMPK), a central regulator of cellular energy metabolism, thereby supporting improved glucose homeostasis and insulin signaling in experimental models of PCOS [50]. In addition, in vitro studies in human endometrial cells exposed to a PCOS-like environment demonstrate that myo-inositol increases AMPK phosphorylation and restores Glucose Transporter Type 4 (GLUT-4) protein levels, promoting glucose uptake in insulin-resistant tissues [51]. Furthermore, animal studies indicate that MI supplementation downregulates pro-inflammatory Interleukin-6 (IL-6) and phosphorylated Signal Transducer and Activator of Transcription 3 (STAT3) signaling while upregulating Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) and GLUT-4 expression, suggesting its involvement in multiple molecular pathways linked to enhanced insulin sensitivity [52].

3.2 Clinical Advantages and Limitations

In the context of PCOS, improved insulin sensitivity confers multiple secondary benefits. By reducing compensatory hyperinsulinemia, it decreases ovarian androgen production and increases SHBG levels, thereby lowering circulating free androgens and ameliorating hyperandrogenism [53]. This metabolic improvement also supports normal folliculogenesis and ovulatory function, as better insulin signaling restores intra-ovarian hormone balance and enhances follicular development[54]. Furthermore, enhanced insulin sensitivity positively impacts the overall metabolic profile, improving glucose tolerance, lowering circulating insulin levels, and favorably modulating lipid metabolism [55]. Insulin-mediated pathways are also closely linked to chronic low-grade inflammation in PCOS, and interventions that improve insulin sensitivity have been shown to reduce inflammatory markers such as IL-6 and Tumor Necrosis Factor Alpha (TNF-α) [56]. Finally, normalization of insulin signaling contributes to improved endometrial receptivity, which may enhance fertility outcomes by restoring proper endometrial function and glucose metabolism [57].

Although numerous studies suggest potential benefits of myo-inositol in PCOS, the overall evidence remains limited and inconclusive. Meta-analyses indicate that its impact on key clinical outcomes, such as pregnancy rates or live birth rates, is still uncertain [58]. The 2024 international evidence-based PCOS guidelines highlight significant limitations in the clinical evidence supporting inositol supplementation. Notably, no studies have adequately assessed live birth or miscarriage rates, which represent the most clinically meaningful endpoints [59,60]. Only a single small trial reported clinical pregnancy rates comparing inositol with placebo, but the extremely wide confidence intervals included the possibility of no effect [59]. Moreover, substantial heterogeneity exists across studies, with I^2 reaching 75% for ovulation outcomes, underscoring the variability in study design, populations, and interventions [59]. Collectively, these findings indicate that, despite some potential benefits on ovulation and metabolic parameters, the evidence supporting inositol's impact on clinically relevant reproductive outcomes remains lacking.

3.3 Comparison to Metformin

Comparisons between inositol and metformin reveal several key points. Inositol performs similarly to metformin for most metabolic parameters [61], whereas metformin may have an advantage for patients with higher waist-to-hip ratio and hirsutism [60]. Importantly, inositol is associated with markedly fewer gastrointestinal adverse effects, which is clinically significant given the common and bothersome gastrointestinal symptoms linked to metformin [60,61]. Evidence on differences in BMI and reproductive outcomes, however, remains very limited and uncertain [60].

3.4 Clinical Contexts for Optimal Inositol Use in PCOS

Inositol may be a suitable option for patients who cannot tolerate metformin due to gastrointestinal side effects [60,61], and it can be used alongside lifestyle interventions in those with metabolic abnormalities who prefer supplements over prescription medications [61,62]. It may also help regulate menstrual cycles in patients not actively seeking fertility[59,61], and emerging evidence suggests potential benefits when used in ART protocols, particularly for folliculogenesis and oocyte quality [63].

4 Berberine

Berberine is a naturally occurring isoquinoline alkaloid found in several medicinal plants, including *Berberis vulgaris* (barberry) and *Coptis chinensis* [64].

4.1 Mechanisms of Berberine Action in PCOS

Berberine improves both metabolic and reproductive disturbances in PCOS through effects on insulin signaling, androgen production, inflammation, lipid metabolism, and gut microbiota.

4.2 Enhancement of insulin sensitivity

Berberine activates AMPK in liver, muscle, and adipose tissue, promoting glucose uptake, suppressing hepatic gluconeogenesis, and improving insulin signaling. This reduction in hyperinsulinemia helps mitigate insulin-driven hyperandrogenism[65]. In ovarian cell models, berberine increases intracellular AMP levels and AMPK signaling, which further promotes glucose uptake and suggests potential direct effects on ovarian metabolic pathways [66]. In insulin-resistant PCOS rat models, berberine administration is associated with improved insulin sensitivity and restoration of metabolic markers, consistent with upstream AMPK-mediated mechanisms [67].

4.2.1 Androgen-lowering effects

Berberine lowers circulating insulin levels, which indirectly reduces ovarian androgen production in PCOS, as hyperinsulinemia enhances LH-stimulated androgen synthesis in theca cells [68]. In insulin-resistant PCOS models, berberine administration decreases serum insulin and testosterone levels, supporting the link between improved insulin sensitivity and reduced hyperandrogenism [69]. Additionally, some experimental studies suggest that berberine may directly modulate ovarian steroidogenic pathways, further contributing to the normalization of androgen levels [70].

4.2.2 Regulation of lipid metabolism

Berberine favorably regulates lipid metabolism, which is often disrupted in women with PCOS. It lowers LDL cholesterol, triglycerides, and total cholesterol, largely through AMPK-mediated effects on hepatic lipid synthesis and clearance [71]. These improvements in lipid profile may contribute to a reduced cardiometabolic risk in PCOS, complementing its insulin-sensitizing and reproductive benefits [72].

By improving dyslipidemia, berberine may indirectly support reproductive function in women with PCOS, as favorable lipid profiles are associated with better ovulatory response and pregnancy outcomes. For example, elevated serum total cholesterol (TC), Low-Density Lipoprotein Cholesterol (LDL-C) and triglycerides (TG) have been

independently linked to lower ovulation rates, reduced clinical pregnancy and live birth outcomes in PCOS patients undergoing ovulation induction, suggesting that dyslipidemia negatively influences ovarian response and fertility [73]. Moreover, disturbances in lipid metabolism indicators are significant mediators of early reproductive outcomes in IVF/ICSI cycles, indicating that lipid homeostasis contributes to oogenesis, embryo development and overall reproductive success in PCOS [74].

4.2.3 Influence on gut microbiota

Berberine has been shown to modulate the intestinal microbiota, benefiting both metabolic and reproductive pathways in PCOS. In animal models, berberine altered gut microbial composition and metabolites, improving insulin resistance, lipid metabolism, and chronic inflammation—key contributors to ovarian dysfunction [75]. These effects were linked to enhanced ovarian function, including better follicle development, increased ovulation, and improved hormonal balance, highlighting the potential role of the gut–ovary axis [76]. In women with PCOS, berberine supplementation has been associated with improved menstrual regularity, ovulation, and pregnancy rates, likely through its effects on gut microbiota and metabolic health [77]. Overall, modulating the gut microbiota with berberine may support both metabolic homeostasis and reproductive outcomes in PCOS, though further research is needed to directly connect microbial changes with fertility.

4.2.4 Anti-inflammatory and antioxidant activity

Berberine exerts significant anti-inflammatory and antioxidant actions, which may improve the ovarian microenvironment and support reproductive function in PCOS. Supplementation with berberine has been shown to reduce systemic levels of pro-inflammatory cytokines, including TNF-α, IL-6, and C-reactive protein, in metabolic disorders associated with insulin resistance [78]. In PCOS animal models, berberine downregulates ovarian expression of inflammatory mediators, restores normal follicular morphology, and improves granulosa cell function [79]. By mitigating chronic low-grade inflammation and oxidative stress, berberine may enhance ovarian steroidogenesis, follicular development, ovulation, and endometrial receptivity, all of which are critical for fertility in women with PCOS [78,79].

4.3 Clinical Use and Reproductive Outcomes of Berberine in PCOS

Despite its favorable metabolic and ovulatory effects, evidence that berberine improves live birth rates or reduces miscarriage rates in women with PCOS is limited and inconsistent. Randomized controlled trials indicate that berberine alone may result in lower cumulative live birth rates compared with standard ovulation-inducing agents such as letrozole, and adding berberine to letrozole does not appear to provide additional benefit [80]. Systematic reviews and meta-analyses similarly conclude that while berberine may improve intermediate outcomes, including ovulation and clinical pregnancy rates, there is no high-quality evidence demonstrating a significant effect on live births or miscarriage prevention [81,82]. Therefore, although berberine can support metabolic and reproductive health in PCOS, its clinical utility for achieving successful pregnancies remains uncertain, and further well-designed trials are required to clarify its role in fertility management.

5 Conclusion

Insulin resistance is a key driver of reproductive dysfunction in polycystic ovary syndrome and represents an important and modifiable therapeutic target in infertility management. Accumulating evidence indicates that insulin-sensitizing agents can meaningfully support reproductive function in women with PCOS by improving ovulatory function, hormonal balance, and the metabolic milieu underlying anovulation. Metformin remains the best-studied option, demonstrating consistent benefits on ovulation, pregnancy rates, and selected ART outcomes, particularly in women with insulin resistance or elevated BMI, although its effect on live birth remains variable. Emerging data suggest that myo-inositol and berberine may also contribute to improved ovulatory and metabolic outcomes with favorable tolerability profiles, highlighting their potential role as adjunctive or alternative therapies in selected patients, however these topics need further investigation. Clinically, insulin-sensitizing treatments may enhance fertility potential when integrated into an individualized, phenotype-driven approach. Future high-quality randomized trials focusing on live birth and miscarriage rates, standardized outcome measures, and precise patient stratification are warranted to further define and optimize the role of these agents in fertility care for women with PCOS.

Disclossure

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Conflicts of Interest

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