LITERATURE REVIEW: OFF LABEL USE ON, METFORMIN AS TREATMENT FOR POLYCYSTIC OVARY SYNDROME (PCOS)

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder affecting reproductive-aged women and is often accompanied by insulin resistance and hyperandrogenism. Metformin, a first-line antidiabetic agent, has been widely used in the treatment of PCOS due to its ability to improve insulin sensitivity, regulate menstrual cycles, reduce androgen levels, and promote ovulation. This literature review aims to critically evaluate and synthesize previous research findings on metformin and the influence of genetic and metabolic factors on individual responses in PCOS patients. Nine clinical studies published in the last five years were analyzed. The findings indicate that metformin consistently improves hormonal and metabolic parameters, particularly in overweight or insulin-resistant patients. Combination therapies, such as metformin with pioglitazone, liraglutide, or exenatide, were shown to be more effective than monotherapy in managing metabolic dysfunction and reproductive abnormalities. However, gastrointestinal side effects and interindividual variability in therapeutic response remain significant challenges. These results suggest that personalized treatment strategies based on patient phenotype and tolerance may optimize outcomes. Further research is needed to establish predictive markers and refine therapeutic regimens for long-term PCOS management.

Keywords: Metformin; PCOS; Insulin Resistance; Hormonal Therapy; Pharmacogenetics

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder commonly found in women of reproductive age, with an estimated prevalence of around 5–10%. This condition is typically characterized by ovulatory dysfunction, elevated androgen levels, and polycystic ovarian morphology, often accompanied by metabolic disturbances such as insulin resistance, overweight, and dyslipidemia. (Pedersen et al., 2018).

Metformin, a commonly used antidiabetic agent, is widely employed as a first-line therapy for type 2 diabetes mellitus and has also been extensively utilized in the management of polycystic ovary syndrome (PCOS). Its therapeutic benefits are primarily attributed to its ability to improve insulin sensitivity, promote weight loss, and correct lipid abnormalities. The American Diabetes Association (ADA) recommends metformin as a first-line treatment for both type 2 diabetes and PCOS, due to its effectiveness in addressing insulin resistance, obesity, and hyperandrogenism (Peng et al., 2023).

Numerous studies have demonstrated that metformin can reduce serum testosterone levels and improve the clinical manifestations of PCOS. However, the molecular mechanisms underlying the therapeutic effects of metformin remain complex and are not yet fully understood. Moreover, the response to metformin therapy among patients with PCOS exhibits considerable interindividual variability. While some patients experience significant improvements in metabolic parameters and reproductive function, others derive only minimal benefits

or exhibit no clinically meaningful response at all. This variability has led to the hypothesis that individual factors—such as insulin resistance status, body composition, and genetic variations in metformin transporters and molecular targets—may influence therapeutic efficacy. In this context, genetic polymorphisms in genes such as OCT1, MATE1, MATE2-K, HNF1A, and ATM have been extensively investigated to evaluate their association with the pharmacodynamic response to metformin, although findings remain inconsistent across studies. (Pedersen et al., 2018).

Although metformin is effective in addressing metabolic complications in patients with PCOS, its use is often limited by gastrointestinal side effects, which may negatively impact patient adherence. As an alternative, acupuncture therapy has gained increasing attention for its potential to enhance insulin sensitivity through modulation of the autonomic nervous system. However, scientific evidence supporting the efficacy of acupuncture remains limited, particularly from randomized controlled trials. (Wen et al., 2022).

In addition, multiple studies have reported that metformin not only improves the frequency and regularity of menstrual cycles in patients with PCOS, but also significantly reduces serum androgen levels and stimulates ovulation, which is often disrupted in this condition. Nevertheless, the therapeutic response to metformin varies considerably among individuals, with some patients showing minimal or no meaningful clinical improvement following treatment. This variability highlights the urgent need for a more comprehensive evaluation of the factors that may influence therapeutic outcomes, such as differences in insulin resistance, body composition and distribution, as well as overall metabolic status. These factors are believed to play a central role in determining individual responsiveness to metformin. Another significant challenge in clinical practice is the lack of clear consensus regarding the optimal dosage, the most effective duration of therapy, and reliable predictive markers of treatment success that can be applied across the diverse phenotypes of PCOS. These uncertainties hinder the development of more targeted and personalized therapeutic protocols. Therefore, further research is warranted to identify clinical, biochemical, and genetic parameters that contribute to the therapeutic efficacy of metformin (Attia et al., 2023).

Accordingly, this study aims to evaluate the effectiveness of metformin in the treatment of PCOS and to explore the potential contribution of genetic and metabolic factors to the variability in treatment response. The findings are expected to contribute to the development of more personalized, evidence-based therapeutic approaches.

METHODS

The method employed in the preparation of this article is a literature review based on research findings from the past five years, sourced from PubMed and Scholar databases. The search keywords used in the reviewed articles included “Metformin Polycystic Ovary Syndrome,” “Pharmacogenetics metformin PCOS,” and “Effectiveness of metformin in PCOS patients,” combined using the Boolean operator “AND” to broaden the scope of relevant search results within the category of open full-access publications. Following several screening stages to match predefined inclusion criteria, a total of nine articles were identified as eligible for review.

RESULT

Table 1. Comparative Summary of Study Findings

No	Author(s) & Year of Study	Journal Name	Title of Study	Study Design	Study Sample	Study Findings
1	Pedersen et al., 2018	*Basic Clinical Pharmacology & Toxicology* (BCPT)	The Pharmacogenetics of Metformin in Women with Polycystic Ovary Syndrome: A Randomized Trial	Randomized Clinical Trial	40 female patients (Caucasia)	Metformin significantly reduced body weight in women with PCOS after 12 months of therapy, with no significant impact from genetic variations (OCT1, MATE1, MATE2-K, HNF1A, ATM). No meaningful changes were observed in insulin sensitivity or most lipid parameters, except a slight increase in triglycerides. Metformin was safe and well-tolerated.
2	Wiweko & Susanto, 2017	Wolters Kluwer - Medknow dalam Journal of Human Reproductive Sciences	The Effect of Metformin and Cinnamon on Serum Anti-Mullerian Hormone in Women Having PCOS: A Double-Blind, Randomized, Controlled Trial	Double-blind, Randomized, Controlled Trial (RCT)	51 female patients	Of the 38 participants, 20 received metformin and 18 DLBS3233. After six months, AMH levels significantly decreased in the metformin group (ΔAMH = 1.83; P = 0.003), but not in the DLBS3233 group (ΔAMH = 1.15; P = 0.077). Side effects were more frequent with metformin (35% nausea; P = 0.006), while DLBS3233 was better tolerated (61.1% with no side effects; P = 0.01). Seven participants became pregnant spontaneously (5 metformin, 2 DLBS3233). Significant BMI reduction occurred

						only in the DLBS3233 group (ΔBMI = 0.54; P = 0.017).
3	Wen et al., 2022	*Human Reproduction*, Oxford University Press	Effect of acupuncture and metformin on insulin sensitivity in women with polycystic ovary syndrome and insulin resistance: a three-armed randomized controlled trial	Double-blind, Randomized, Controlled Trial (RCT)	342 female patients	Acupuncture was not more effective than either metformin or sham acupuncture in improving insulin sensitivity in women with PCOS and insulin resistance. Metformin remained superior in reducing insulin resistance, despite its frequent association with gastrointestinal side effects. Acupuncture, on the other hand, was associated with milder side effects and holds potential as a non-pharmacological alternative for patients who are intolerant to metformin.
4	Kshatri et al., 2022	Journal of family medicine and primary care	A randomized, controlled trial comparing the metformin, oral contraceptive pills and their combination in patients with polycystic ovarian syndrome	Parallel-Group Randomized Controlled Trial (RCT)	90 female patients	All treatment groups (metformin, oral contraceptive pills [OCP], and their combination) showed improvements in clinical symptoms such as menstrual irregularities and hirsutism. The combination of metformin and OCP yielded the most optimal results in reducing insulin resistance, inflammatory markers, and improving body composition. Metformin was effective in improving lipid profiles, insulin

						resistance, and inflammation, while OCP was more effective in alleviating hyperandrogenic symptoms but tended to worsen lipid profiles and body fat percentage. No severe adverse effects were reported in any of the groups. Overall, combination therapy was considered the most effective in improving clinical, hormonal, and metabolic aspects in patients with PCOS.
5	Zhao et al., 2024	Journal of Ovarian Research, 2024, 17:42	Metformin versus metformin plus pioglitazone on gonadal and metabolic profiles in normal-weight women with polycystic ovary syndrome: a single-center, open-labeled prospective randomized controlled trial	Parallel-Group Randomized Controlled Trial (RCT)	60 female patients	Both MET and PIOMET improved menstrual cycles and hormonal profiles. PIOMET was superior in increasing SHBG, AMH, and postprandial glucose. Neither treatment affected body weight. Larger studies are needed for confirmation.
6	Rui-Lin Ma et al., 2021	Chinese Medical Journal	Short-term combined treatment with exenatide and metformin for overweight/ obese	Prospective, Open-Label, Randomized Clinical Trial with Two Treatment Arms	50 female patients	This study demonstrated that the combination of once-weekly exenatide and metformin over a 12-week period resulted in significantly greater reductions in body weight, BMI, and waist

		women with polycystic ovary syndrome	circumference compared to metformin alone in obese patients with PCOS. Total testosterone levels decreased significantly in both groups without any intergroup differences, while DHEAS levels remained unchanged. The combination group also showed significant improvements in fasting glucose, 2-hour OGTT glucose and insulin levels, as well as an increase in the Matsuda Index, changes that were not observed in the metformin-only group. Lipid profiles revealed increases in HDL-c, ApoA1, and triglycerides in both groups; however, total cholesterol increased only in the metformin group. Mild to moderate gastrointestinal side effects occurred in both groups, with no severe adverse events reported and overall good tolerability. In conclusion, the combination of exenatide and metformin appears to be more effective in managing body weight and glucose metabolism in obese women with PCOS, with minimal side effects, although long-term studies are needed to confirm these findings.

7	(Akhtar et al., 2021)	IMC J Med Sci 2021; 15(2):001	Effects of metformin on polycystic ovary syndrome: a randomized, double-blind, placebo-controlled study	Randomized Controlled Trial (RCT)	80 female patients	After a 9-month intervention, the metformin group showed a significant reduction in BMI and waist circumference compared to the placebo group, particularly among patients with a BMI >25 kg/m². In contrast, patients with a BMI <23 kg/m² in the metformin group experienced a significant increase in body weight compared to placebo. Menstrual cycles became significantly more regular in the metformin group, accompanied by increased progesterone scores, reduced anovulation, and improvements in signs of hirsutism. Gastrointestinal side effects, particularly diarrhea, were more frequently reported in the metformin group but tended to improve over time. This double-blind, randomized, long-duration study underscores the importance of lifestyle modification in conjunction with metformin therapy for managing PCOS symptoms, including androgenic activity, weight loss, waist circumference, BMI, and menstrual irregularities.
8	Ghalia M. Attia et al, 2023	Cureus	Role of Metformin in Polycystic	Descriptive Qualitative Study	201 female patients	Polycystic Ovary Syndrome (PCOS), with a prevalence ranging from 4% to

	Ovary Syndrome (PCOS)-Related Infertility	21%, is characterized by anovulation, hyperandrogenism, and insulin resistance, all of which contribute to infertility. Metformin, an antidiabetic agent, has been shown to effectively enhance insulin sensitivity, reduce androgen levels, regulate menstrual cycles, and induce ovulation, either as monotherapy or in combination with other agents such as clomiphene citrate. It is particularly beneficial for women with mild to moderate obesity who do not respond to clomiphene alone. In in vitro fertilization (IVF) programs, metformin may lower the risk of ovarian hyperstimulation syndrome, although its effect on pregnancy success rates remains inconsistent. Gastrointestinal side effects are commonly reported but generally well-tolerated, especially when dosages—typically 500–850 mg taken two to three times daily—are gradually titrated. Metformin exerts its therapeutic effects by increasing peripheral insulin sensitivity, reducing hepatic glucose production, decreasing intestinal glucose absorption,

						and restoring normal menstrual cycles and ovulation in PCOS patients.
9	Chuan Xing et al., 2022	Frontiers	Effect of metformin versus metformin plus liraglutide on gonadal and metabolic profiles in overweight patients with polycystic ovary syndrome	Open-Label Randomized Clinical Trial	60 female patients	The study findings showed that both treatment approaches—metformin alone and the combination of metformin with liraglutide—were effective in improving menstrual cycles, anthropometric parameters, glucose metabolism, and insulin resistance in overweight patients with PCOS. However, the combination therapy proved to be more effective in addressing reproductive dysfunction and hyperandrogenemia, as indicated by significant increases in LH, progesterone, total testosterone, and SHBG levels, along with a greater reduction in the free androgen index compared to metformin monotherapy. In conclusion, although both therapies provide clinical benefits, the metformin–liraglutide combination offers more optimal outcomes in managing hormonal and metabolic abnormalities, potentially through modulation of the

	hypothalamic–pituitary–ovarian axis.

DISCUSSION

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder that significantly affects metabolic and reproductive health in women of reproductive age. A primary feature of PCOS is insulin resistance, which not only disrupts glucose homeostasis but also exacerbates hyperandrogenism and ovulatory dysfunction. Consequently, metformin, a biguanide antidiabetic agent, is one of the most commonly used non-hormonal therapies for managing PCOS due to its ability to improve insulin sensitivity, suppress hepatic glucose production, and enhance reproductive hormonal profiles.

Analysis of the nine reviewed studies demonstrates a consistent role of metformin in improving multiple clinical aspects of PCOS, although its effectiveness may vary among individuals. The randomized clinical trial by Pedersen et al. (2018) revealed that metformin significantly reduced body weight after 12 months of treatment. However, genetic polymorphisms in genes such as OCT1, MATE1, MATE2-K, HNF1A, and ATM showed no significant influence on clinical response, suggesting that while pharmacogenetics may be relevant, they are not sole determinants of therapeutic outcomes.

In contrast, clinical factors such as body mass index (BMI) and baseline metabolic conditions appear to have a greater impact. Akhtar et al. (2021) reported more pronounced reductions in body weight and waist circumference among patients with BMI >25 kg/m², indicating that metformin is more effective in overweight or obese individuals. This aligns with its primary mechanism of action focused on enhancing insulin sensitivity.

However, not all effects of metformin are uniformly positive. Gastrointestinal side effects, such as nausea and diarrhea, were frequently reported, as seen in the studies by Wiweko & Susanto (2017) and Akhtar et al. (2021). Although these side effects are generally mild and well-tolerated, they remain a challenge for patient adherence to long-term therapy. In this context, patient education and gradual dose titration are essential to minimize adverse events.

One of the key findings from the literature is that combination therapy involving metformin and other pharmacological agents may yield superior clinical outcomes. The study by (Ma et al., 2021) demonstrated that the combination of metformin and exenatide was significantly more effective in reducing body weight, BMI, and waist circumference compared to metformin monotherapy. Additionally, this combination showed greater improvements in blood glucose parameters and insulin sensitivity, as evidenced by an increase in the Matsuda Index. Similar findings were reported by(Xing et al., 2022), where the combination of metformin and liraglutide resulted in significant improvements in reproductive hormones such as LH, progesterone, and SHBG, along with a greater reduction in the free androgen index compared to metformin alone. These results suggest that combination therapy may offer a more effective strategy for simultaneously addressing both the metabolic and reproductive aspects of PCOS.

in the context of fertility outcomes, Attia et al. (2023) highlighted that metformin can induce ovulation and improve menstrual regularity, both as monotherapy and in combination with clomiphene citrate. This aligns with the findings of Zhao et al. (2024), who compared metformin monotherapy with a combination of metformin and pioglitazone (PIOMET). Both treatments were shown to enhance menstrual cycles and hormonal profiles, with the combination therapy demonstrating superior effects on increasing

SHBG and AMH levels. However, these improvements were not always accompanied by weight loss, indicating that metformin may exert beneficial hormonal effects independently of significant anthropometric changes.

Meanwhile, a systematic review by Kutenaei et al. (2021) compared the effectiveness of metformin with myo-inositol and found that although both agents were effective in improving ovarian function and menstrual cycles, a combination therapy or individualized approach based on patient characteristics may be more rational. Myo-inositol was generally better tolerated and may serve as an alternative for patients who are intolerant to metformin.

Overall, these findings indicate that the effectiveness of metformin in PCOS therapy is highly dependent on patient phenotype, the severity of insulin resistance, and the presence of obesity. Metformin therapy is most beneficial in PCOS patients with evident insulin resistance, who are overweight or obese, and who present with menstrual irregularities and hyperandrogenism. However, metformin monotherapy may not be sufficient for all patients. Therefore, combination therapy—either with other insulin sensitizers such as pioglitazone or with incretin-based agents such as GLP-1 agonists (liraglutide or exenatide) should be considered in cases that do not respond adequately to monotherapy. These studies also emphasize the need for an individualized therapeutic approach in the management of PCOS, taking into account pharmacogenetic factors, metabolic parameters, and the specific clinical complaints of each patient.

In addition, the study by Wen et al. (2022) provides valuable insights into the potential of non-pharmacological therapies for managing PCOS, particularly in patients with insulin resistance. In a three-arm randomized controlled trial involving acupuncture, sham acupuncture, and metformin, the results showed that acupuncture was not more effective than the other two groups in improving insulin sensitivity, which is a primary therapeutic target in metabolically compromised PCOS patients. Metformin remained the superior choice, as evidenced by a significant reduction in insulin resistance. However, its use continues to be limited by gastrointestinal side effects such as nausea and diarrhea, which often impact patient adherence to long-term treatment. Conversely, acupuncture demonstrated a more favorable safety profile with milder side effects, although its overall effectiveness was limited. Nevertheless, these findings suggest that acupuncture may be considered as an adjunct or alternative therapy for patients who are intolerant to metformin or have contraindications to pharmacological treatment. This further reinforces the importance of a personalized therapeutic approach, in which patient preferences, drug tolerability, and individual metabolic profiles are key considerations in selecting long-term treatment strategies for PCOS.

Meanwhile, Kshatri et al. (2022) evaluated the effectiveness of metformin, oral contraceptive pills (OCP), and their combination in a prospective clinical trial. The results indicated that the combination of metformin and OCP produced the most optimal improvements in insulin resistance, inflammatory markers, and body composition. Metformin was more effective in improving metabolic parameters such as lipid profiles and insulin resistance, while OCPs were superior in addressing hyperandrogenism. However, OCPs tended to worsen lipid profiles, highlighting the need to consider patients' metabolic risk when selecting treatment. The combination therapy provided comprehensive clinical benefits across hormonal, metabolic, and symptomatic dimensions of PCOS, supporting the notion that a multidisciplinary approach may offer greater advantages than monotherapy.

Although metformin therapy is generally considered safe, regular monitoring of gastrointestinal side effects, along with patient education to enhance treatment adherence, remains a critical aspect of clinical practice.

With the growing understanding of the clinical heterogeneity of PCOS, it is essential

for clinicians to consider metformin as part of a multimodal approach that includes lifestyle modification, dietary interventions, and regular monitoring of hormonal and metabolic parameters.

CONCLUSION

Based on the review of nine studies, metformin has been proven effective in improving various clinical parameters in PCOS patients, such as reducing androgen levels, regulating menstrual cycles, stimulating ovulation, and enhancing insulin sensitivity, particularly in patients with obesity or insulin resistance. Combination therapy with other agents such as pioglitazone, liraglutide, or exenatide showed superior results in addressing metabolic and hormonal disturbances compared to metformin monotherapy. However, interindividual variability in therapeutic response remains a clinical challenge, which may be influenced by genetic factors, metabolic status, and drug tolerability. Gastrointestinal side effects, such as nausea and diarrhea, are commonly reported but generally tolerable and tend to diminish over time. Therefore, a personalized therapeutic approach based on patient characteristics and regular monitoring is necessary to optimize the benefits of metformin, along with further research to identify predictors of treatment success and determine optimal combination regimens for long-term PCOS management.

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