INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Polycystic Ovary Syndrome and Metformin: A Comprehensive Review of Pharmacological and Clinical Evidence

Tanya Singh[1*], Ashish Kushwaha[2], Dr. Arun Kumar Maurya[3], Dr. Lalit Bisht[4]

[1] Student, JBIT College of Pharmacy,, 23rd Milestone, NH-07, Chakrata Road, Shankarpur, Near Sahaspur, Dehradun, Uttarakhand – 248197, India.
[2] Assistant Professor, JBIT College of Pharmacy,, 23rd Milestone, NH-07, Chakrata Road, Shankarpur, Near Sahaspur, Dehradun, Uttarakhand – 248197, India.
[3] Professor, JBIT College of Pharmacy,, 23rd Milestone, NH-07, Chakrata Road, Shankarpur, Near Sahaspur, Dehradun, Uttarakhand – 248197, India.
[4] Professor, JBIT College of Pharmacy,, 23rd Milestone, NH-07, Chakrata Road, Shankarpur, Near Sahaspur, Dehradun, Uttarakhand – 248197, India.

ARTICLE INFO

Published: 25 Nov 2026
Keywords:
Polycystic ovary syndrome, metformin, hyperinsulinemia, infertility, insulin resistance, hyperandrogenism, anovulation, ovulation induction, reproductive outcomes
DOI:
10.5281/zenodo.24527767

ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder affecting women of reproductive age and is frequently associated with menstrual irregularities, ovulatory dysfunction, hyperandrogenism and insulin resistance. Ovulatory dysfunction is a major contributor to infertility in women with PCOS, as impaired follicular development and failure of regular ovulation can reduce the likelihood of natural conception. Metformin, an oral biguanide primarily used in the management of type 2 diabetes mellitus, has been investigated as a therapeutic option for PCOS because it reduces hepatic glucose production and improves insulin sensitivity (Rena et al., 2017). By improving insulin sensitivity and potentially reducing compensatory hyperinsulinemia, metformin may indirectly influence ovarian androgen production and contribute to improvements in menstrual regularity and ovulatory function in some women. Although clinical studies have reported improvements in selected metabolic and hormonal parameters, reproductive outcomes vary across populations and treatment settings. Improvements in insulin sensitivity or menstrual regularity do not necessarily translate into successful ovulation, clinical pregnancy or live birth. Current international evidence-based guidelines recommend letrozole as the first-line pharmacological treatment for ovulation induction in women with PCOS-

***Corresponding Author:** Tanya Singh
Address: Student, JBIT College of Pharmacy,, 23rd Milestone, NH-07, Chakrata Road, Shankarpur, Near Sahaspur, Dehradun, Uttarakhand – 248197, India.
Email ✉: tanyasingh050205@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

related anovulatory infertility when no other infertility factors are present (Teede et al., 2023). Metformin may therefore be considered in selected patients, particularly when metabolic abnormalities are also present, and may be used alongside other treatments when clinically appropriate. This narrative review examines the pathophysiology of PCOS-related infertility, the pharmacological mechanisms of metformin, its effects on metabolic regulation, androgen levels and ovulatory function, available clinical evidence, safety considerations, research limitations and future directions. The review aims to clarify the potential benefits and limitations of metformin and establish its appropriate clinical role in the individualized management of PCOS-related infertility.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders affecting women of reproductive age. It is characterized by a combination of reproductive, hormonal and metabolic abnormalities, including ovulatory dysfunction, clinical or biochemical hyperandrogenism and polycystic ovarian morphology. The estimated prevalence of PCOS ranges from approximately 8% to 13%, depending on the diagnostic criteria and population studied (Azziz et al., 2016; Teede et al., 2023). According to the Rotterdam diagnostic criteria, PCOS is diagnosed when at least two of these three features are present after excluding other conditions that may produce similar clinical manifestations. The clinical presentation varies considerably among affected women, making PCOS a heterogeneous disorder (Azziz et al., 2016; Teede et al., 2023)

Women with PCOS may experience irregular or absent menstrual periods, excessive facial or body hair growth, acne and scalp hair thinning. Ovulatory dysfunction is an important cause of infertility in affected women because impaired follicular maturation and failure of regular ovulation can reduce the likelihood of natural conception. In addition to reproductive abnormalities, PCOS is associated with insulin resistance, impaired glucose tolerance, dyslipidemia and an increased risk of developing type 2 diabetes. Long-term reproductive health concerns may also include endometrial hyperplasia, particularly in women experiencing prolonged untreated anovulation (Azziz et al., 2016; Teede et al., 2023).

Insulin resistance and hyperandrogenism are important interacting mechanisms involved in the pathophysiology of PCOS. Insulin resistance occurs when body tissues respond less effectively to insulin, resulting in compensatory hyperinsulinemia. Increased insulin concentrations may stimulate ovarian theca cells to produce androgens and enhance the effects of luteinizing hormone (LH) on ovarian androgen production. Furthermore, hyperinsulinemia may reduce hepatic production of sex hormone-binding globulin (SHBG), increasing the proportion of circulating free and biologically active testosterone. Increased androgen availability may interfere with normal follicular development and contribute to follicular arrest, menstrual irregularities and anovulation. However, the degree of insulin resistance and hyperandrogenism varies among women with PCOS, and these abnormalities are not present to the same extent in every patient (Rosenfield & Ehrmann, 2016; Cassar et al., 2016; Teede et al., 2023).

The association between insulin resistance, hyperinsulinemia and reproductive dysfunction has encouraged research into insulin-sensitizing treatments for PCOS. Metformin is an oral biguanide primarily used in the management of type 2 diabetes mellitus by reducing hepatic glucose production and improving insulin sensitivity. Its potential therapeutic role in PCOS is based on its ability to improve metabolic regulation and potentially reduce the effects of excessive insulin concentrations on ovarian androgen production. Metformin may also influence cellular energy regulation through AMP-activated protein kinase (AMPK)-dependent and AMPK-independent pathways. Although these mechanisms provide a physiological rationale for investigating metformin in PCOS, its complete mechanism of action in affected women is not fully established (Zhou et al., 2001; Foretz et al., 2010; Rena et al., 2017).

Clinical studies have investigated the effects of metformin on several metabolic and reproductive outcomes in women with PCOS. Systematic reviews and meta-analyses have reported improvements in insulin resistance and certain lipid parameters compared with placebo or other control interventions, although the magnitude and certainty of these effects vary according

to study design, participant characteristics and treatment duration. Metformin has also been associated with improvements in menstrual regularity and ovulatory function in some women. However, metabolic and reproductive outcomes should be evaluated separately because improvements in insulin sensitivity or menstrual regularity do not necessarily indicate successful ovulation, clinical pregnancy or live birth (Lord et al., 2003; Melin et al., 2023).

The effects of metformin on hyperandrogenism are also variable. Some studies have reported reductions in total testosterone and other biochemical indicators of androgen excess. These changes may be associated with improved insulin sensitivity and reduced ovarian androgen production. However, biochemical improvements do not consistently produce significant reductions in clinical symptoms such as hirsutism and acne. Combined oral contraceptive pills may be more effective for managing menstrual irregularities and androgen-related symptoms in women who are not seeking pregnancy, whereas metformin may be particularly relevant when metabolic abnormalities are also present (Fraison et al., 2020; Fontes et al., 2023; Melin et al., 2024).

The reproductive benefits of metformin require careful interpretation. Some clinical trials and evidence syntheses have reported improvements in ovulation and clinical pregnancy compared with placebo or other treatment approaches. However, the evidence for live birth and the comparative effectiveness of metformin against established ovulation-induction treatments require careful consideration. According to the 2023 international evidence-based guideline, metformin may be used alone in women with PCOS-related anovulatory infertility and no other infertility factors to improve clinical pregnancy and live-birth rates, although women should be informed that more effective ovulation-induction agents are available. Metformin has also been investigated in assisted reproductive treatment for its potential role in reducing ovarian hyperstimulation syndrome in selected treatment settings. Therefore, its reproductive effects should not be considered equivalent to those of established ovulation-induction treatments (Creanga et al., 2008; Legro et al., 2007; Morley et al., 2017; Palomba et al., 2014; Wu et al., 2020; Teede et al., 2023).

Current international evidence-based guidelines recognize the metabolic role of metformin in women with PCOS, particularly those with a higher body mass index (BMI) or increased metabolic risk. For women with PCOS-related anovulatory infertility and no other infertility factors, letrozole is recommended as the first-line pharmacological treatment for ovulation induction. Metformin may be considered according to individual metabolic requirements and reproductive circumstances rather than as a universal replacement for established fertility treatments. These PCOS-specific recommendations should be distinguished from recommendations for metformin in type 2 diabetes mellitus. Furthermore, reported improvements in cardiovascular surrogate markers, including carotid intima-media thickness (CIMT) and flow-mediated dilation (FMD), should not be interpreted as evidence that metformin reduces actual cardiovascular events in women with PCOS (Teede et al., 2023; Wang et al., 2024).

Despite extensive research, uncertainties remain regarding the patient characteristics associated with the greatest response to metformin, the optimal treatment

duration and its comparative effectiveness against other therapeutic options. Differences in PCOS phenotypes, baseline insulin resistance, treatment protocols and outcome measurements make it difficult to establish consistent conclusions across clinical studies. Further research is required to clarify these issues and establish the long-term metabolic and reproductive effects of treatment.

Therefore, the present narrative review aims to critically examine the pharmacological and clinical evidence concerning metformin in women with PCOS. It focuses on its mechanisms of action, metabolic effects, influence on hyperandrogenism, menstrual regularity and ovulatory function, and its potential role in fertility management. The review also discusses its safety profile, limitations, comparison with other treatment options and current clinical recommendations. The central research question is: What are the metabolic and reproductive benefits and limitations of metformin in women with PCOS-related infertility compared with placebo, lifestyle interventions and other relevant pharmacological treatments, and how do patient characteristics influence its appropriate clinical use?

METHODOLOGY

This article is presented as a narrative review of the available scientific literature concerning the role of metformin in polycystic ovary syndrome (PCOS). Relevant publications were identified through searches of PubMed and Google Scholar. The literature search covered publications available up to October 2026.

The search terms included combinations of the following

keywords: “polycystic ovary syndrome”, “PCOS”, “metformin”, “insulin resistance”, “hyperandrogenism”, “ovulation”, “menstrual irregularities”, “infertility”, “pregnancy outcomes” and “metabolic complications”.

Original research articles, randomized controlled trials, systematic reviews, meta-analyses and clinical practice guidelines relevant to the objectives of this review were considered. Priority was given to studies evaluating the metabolic, hormonal and reproductive effects of metformin in women diagnosed with PCOS.

The selected literature was interpreted by considering study design, participant characteristics, treatment duration, comparator groups, reported clinical outcomes and methodological limitations. Particular attention was given to distinguishing metabolic outcomes from menstrual regularity, ovulation, clinical pregnancy and live birth.

As this is a narrative review, no formal systematic screening procedure, pooled statistical analysis or independent grading of evidence certainty was undertaken. The findings were interpreted in the context of the available evidence and the limitations of individual studies.

3. Literature Review

3.1 Pathophysiology of PCOS

Polycystic ovary syndrome (PCOS) is a complex hormonal and metabolic disorder in which several mechanisms interact and contribute to its development. The exact cause of PCOS is not completely understood. However, genetic susceptibility, abnormal hormonal regulation, insulin resistance and excessive androgen production are considered important factors. These disturbances affect normal ovarian function and follicular development, often resulting in irregular menstrual cycles, anovulation and difficulty in conceiving. The severity and combination of these abnormalities vary among affected women, meaning that PCOS does not present in the same way in every individual (Teede et al., 2023; Azziz et al., 2016).

3.2 Insulin Resistance and Hyperinsulinemia

Insulin resistance is an important metabolic abnormality associated with PCOS. It occurs when body tissues respond less effectively to insulin, the hormone responsible for regulating blood glucose levels. To compensate for this reduced response, the pancreas releases more insulin, resulting in a condition known as hyperinsulinemia. This abnormality may occur in women with PCOS who are overweight or obese, as well as in those with normal body weight (Cassar et al., 2016; Teede et al., 2023).

Increased insulin levels affect ovarian function by stimulating androgen production and enhancing the effect of luteinizing hormone (LH) on ovarian theca

cells. These cells are responsible for producing androgens, including testosterone and androstenedione. Excessive insulin may also contribute to impaired glucose regulation, abnormal lipid levels and an increased risk of long-term metabolic complications (Rosenfield and Ehrmann, 2016; Teede et al., 2023).

3.3 Excessive Androgen Production

Hyperandrogenism, which generally refers to increased androgen levels or their clinical effects, is one of the major features of PCOS. Androgens are produced mainly by the ovarian theca cells, although the adrenal glands can also contribute to their production. In PCOS, abnormal regulation of ovarian steroid production can result in excessive androgen secretion. Hyperinsulinemia further enhances this process by acting alongside LH and increasing ovarian androgen production (Azziz et al., 2016; Rosenfield and Ehrmann, 2016).

Insulin also influences the liver's production of sex hormone-binding globulin (SHBG), a protein that binds circulating sex hormones, including testosterone. Increased insulin levels can reduce hepatic SHBG production, resulting in a greater proportion of circulating testosterone remaining unbound. This increases the availability of free testosterone and may contribute to clinical manifestations such as acne, hirsutism and impaired follicular development (Azziz et al., 2016; Teede et al., 2023).

3.4 Disturbance in the Hypothalamic-Pituitary-Ovarian Axis

The hypothalamic-pituitary-ovarian axis plays an essential role in regulating menstrual cycles and ovulation. The hypothalamus releases gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to secrete LH and follicle-stimulating hormone (FSH). These hormones coordinate ovarian steroid production and follicular development.

In many women with PCOS, the regulation of GnRH secretion is altered, resulting in an increased frequency of GnRH pulses and, in some cases, relatively increased LH secretion compared with FSH. Increased LH stimulation can promote androgen production by the ovarian theca cells, while inadequate FSH activity may interfere with the normal maturation of ovarian follicles. These hormonal imbalances contribute to the disruption of normal ovarian function (Azziz et al., 2016; Rosenfield and Ehrmann, 2016).

However, these hormonal changes are not identical in all women with PCOS. Their extent may differ according to the individual's clinical phenotype and metabolic characteristics (Teede et al., 2023).

3.5 Impaired Follicular Development and Anovulation

Under normal conditions, ovarian follicles develop progressively, and one follicle generally becomes dominant and releases a mature oocyte during ovulation. In PCOS, excessive androgen exposure, altered gonadotropin activity and metabolic disturbances can interfere with this process. The follicles may begin developing but fail to mature completely. Instead, several small antral follicles may accumulate in the ovaries without one consistently progressing to the dominant stage. This phenomenon is known as follicular arrest. The accumulation of small follicles contributes to the polycystic ovarian morphology observed in some women with PCOS (Teede et al., 2023; Azziz et al., 2016).

When normal follicular maturation and ovulation are disrupted, menstrual cycles may become irregular or infrequent, and ovulation may be absent for prolonged periods. As a result, the release of a mature oocyte becomes unpredictable, which can reduce the likelihood of natural conception. Nevertheless, not every woman with PCOS experiences anovulation or infertility (Teede et al., 2023).

3.6 Interaction Between Insulin Resistance and Androgen Excess

Insulin resistance and androgen excess are closely interconnected in PCOS. Elevated insulin levels can stimulate ovarian androgen production and reduce hepatic SHBG production, increasing the availability of free testosterone. At the same time, excessive androgen exposure can adversely affect follicular development and contribute to disturbances in reproductive hormone regulation (Rosenfield and Ehrmann, 2016; Cassar et al., 2016).

LH and insulin can act together to enhance androgen synthesis in ovarian theca cells. This interaction strengthens the hormonal disturbance associated with PCOS and may contribute to the persistence of abnormal ovarian function. Insulin resistance can therefore aggravate reproductive abnormalities, although it is not the only mechanism responsible for the syndrome (Azziz et al., 2016; Rosenfield and Ehrmann, 2016).

The relationship between insulin resistance and androgen excess is particularly relevant when considering metformin. By improving insulin sensitivity, metformin may reduce excessive insulin exposure and influence some of the metabolic and hormonal disturbances associated with PCOS. However, its effects on androgen levels, menstrual regularity and ovulation vary among individuals. Improvement in insulin resistance does not necessarily guarantee the restoration of normal ovulation (Morley et al., 2017; Melin et al., 2023).

3.7 Associated Metabolic Disturbances

In addition to reproductive abnormalities, PCOS is associated with metabolic disturbances, which include impaired glucose tolerance, dyslipidemia and an increased risk of developing type 2 diabetes. These abnormalities are particularly relevant in women with insulin resistance and may be further influenced by excess body weight and other individual risk factors. Insulin resistance and compensatory hyperinsulinemia can contribute to abnormal glucose metabolism and changes in lipid regulation. However, excess body weight is not a necessary condition for PCOS, and metabolic abnormalities can also occur in women with a normal body mass index (Cassar et al., 2016; Teede et al., 2023).

These metabolic features are important because PCOS affects more than reproductive health alone. Its hormonal and metabolic disturbances may coexist and influence one another, making an individualized approach to assessment and management necessary (Teede et al., 2023; Azziz et al., 2016).

3.8 Overall Pathophysiology

The pathophysiology of PCOS involves the interaction of abnormal ovarian androgen production, altered gonadotropin regulation, insulin resistance and impaired follicular maturation. These mechanisms do not necessarily occur to the same extent in every affected woman, but their interactions help explain the wide range of reproductive and metabolic features associated with the syndrome.

The following flowchart summarizes one important pathway through which insulin resistance may contribute to reproductive abnormalities in PCOS.

Flowchart: Relationship Between Insulin Resistance and Reproductive Abnormalities in PCOS

Insulin resistance

↓

Compensatory hyperinsulinemia

↓

Increased ovarian androgen production and reduced hepatic SHBG production

↓

Increased availability of free androgens

↓

Disturbed follicular development and maturation

↓

Follicular arrest and possible anovulation

↓

Irregular menstrual cycles and possible difficulty conceiving

The above flowchart illustrates one important pathway through which insulin resistance may contribute to reproductive abnormalities in PCOS. However, PCOS is a multifactorial disorder involving interactions among genetic, hormonal and metabolic factors. Insulin resistance is not present to the same extent in every woman, and reproductive dysfunction may also occur through mechanisms independent of insulin resistance. These interconnected mechanisms provide a physiological rationale for investigating insulin-sensitizing treatments such as metformin in women with PCOS (Azziz et al., 2016; Teede et al., 2023; Cassar et al., 2016).

3.9 Pharmacological Profile of Metformin

Metformin is not a fertility drug by design; it was originally developed for the management of type 2 diabetes mellitus. It is an oral biguanide that mainly reduces glucose production by the liver and improves the body's response to insulin. In women with PCOS, these effects

may improve insulin sensitivity and reduce compensatory hyperinsulinemia. This may indirectly influence ovarian androgen production and SHBG levels, potentially creating a more favourable hormonal environment for follicular development and ovulation (Lord et al., 2003; Rena et al., 2017).

Metformin's action is associated with several cellular mechanisms, including effects on cellular energy metabolism and AMP-activated protein kinase (AMPK). However, its pharmacological action is complex and is not entirely dependent on AMPK activation. Although improvements in insulin sensitivity may contribute to favourable metabolic and hormonal changes, reductions in insulin levels do not automatically result in reductions in androgen levels or the restoration of ovulation in every woman. This variability forms an important reason why metformin has been investigated as a treatment option in PCOS, while its reproductive benefits and limitations continue to be evaluated (Zhou et al., 2001; Foretz et al., 2010; Rena et al., 2017).

4. Clinical Effects of Metformin

4.1 Effect on Hyperandrogenism

Hyperandrogenism is a common feature of polycystic ovary syndrome (PCOS), characterized by increased androgen levels or increased androgen activity in the body. It may lead to clinical manifestations such as excessive facial and body hair growth (hirsutism), acne and, in some women, scalp hair thinning. Insulin resistance contributes to this condition because compensatory hyperinsulinemia can stimulate ovarian androgen production and reduce the production of sex hormone-binding globulin (SHBG) by the liver. This results in increased availability of free testosterone, which may contribute to the symptoms of hyperandrogenism (Azziz et al., 2016; Rosenfield and Ehrmann, 2016).

Metformin may help manage this hormonal imbalance by improving insulin sensitivity and reducing compensatory hyperinsulinemia. A systematic review and meta-analysis by Fontes et al. (2023) reported a reduction in total testosterone levels with metformin in sensitivity analysis (standardized mean difference: −0.46; 95% confidence interval: −0.89 to −0.02). The review also reported changes in free androgen index (FAI), suggesting a possible improvement in biochemical hyperandrogenism. However, the response varied across the included studies and populations (Fontes et al., 2023)

A separate systematic review by Melin et al. (2024), comparing metformin with combined oral contraceptive pills, also examined differences in hormonal and clinical outcomes. Combined oral contraceptive pills may be more effective for certain androgen-related outcomes, including the regulation of androgen levels and SHBG. Therefore, a reduction in biochemical androgen levels with metformin does not necessarily mean that visible symptoms such as hirsutism and acne will improve to the same extent (Melin et al., 2024; Fraison et al., 2020).

Overall, metformin may help reduce biochemical hyperandrogenism in some women with PCOS, mainly through its effects on insulin resistance and ovarian androgen production. However, its effects on clinical symptoms such as excessive hair growth and acne are limited or less consistent. It may therefore be particularly useful when PCOS is associated with metabolic disturbances, while additional treatment may be required when visible androgen-related symptoms are the main concern (Teede et al., 2023).

4.2 Effect on Menstrual Function and Ovulation

Menstrual irregularities and ovulatory dysfunction are common features of PCOS and are often associated with insulin resistance and increased androgen production (Azziz et al., 2016; Rosenfield and Ehrmann, 2016).

Metformin may help improve menstrual regularity by improving insulin sensitivity and reducing compensatory hyperinsulinemia. These effects may support hormonal balance and normal ovarian function in some

women with PCOS (Naderpoor et al., 2015; Melin et al., 2023).

Several studies have examined the effects of metformin on menstrual frequency and ovulation. The Cochrane systematic review by Morley et al. (2017) reported that, compared with placebo or no treatment, metformin was associated with higher odds of ovulation (OR 2.55; 95% CI 1.81–3.59) and increased menstrual frequency (OR 1.72; 95% CI 1.14–2.61). However, the certainty of evidence was moderate for ovulation and low for menstrual frequency. These findings suggest a potential benefit, although the results should be interpreted in view of differences among the included studies (Morley et al., 2017).

The improvement in menstrual regularity does not necessarily mean that normal ovulation has been restored in every woman. The response to metformin varies according to individual metabolic and hormonal characteristics, and some women may continue to experience irregular cycles or anovulation despite treatment (Teede et al., 2023; Melin et al., 2023).

Overall, metformin may be useful for managing menstrual irregularities and supporting ovulatory function, particularly in women with PCOS who also have metabolic disturbances. However, its use should be guided by individual clinical needs and treatment goals (Teede et al., 2023).

4.3 Effect on Fertility Outcomes

Metformin has been studied as a treatment option for women with PCOS who experience infertility due to irregular or absent ovulation. By improving insulin sensitivity and reducing compensatory hyperinsulinemia, metformin may help improve the hormonal environment and support ovulation, potentially increasing the chances of conception in some women (Lord et al., 2003; Morley et al., 2017).

However, improvements in ovulation do not always lead to successful pregnancy or live birth. The Cochrane review by Morley et al. (2017) reported higher odds of clinical pregnancy with metformin compared with placebo or no treatment (OR 1.93; 95% CI 1.42–2.64). It also reported a possible improvement in live-birth rates (OR 1.59; 95% CI 1.00–2.51). However, the certainty of evidence was moderate for clinical pregnancy and low for live birth. Therefore, the results should be interpreted cautiously.

The effectiveness of metformin also differs according to the treatment used for comparison. In the comparison between metformin and clomiphene citrate, the Cochrane review reported inconsistent findings for live birth, with very low-certainty evidence. The randomized controlled trial by Legro et al. (2007) also demonstrated differences in reproductive outcomes between metformin, clomiphene citrate and their combination. These findings indicate that metformin should not automatically be considered equivalent to established ovulation-induction treatments (Legro et al., 2007; Morley et al., 2017).

The 2023 International Evidence-based Guideline states that metformin alone may be used in women with PCOS-related anovulatory infertility and no other infertility factors to improve clinical pregnancy and live-birth rates. However, women should be informed that more effective ovulation-induction agents are available. The guideline recommends letrozole as the first-line pharmacological treatment in these women (Teede et al., 2023).

Therefore, metformin may have a role in managing PCOS-related infertility, particularly when insulin resistance or metabolic disturbances are present. However, treatment selection should consider the woman's individual condition, other possible infertility factors and fertility goals (Teede et al., 2023).

4.4 Metformin in Combination with Lifestyle Intervention

Lifestyle modification, including a balanced diet, regular physical activity and weight management where appropriate, is an important part of PCOS management, particularly in women who are overweight or have metabolic risk factors (Teede et al., 2023).

Combining metformin with lifestyle interventions may provide additional metabolic benefits in some women. These may include improvements in insulin sensitivity, body weight and selected metabolic parameters compared with placebo or lifestyle measures alone. A systematic review and meta-analysis by Naderpoor et al. (2015) examined the effects of metformin combined with lifestyle modification in women with PCOS.

Melin et al. (2023) also evaluated metformin with and without lifestyle modification in comparison with placebo and reported improvements in selected metabolic outcomes, including insulin resistance and body mass index.

However, the additional benefits of combining metformin with lifestyle changes may vary among individuals, and evidence regarding improvements in fertility outcomes remains limited. Therefore, metformin should be considered an additional treatment option when clinically appropriate rather than a replacement for lifestyle management. Treatment decisions should be guided by the woman's metabolic and reproductive needs (Teede et al., 2023; Melin et al., 2023).

4.5 Dosage, Administration, Safety and Tolerability

Metformin is generally started at a low dose, followed by gradual dose increases to improve tolerability and minimize gastrointestinal adverse effects. The dose and duration of treatment should be determined by the treating healthcare professional according to the patient's clinical condition and response to treatment (Teede et al., 2023).

Nausea, diarrhea, abdominal discomfort and other gastrointestinal disturbances are the most commonly reported adverse effects. These effects are generally mild and may improve over time or with gradual dose adjustment. Taking metformin with meals may also help improve gastrointestinal tolerability (Teede et al., 2023; Morley et al., 2017).

Long-term use of metformin has also been associated with reduced vitamin B12 levels in some patients. Monitoring of vitamin B12 may be considered, particularly in individuals with risk factors or symptoms of deficiency (American Diabetes Association Professional Practice Committee, 2024).

Although metformin is generally well tolerated, it should be used with appropriate clinical supervision, especially in patients with impaired renal function. Severe renal impairment increases the risk of metformin accumulation and a rare but serious complication known as lactic acidosis. Renal function should therefore be assessed before and during treatment, according to clinical recommendations (American Diabetes Association Professional Practice Committee, 2024; NICE, 2026).

Overall, metformin has a well-established safety profile when prescribed appropriately. Gradual dose titration, administration with meals and attention to possible adverse effects can help improve treatment tolerability.

4.6 Comparison with Other Treatment Options for PCOS-Related Infertility

For women with PCOS who experience anovulatory infertility without other infertility factors, letrozole is recommended as the first-line pharmacological treatment for inducing ovulation (Teede et al., 2023). Clomiphene citrate is another established ovulation-induction agent, while gonadotropins may be considered when oral treatments are unsuccessful or when further treatment is required (Teede et al., 2023).

Unlike these ovulation-induction agents, metformin mainly improves insulin sensitivity and addresses the metabolic abnormalities associated with PCOS. Although it may support ovulatory function in some women, it is generally less effective than established ovulation-induction treatments when the primary objective is achieving pregnancy (Morley et al., 2017; Palomba et al., 2014).

In certain cases, metformin may be considered for women with PCOS, particularly when metabolic disturbances are also present. It may also be used in combination with other fertility treatments when clinically appropriate. The decision regarding treatment should be individualized according to the patient's metabolic condition, reproductive health and fertility goals (Teede et al., 2023; Palomba et al., 2014).

Generally, letrozole remains the recommended first-line pharmacological treatment for women with PCOS-related anovulatory infertility who have no other infertility factors. Metformin has a more specific role in addressing metabolic abnormalities and may provide additional reproductive benefits in selected patients (Teede et al., 2023).

4.7 Current Guidelines and Clinical Recommendations

The 2023 International Evidence-based Guideline for the Assessment and Management of PCOS recommends letrozole as the first-line pharmacological treatment for ovulation induction in women with PCOS-related anovulatory infertility when no other infertility factors are present. Metformin may be used alone in selected women to improve clinical pregnancy and live-birth rates, but they should be informed that more effective ovulation-induction agents are available (Teede et al., 2023).

For metabolic management, metformin is recommended for consideration in adults with PCOS, particularly those with a body mass index (BMI) of 25 kg/m² or above, to improve metabolic outcomes such as insulin resistance, glucose regulation and lipid profiles. Its use may also be considered in certain women with a lower BMI, depending on individual clinical circumstances and metabolic risk factors (Teede et al., 2023).

The guideline also emphasizes the importance of lifestyle management, individualized treatment decisions and consideration of other infertility factors before starting fertility treatment. Metformin should therefore be selected according to the patient's metabolic and reproductive needs rather than being considered a universal treatment for all women with PCOS.

In addition, diabetes management guidelines recognize metformin as an established glucose-lowering medication for appropriate patients with type 2 diabetes mellitus. These recommendations relate to diabetes management and should be distinguished from the specific recommendations for PCOS-related infertility (American Diabetes Association Professional Practice Committee, 2024; NICE, 2026).

Overall, current clinical recommendations support the use of metformin mainly for its metabolic benefits in PCOS, while letrozole remains the preferred first-line pharmacological option for ovulation induction in women with anovulatory infertility and no other infertility factors (Teede et al., 2023).

5. Advantages of Metformin

Improvement in insulin sensitivity: Metformin improves the body's response to insulin and helps reduce excessive insulin levels, making it useful in managing insulin resistance associated with PCOS (Azziz et al., 2016; Lashen, 2010).

- **Metabolic benefits:** Metformin may improve glucose-related parameters and certain metabolic outcomes, particularly in women with PCOS who have a higher BMI or additional metabolic risk factors (Teede et al., 2023; Melin et al., 2023).
- **Improvement in menstrual regularity:** Studies have reported that metformin may help regulate menstrual cycles in some women with PCOS, possibly through improvements in insulin sensitivity and related hormonal disturbances (Lord et al., 2003; Creanga et al., 2008).
- **Support for ovulation:** Metformin may improve ovulatory function in some women with PCOS, particularly when insulin resistance contributes to reproductive hormonal disturbances (Lord et al., 2003; Morley et al., 2017).
- **Potential benefits for fertility:** By supporting ovulatory function, metformin may improve the chances of conception in selected women with PCOS-related infertility. However, its effects on clinical pregnancy and live birth rates are variable (Legro et al., 2007; Morley et al., 2017).
- **Possible reduction in androgen levels:** Metformin may reduce certain biochemical indicators of hyperandrogenism by improving insulin sensitivity and potentially reducing insulin-related stimulation of ovarian androgen production (Lashen, 2010; Fontes et al., 2023).
- **Can be combined with lifestyle modification:** Metformin may provide additional metabolic benefits when used alongside lifestyle interventions, including a balanced diet and regular physical activity, in selected women with PCOS (Naderpoor et al., 2015; Teede et al., 2023).
- **Extensive clinical experienc**e: Metformin has been used for many years in the management of type 2 diabetes and has a well-established clinical

safety profile when prescribed appropriately. However, gastrointestinal adverse effects and the possibility of vitamin B12 deficiency remain important considerations (American Diabetes Association, 2024; NICE, 2026).

Overall, metformin offers several potential advantages in PCOS, particularly in improving insulin sensitivity and metabolic health, with additional possible benefits for menstrual regularity, ovulation and biochemical androgen levels. However, its effects on fertility vary, and treatment should be selected according to the individual's clinical condition and treatment goals (Teede et al., 2023; Melin et al., 2023).

6. Limitations of Metformin

- Variation in treatment response: Metformin does not produce the same results in every woman with PCOS. While some women experience improvements in metabolic health and reproductive function, others may show limited benefits (Teede et al., 2023; Melin et al., 2023).
- Gastrointestinal adverse effects: Digestive problems, including nausea, diarrhoea and abdominal discomfort, are among the most frequently reported side effects of metformin. These effects may make it difficult for some women to continue treatment, particularly when therapy is first started (Lashen, 2010; American Diabetes Association, 2024).
- Uncertain benefits for fertility: Metformin may support ovulation in some women with PCOS, but this does not always result in pregnancy or live birth. It may also be less effective than established ovulation-induction medicines for achieving certain fertility outcomes (Legro et al., 2007; Morley et al., 2017).
- Inconsistent improvement in menstrual cycles: Although metformin can help some women achieve more regular menstrual cycles, the improvement is not universal. Menstrual irregularities and ovulatory problems may continue despite treatment (Lord et al., 2003; Teede et al., 2023).
- Limited improvement in visible androgen-related symptoms: Metformin may reduce certain androgen levels measured through blood tests, but its effects on symptoms such as excessive facial hair and acne are less predictable (Fontes et al., 2023; Melin et al., 2024).
- Risk of reduced vitamin B12 levels: Long-term use of metformin may lower vitamin B12 levels in some patients. Monitoring may be necessary, particularly in individuals with symptoms or other risk factors for vitamin B12 deficiency (American Diabetes Association, 2024).
- Not the preferred first-line treatment for ovulation induction: Although metformin may have a role in selected women with PCOS-related infertility, it is not recommended as the first-choice medicine for inducing ovulation when letrozole is suitable (Teede et al., 2023).
- Need for individualized treatment: Since PCOS affects women differently, metformin may not be suitable or equally effective for everyone. Its use should be considered according to the individual's metabolic condition, reproductive goals and ability to tolerate the medicine (Teede et al., 2023; Melin et al., 2023).

Overall, metformin can be helpful in managing insulin resistance and certain features of PCOS, but its benefits are not the same for every woman. Its variable effects on fertility and androgen-related symptoms, along with possible adverse effects, highlight the importance of selecting treatment according to individual needs rather than relying on metformin alone for all aspects of PCOS management (Teede et al., 2023; Melin et al., 2023).

6. Future Perspectives

Further research is needed to clarify the role of metformin in PCOS-related infertility. It remains uncertain which women are most likely to benefit from this treatment, as responses may vary according to metabolic status, BMI and PCOS phenotype (Creanga et al., 2008; Lord et al., 2003; Teede et al., 2023). Women with insulin resistance or additional metabolic risk factors may experience greater metabolic benefits, although further studies are needed to identify which patient groups are most likely to obtain reproductive benefits (Melin et al., 2023; Teede et al., 2023).

Future clinical trials should include larger populations and longer follow-up periods. They should prioritize live-birth outcomes rather than focusing only on changes in hormone levels, ovulation or clinical pregnancy rates. Assessing the long-term health of children born following maternal metformin treatment would also be valuable (Morley et al., 2017; Teede et al., 2023).

Further comparative studies are required to evaluate metformin against established ovulation-induction treatments, particularly letrozole, and to determine when metformin should be used alone or in combination with other treatments. More research is also needed to establish the most appropriate dose and duration of treatment for different groups of women with PCOS (Palomba et al., 2014; Teede et al., 2023).

Future studies should also investigate the relationship between changes in insulin signalling, ovarian function, oocyte quality and endometrial receptivity. Such research may help identify the mechanisms through which metabolic improvements influence reproductive outcomes.

Until more consistent evidence becomes available, metformin is likely to remain an additional treatment option for selected women with PCOS. It may be particularly useful when metabolic abnormalities are also present, but it is not expected to replace letrozole as the preferred first-line pharmacological treatment for ovulation induction in women with PCOS-related anovulatory infertility when no other infertility factors are present (Teede et al., 2023; International PCOS Network, 2023).

DISCUSSION

Metformin has a role in the management of infertility associated with polycystic ovary syndrome, although its reproductive benefits are variable. It is particularly relevant in women who have insulin resistance or other metabolic abnormalities. By improving insulin sensitivity and reducing excessive insulin levels, metformin may reduce insulin-related stimulation of ovarian androgen production. This may contribute to improvements in androgen levels, menstrual regularity and ovulatory function in some women. However, these effects are not universal, and improvements in insulin sensitivity do not necessarily lead to successful ovulation or conception (Lord et al., 2003; Creanga et al., 2008; Morley et al., 2017).

Early meta-analyses by Lord et al. (2003) and Creanga et al. (2008) reported improvements in ovulation and certain reproductive outcomes following metformin treatment. However, the available studies had limitations, including relatively small populations and limited information on live-birth outcomes. The later Cochrane review by Morley et al. (2017), which included 48 trials involving 4,451 women, also reported improvements in ovulation and clinical pregnancy compared with placebo or no treatment. It suggested a possible improvement in live-birth rates, although the certainty of this evidence was low. More recent reviews by Melin et al. (2023) and Fontes et al. (2023) have provided further evidence regarding the metabolic and biochemical effects of metformin, including its influence on insulin resistance and androgen levels. Nevertheless, the response to treatment remains variable, and improvements in metabolic or hormonal parameters do not always translate into better reproductive outcomes.

The possible effects of metformin can be explained partly by its cellular and metabolic actions. Metformin reduces hepatic glucose production and improves insulin sensitivity through mechanisms involving both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent pathways (Zhou et al., 2001; Rena et al., 2017; Foretz et al., 2010). A reduction in excessive insulin levels may decrease insulin-related stimulation of ovarian theca cells and androgen production. Reduced insulin levels may also contribute to increased hepatic production of sex hormone-binding globulin (SHBG), which can lower the amount of circulating free testosterone. However, these hormonal changes vary among individuals and should not be considered a guaranteed response to treatment (Rosenfield and Ehrmann, 2016; Fontes et al., 2023).

Regular ovulation is an important step towards natural conception, but it does not guarantee pregnancy or live birth. Reproductive outcomes are also influenced by factors such as oocyte quality, endometrial receptivity, sperm quality, other infertility factors and treatment adherence (Azziz et al., 2016). Evidence regarding the effect of metformin on live-birth rates remains

uncertain, particularly when it is compared with or added to established ovulation-induction treatments (Morley et al., 2017; Palomba et al., 2014). For this reason, current international guidelines recommend letrozole as the preferred first-line pharmacological treatment for women with PCOS-related anovulatory infertility when no other infertility factors are present (Teede et al., 2023; International PCOS Network, 2023).

Table 1: ***Summary of major systematic reviews and meta-analyses evaluating the effects of metformin on reproductive, metabolic and androgenic outcomes in women with polycystic ovary syndrome.***

Author (Year)	Number of RCTs / Participants	Main Comparisons	Key Findings	Reference
Lord et al. (2003)	13 RCTs	Metformin vs placebo/ clomiphene	Improved ovulation and menstrual regularity; limited live-birth data	Lord et al. 2003
Creanga et al. (2008)	17 RCTs / 1,639 women	Metformin ± clomiphene	Modest increase in ovulation and pregnancy; no clear live-birth benefit	Creanga et al. 2008
Tang et al. (2012)	38 RCTs	Insulin-sensitizers vs placebo	Metformin improved ovulation and clinical pregnancy; live-birth evidence weak	Tang et al. 2012
Naderpoor et al. (2015)	12 RCTs	Metformin + lifestyle vs lifestyle	Greater reduction in BMI and fasting insulin; improved cycle regularity	Naderpoor et al. 2015
Morley et al. (2017)	48 RCTs	Metformin vs placebo / other	Increased ovulation and clinical pregnancy; live-birth data still limited	Morley et al. 2017
Fraison et al. (2020)	27 RCTs	Metformin vs COCP	COCP superior for hirsutism and acne; metformin better for metabolic outcomes	Fraison et al. 2020
Wu et al. (2020)	12 RCTs (IVF patients)	Metformin in IVF	Reduced risk of OHSS; no significant difference in pregnancy rates	Wu et al. 2020
Melin et al. (2023)	24 RCTs	Metformin ± lifestyle vs placebo	Improved insulin resistance, lipids and menstrual cyclicity	Melin et al. 2023
Fontes et al. (2023)	16 RCTs	Metformin vs placebo / other	Modest reduction in total testosterone and free androgen index	Fontes et al. 2023
Melin et al. (2024)	Network meta-analysis	Metformin vs COCP vs combination	COCP better for hyperandrogenism; metformin better metabolically	Melin et al. 2024

In women undergoing in vitro fertilization (IVF), metformin has also been investigated for its possible role in reducing the risk of ovarian hyperstimulation syndrome (OHSS). A systematic review by Wu et al. (2020) reported a potential benefit in this area, although the effects on pregnancy outcomes were not consistent across all analyses. When compared with combined oral contraceptive pills, metformin generally has a more favorable metabolic profile, whereas COCPs are more effective for certain androgen-related symptoms, such as hirsutism and acne (Fraison et al., 2020; Melin et al., 2024). In addition, combining metformin with lifestyle modification may improve selected outcomes, including BMI and menstrual-cycle frequency, compared with lifestyle intervention alone (Naderpoor et al., 2015).

Metformin is therefore a useful option for addressing certain metabolic abnormalities associated with PCOS, but its role in fertility treatment is more selective. Its tolerability is another important consideration. Gastrointestinal adverse effects, including nausea, diarrhea, abdominal discomfort and sometimes a metallic taste, may occur, particularly during the initial stages of treatment. Gradual dose escalation may help improve tolerability, although some patients may still experience persistent symptoms. Long-term use may also reduce vitamin B12 levels in some individuals,

supporting the need for appropriate monitoring when clinically indicated (Lashen, 2010; American Diabetes Association, 2024; NICE, 2026).

Several limitations should be considered when interpreting the available evidence. Many earlier clinical trials included relatively small populations, had short treatment or follow-up periods, and focused on ovulation or hormonal changes rather than live birth as the primary outcome. Differences in metformin doses, treatment duration, diagnostic criteria, patient characteristics and lifestyle interventions also make direct comparisons between studies difficult. In addition, some PCOS phenotypes and patient groups remain less well represented in clinical research. Further evidence is also needed regarding the role of metformin in combination with newer metabolic treatments and its long-term reproductive effects.

Future research should include larger, well-designed clinical trials that report live birth as an important outcome and examine differences according to insulin resistance, BMI and PCOS phenotype. Longer follow-up is also required to understand whether metformin use influences the future risk of type 2 diabetes and cardiovascular complications in women with PCOS. Studies investigating the relationship between insulin signaling, oocyte quality and endometrial receptivity may further improve patient selection and treatment decisions.

Overall, metformin should be considered part of an individualized treatment strategy rather than a universal fertility treatment for PCOS. It may be particularly useful in women whose reproductive difficulties occur alongside insulin resistance or other metabolic disturbances, especially when combined with lifestyle modification and, where appropriate, established fertility treatments (Teede et al., 2023; Azziz et al., 2016). However, current evidence does not support replacing letrozole with metformin as the preferred first-line ovulation-induction treatment in most women with PCOS-related anovulatory infertility. Further well-designed studies focusing on live-birth outcomes and long-term follow-up are needed to clarify which women are most likely to benefit from metformin treatment (Teede et al., 2023; Morley et al., 2017).

Table 2: ***Comparative outcomes of metformin and other treatment approaches in women with PCOS***

Outcome	Metformin alone	Combined Oral Contraceptive Pill (COCP)	Letrozole	Metformin + Lifestyle	Key References
Menstrual regularity	Moderate improvement	Strong improvement	Not a primary use	Potentially stronger improvement	Melin et al. (2023); Naderpoor et al. (2015)
Ovulation rate	Modest increase	Not indicated for ovulation induction	High effectiveness	Modest–moderate improvement	Morley et al. (2017); Teede et al. (2023)
Clinical pregnancy rate	Possible modest benefit	Not indicated for fertility treatment	High effectiveness	Possible modest benefit	Tang et al. (2012); Legro et al. (2007)
Live-birth rate	Uncertain / limited benefit	Not indicated for fertility treatment	Preferred first-line option for ovulation induction	Evidence remains uncertain	Morley et al. (2017); Teede et al. (2023)
Hirsutism / acne	Minimal effect	Strong improvement	Minimal direct effect	Minimal direct effect	Fraison et al. (2020); Fontes et al. (2023)
Insulin resistance (HOMA-IR)	Moderate improvement	Neutral / possible worsening	Generally neutral	Potentially greater improvement	Melin et al. (2023); Cassar et al. (2016)
BMI / body weight	Small reduction	Neutral / possible slight increase	Generally neutral	Potentially greater reduction	Naderpoor et al. (2015)

Outcome	Metformin alone	Combined Oral Contraceptive Pill (COCP)	Letrozole	Metformin + Lifestyle	Key References
Risk of ovarian hyperstimulation syndrome (OHSS) in IVF	May reduce risk in selected protocols	Not applicable as an OHSS-prevention treatment	Not applicable as an OHSS-prevention treatment	May reduce risk in selected protocols	Wu et al. (2020)

Legend: Comparative effectiveness of metformin versus combined oral contraceptive pills, letrozole and lifestyle intervention across key clinical outcomes in PCOS.

8. Mechanism of Action of Metformin

Metformin mainly helps women with polycystic ovary syndrome (PCOS) by improving insulin sensitivity and reducing excessive insulin levels in the blood. Inside the cells, metformin influences an enzyme called AMP-activated protein kinase (AMPK), which acts as an energy sensor and helps regulate cellular metabolism. Activation of AMPK can reduce glucose production in the liver and improve glucose utilization in the body (Zhou et al., 2001; Rena et al., 2017). Metformin can also reduce hepatic glucose production through AMPK-independent pathways by lowering the energy state inside liver cells (Foretz et al., 2010).

Metformin may also affect mitochondrial complex I, which can alter the energy balance within cells and influence AMPK activity. However, its mechanism of action is not limited to this pathway. Both AMPK-dependent and AMPK-independent mechanisms contribute to its glucose-lowering effects (Rena et al., 2017; Foretz et al., 2010).

The improvement in insulin sensitivity and reduction in excessive insulin levels may produce several beneficial changes in women with PCOS. High insulin levels can act together with luteinizing hormone (LH) to stimulate androgen production by ovarian theca cells. Hyperinsulinemia may also reduce the production of sex hormone-binding globulin (SHBG) by the liver. When insulin levels decrease, ovarian androgen production may be reduced, while SHBG levels may increase. This can lower the amount of free circulating androgens in some women (Rosenfield and Ehrmann, 2016; Cassar et al., 2016).

A reduction in excessive androgen levels may contribute to a more favorable hormonal environment for follicular development and ovulation. However, these reproductive effects are indirect and may vary among women with PCOS. Improvement in insulin sensitivity does not necessarily guarantee regular ovulation or successful conception.

These mechanisms help explain why metformin may improve certain metabolic and hormonal parameters and menstrual regularity in some women, while its effects on pregnancy and live-birth outcomes remain less consistent. This is because fertility also depends on other factors, including follicular development, oocyte quality, endometrial receptivity and other causes of infertility.

CONCLUSION

Polycystic ovary syndrome (PCOS) is a complex hormonal and metabolic disorder that affects women of reproductive age. It may cause menstrual irregularities, ovulatory dysfunction, hyperandrogenism and metabolic disturbances, which can affect reproductive health and fertility.

Based on the studies reviewed, metformin has shown useful benefits in the management of PCOS, particularly in women with insulin resistance and associated metabolic abnormalities. It improves insulin sensitivity and reduces excessive glucose production in the liver. It may also influence certain hormonal and reproductive abnormalities associated with this condition.

Clinical studies suggest that metformin can improve menstrual regularity and ovulatory function in some women with PCOS. It may also support fertility outcomes in selected patients, either alone or in combination with other treatments. However, its effectiveness varies among individuals, and improvements in metabolic parameters or ovulation do not always result in pregnancy or live birth. Its effects on weight, androgen-related symptoms and reproductive outcomes are also not equally consistent across all studies.

Current evidence-based guidelines recommend letrozole as the first-line pharmacological treatment for

ovulation induction in women with PCOS-related anovulatory infertility when no other infertility factors are present. Therefore, metformin should not be considered a replacement for established ovulation-induction treatments when these are appropriate.

Another important finding is that metformin should not replace healthy lifestyle practices. Appropriate dietary habits, regular physical activity and individualized medical care remain important components of PCOS management. Gastrointestinal discomfort, including nausea, diarrhea and abdominal discomfort, is among the commonly reported adverse effects of metformin and should be considered when evaluating its suitability for an individual patient. Long-term use may also be associated with reduced vitamin B12 levels in some individuals.

Despite the considerable research conducted on metformin, several questions remain unanswered. Differences in study design, treatment duration, patient characteristics and reported outcomes make it difficult to draw the same conclusions for every woman with PCOS. Further well-designed clinical studies are needed to identify which groups of patients are most likely to benefit and to clarify the long-term reproductive and metabolic effects of treatment.

Overall, metformin remains a useful treatment option for selected women with PCOS, especially when insulin resistance and metabolic disturbances are important considerations. Its role in improving reproductive outcomes is promising but should be evaluated carefully. The most appropriate approach is individualized treatment based on the patient's symptoms, metabolic profile, fertility goals and response to therapy. A better understanding of these factors will help healthcare professionals use metformin more effectively and improve the overall quality of care for women with PCOS.

10. Acknowledgement

I would like to express my sincere gratitude to my respected guide, Mr. Ashish Kushwaha, for his valuable guidance, encouragement and continuous support throughout the preparation of my review paper entitled "Polycystic Ovary Syndrome and Metformin: A Comprehensive Review of Pharmacological and Clinical Evidence" His guidance has helped me develop a better understanding of the topic and complete this work successfully.

I would also like to acknowledge the researchers and authors whose published studies, research papers and scientific articles provided valuable information and contributed to the preparation of this review paper. Finally, I am grateful to everyone who directly or indirectly supported and encouraged me in completing this work.

11. Declaration

I hereby declare that the review paper entitled **"Polycystic Ovary Syndrome and Metformin: A Comprehensive Review of Pharmacological and Clinical Evidence"** has been prepared by me as part of the academic requirements of the Bachelor of Pharmacy (B.Pharm), 7th Semester, at JBIT College of Pharmacy, Dehradun.

The manuscript is based on a review of previously published research articles, systematic reviews, meta-analyses and clinical practice guidelines relevant to the role of metformin in PCOS. All sources consulted during the preparation of this manuscript have been acknowledged through appropriate in-text citations and references. Every effort has been made to present the available scientific evidence accurately and objectively.

I declare that this manuscript has been prepared for academic purposes and that the ideas, findings and information obtained from other sources have been appropriately cited. I accept responsibility for the final content of the manuscript and its compliance with the academic requirements of my institution.

• Availability of Data and Materials

The materials discussed in this review paper were obtained from previously published research articles, review papers, systematic reviews, meta-analyses and clinical practice guidelines concerning metformin and PCOS. The sources used are cited in the manuscript and provided in the reference list. No new primary datasets were generated for this review.

• Declaration of AI Use

AI-based tools were used to assist with language improvement, paraphrasing and the organization of certain sections of the manuscript. The content was reviewed and edited during the preparation of the final document. The author takes responsibility for the accuracy of the scientific information, appropriate acknowledgement of sources and final content of the manuscript.

12. Conflict of Interest

The author declares no conflict of interest.

REFERENCES

1. Teede HJ, Tay CT, Laven JSE, Dokras A, Moran LJ, Piltonen TT, et al. Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. Fertil Steril. 2023;120 (4):767–793. doi:10.1016/j.fertnstert.2023.07.025.
2. Azziz R, Carmina E, Chen Z, Dunaif A, Laven JSE, Legro RS, et al. Polycystic ovary syndrome. Nat Rev Dis Primers. 2016;2:16057. doi:10.1038/nrdp.2016.57.
3. Lord JM, Flight IHK, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ. 2003;327 (7421):951–953. doi:10.1136/bmj.327.7421.951.
4. Creanga AA, Bradley HM, McCormick C, Witkop CT. Use of metformin in polycystic ovary syndrome: a meta-analysis. Obstet Gynecol. 2008;111 (4):959–968. doi:10.1097/AOG.0b013e31816a4ed4.
5. Lashen H. Role of metformin in the management of polycystic ovary syndrome. Ther Adv Endocrinol Metab. 2010;1 (3):117–128. doi:10.1177/2042018810380215.
6. Morley LC, Tang T, Yasmin E, Norman RJ, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2017;11 (11):CD003053. doi:10.1002/14651858.CD003053.pub6.
7. Melin J, Forslund M, Alesi S, Piltonen T, Romualdi D, Spritzer PM, et al. The impact of metformin with or without lifestyle modification versus placebo on polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Eur J Endocrinol. 2023;189 (2):S38–S64. doi:10.1093/ejendo/lvad098.
8. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2024. Diabetes Care. 2024;47 (Suppl 1):S158–S178. doi:10.2337/dc24-S009.
9. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. NICE guideline NG28. London: NICE; 2015. Last updated 18 February 2026.
10. Palomba S, Falbo A, La Sala GB. Metformin and gonadotropins for ovulation induction in patients with polycystic ovary syndrome: a systematic review with meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2014;12:3. doi:10.1186/1477-7827-12-3.
11. International PCOS Network. International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023. Monash University; 2023.
12. Fontes AFS, Reis FM, Cândido AL, Gomes KB, Tosatti JAG. Influence of metformin on hyperandrogenism in women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized clinical trials. Eur J Clin Pharmacol. 2023;79 (4):445–460. doi:10.1007/s00228-023-03461-z.
13. Melin J, Forslund M, Alesi S, Piltonen T, Romualdi D, Spritzer PM, et al. Metformin and combined oral contraceptive pills in the management of polycystic ovary syndrome: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2024;109 (2):e817–e836. doi:10.1210/clinem/dgad465.
14. Fraison E, Kostova E, Moran LJ, Bilal S, Ee CC, Venetis C, et al. Metformin versus the combined oral contraceptive pill for hirsutism, acne, and menstrual pattern in polycystic ovary syndrome.

Cochrane Database Syst Rev. 2020;8 (8):CD005552. doi:10.1002/14651858.CD005552.pub3.

15. Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev. 2016;37 (5):467–520. doi:10.1210/er.2015-1104.
16. Cassar S, Misso ML, Hopkins WG, Shaw CS, Teede HJ, Stepto NK. Insulin resistance in polycystic ovary syndrome: a systematic review and meta-analysis of euglycaemic-hyperinsulinaemic clamp studies. Hum Reprod. 2016;31 (11):2619–2631. doi:10.1093/humrep/dew243.
17. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest. 2001;108 (8):1167–1174. doi:10.1172/JCI13505.
18. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60 (9):1577–1585. doi:10.1007/s00125-017-4342-z.
19. Foretz M, Hébrard S, Leclerc J, Zarrinpashneh E, Soty M, Mithieux G, et al. Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. J Clin Invest. 2010;120 (7):2355–2369. doi:10.1172/JCI40671.
20. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med. 2007;356 (6):551–566. doi:10.1056/NEJMoa063971.
21. Naderpoor N, Shorakae S, de Courten B, Misso ML, Moran LJ, Teede HJ. Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. Hum Reprod Update. 2015;21 (5):560–574. doi:10.1093/humupd/dmv025.
22. Wang F, Yan Y, Wang D, et al. Effects of Metformin on CIMT and FMD in PCOS patients: a systematic review and meta-analysis. BMC Womens Health. 2024;24:426. doi:10.1186/s12905-024-03275-w.
23. Wu Y, Tu M, Huang Y, Liu Y, Zhang D. Association of Metformin With Pregnancy Outcomes in Women With Polycystic Ovarian Syndrome Undergoing In Vitro Fertilization: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3 (8):e2011995. doi:10.1001/jamanetworkopen.2020.11995.

HOW TO CITE: Tanya Singh, Ashish Kushwaha, Dr. Arun Kumar Maurya, Dr. Lalit Bisht, Polycystic Ovary Syndrome and Metformin: A Comprehensive Review of Pharmacological and Clinical Evidence, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 11, 4588-4605. https://doi.org/10.5281/zenodo.24527767