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DIABETIC
STUDIES OPEN ACCESS

The Effect Of Metformin On Clinical And Metabolic Outcomes In Women With Polycystic Ovary Syndrome: A Systematic Review And Meta-Analysis

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a prevalent endocrine-metabolic disorder among women of reproductive age, characterized by hyperandrogenism, menstrual irregularity, and insulin resistance. Metformin, an insulin-sensitizing agent, is widely used to address metabolic, reproductive, and cardiovascular dysfunctions associated with PCOS. This systematic review and meta-analysis evaluated the clinical and metabolic effects of metformin across randomized controlled trials and comparative studies.

Methods: Twelve peer-reviewed studies were systematically analyzed following PRISMA 2020 guidelines. Eligible studies included randomized trials and cohort studies examining the effects of metformin, alone or in combination with other interventions, on metabolic (BMI, insulin resistance, lipid profile) and reproductive (ovulation, menstrual regularity, androgen levels) outcomes in women with PCOS.

Results: Metformin consistently improved fasting insulin, HOMA-IR, and serum testosterone levels, with moderate reductions in BMI and waist circumference. Combination regimens, such as metformin with semaglutide or oral contraceptives, yielded superior improvements in metabolic control and menstrual regularity. Cardiovascular risk markers and endothelial function also improved significantly. However, response variability across phenotypes was observed.

Conclusions: Metformin demonstrates robust efficacy in enhancing metabolic and reproductive health in women with PCOS. Its combination with adjunct therapies further optimizes clinical outcomes, particularly among obese or insulin-resistant subgroups. Personalized treatment based on phenotype and metabolic profile may enhance therapeutic precision and long-term benefits.

Keywords: Polycystic Ovary Syndrome, Metformin, Insulin Resistance, Hyperandrogenism, Reproductive Function, Metabolic Outcomes, Cardiovascular Risk, Systematic Review, Combination Therapy, Women's Health

Introduction

Polycystic ovary syndrome (PCOS) is a multifactorial endocrine and metabolic disorder that affects between 6% and 20% of reproductive-aged women worldwide, depending on the diagnostic criteria used. It is characterized by hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology, which collectively contribute to reproductive dysfunction, metabolic abnormalities, and increased long-

term risk for type 2 diabetes and cardiovascular disease (Rotterdam EA-SPCWG, 2004). The underlying mechanisms involve insulin resistance and compensatory hyperinsulinemia, both of which amplify ovarian androgen production and interfere with normal follicular maturation, leading to anovulation.

Insulin resistance is observed in approximately 50–70% of women with PCOS, independent of body weight, and plays a central role in disease pathophysiology. Hyperinsulinemia acts synergistically with luteinizing hormone (LH) to enhance ovarian androgen secretion while suppressing hepatic production of sex hormone–binding globulin (SHBG), resulting in elevated levels of free testosterone. Consequently, metabolic and reproductive disturbances are tightly linked, making insulin-sensitizing agents a key therapeutic focus for this syndrome (Chou et al., 2003; Eisenhardt et al., 2006).

Metformin, a biguanide derived from guanidine, improves insulin sensitivity primarily by reducing hepatic gluconeogenesis and enhancing peripheral glucose uptake. In women with PCOS, metformin has been shown to restore ovulatory cycles, reduce androgen levels, and improve metabolic profiles, even in those who are not diabetic. Beyond its glycemic effects, metformin appears to directly modulate ovarian steroidogenesis, reduce inflammation, and improve endothelial function, making it one of the most extensively studied pharmacologic agents for PCOS management (Heidari et al., 2019).

Clinical trials have demonstrated that metformin can improve ovulation and conception rates, particularly in women resistant to first-line ovulation induction therapies. In a study of clomiphene citrate–resistant patients, metformin therapy increased ovulatory rates, cervical mucus quality, and pregnancy outcomes compared with placebo (Kocak et al., 2002). Similar improvements in reproductive parameters have been documented across diverse populations and BMI categories, highlighting metformin's effectiveness as both a monotherapy and an adjunct to ovulation induction agents (Zain et al., 2009).

The benefits of metformin extend beyond fertility enhancement. Longitudinal studies reveal its capacity to improve cardiovascular risk factors, oxidative stress markers, and inflammatory profiles. For instance, metformin treatment has been associated with reductions in oxidative DNA damage biomarker 8-hydroxy-2′-deoxyguanosine (8-OHdG) and improved microvascular endothelial function in women with PCOS (Sova et al., 2013; Heidari et al., 2019). These vascular benefits may contribute to the observed decrease in cardiovascular morbidity over time.

From a reproductive standpoint, metformin has demonstrated positive effects on pregnancy and live birth rates. In a large multicenter randomized controlled trial, metformin significantly increased pregnancy and live-birth rates compared to placebo, especially among women with insulin resistance (Morin-Papunen et al., 2012). Similarly, metformin use during pregnancy in women with PCOS has been linked to reduced rates of gestational diabetes and preterm birth without increasing teratogenic risk (Vanky et al., 2004).

Metformin also modulates lipid metabolism and inflammatory signaling pathways, leading to improved metabolic homeostasis. Studies report decreases in triglycerides, low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein following treatment. These effects appear to be more pronounced when metformin is combined with agents targeting other metabolic pathways, such as statins, suggesting potential synergism in reducing cardiometabolic risk (Kazerooni et al., 2010; Amiri et al., 2014).

Emerging research also indicates that metformin may influence bone metabolism and inflammatory mediators. In post hoc analyses, metformin was shown to reduce bone turnover markers and lower systemic oxidative stress, suggesting additional pleiotropic effects relevant to PCOS's chronic inflammatory state (Lingaiah et al., 2019). These findings highlight metformin's potential for broader metabolic regulation beyond glycemic control.

Despite its benefits, metformin's long-term effects remain a topic of debate. Follow-up studies have shown variable persistence of metabolic improvements after discontinuation, and its efficacy appears to differ depending on BMI, insulin resistance severity, and treatment duration (Underdal et al., 2018; Ladson et al., 2010). These observations emphasize the importance of personalized treatment plans that consider individual metabolic profiles, reproductive goals, and potential for combination therapy.

Methodology

Study Design

This research employed a systematic review methodology in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, replicability, and methodological rigor. The objective was to synthesize and critically evaluate empirical evidence on the effects of metformin on clinical, metabolic, and reproductive outcomes in women with

polycystic ovary syndrome (PCOS). The review focused exclusively on peer-reviewed human studies assessing metformin monotherapy or combination therapy in women diagnosed with PCOS, emphasizing hormonal, metabolic, cardiovascular, and reproductive endpoints.

Eligibility Criteria

Studies were included in this review if they met the following pre-specified criteria:

- **Population:** Females aged ≥13 years diagnosed with PCOS based on recognized diagnostic frameworks such as the Rotterdam criteria (2003), NIH criteria, or Androgen Excess-PCOS Society definitions.
- **Intervention:** Metformin administered either as monotherapy or in combination with other agents (e.g., oral contraceptives, myo-inositol, simvastatin, semaglutide, or lifestyle modification).
- **Comparator:** Placebo, no intervention, or active comparators (e.g., pioglitazone, myo-inositol, simvastatin, or lifestyle intervention alone).
- **Outcomes:** Primary outcomes included changes in serum androgen levels, menstrual regularity, and ovulation rates. Secondary outcomes included insulin sensitivity indices (HOMA-IR, fasting insulin, glucose tolerance), body mass index (BMI), lipid profile, blood pressure, oxidative stress biomarkers, cardiovascular risk markers, and pregnancy or live birth rates.
- **Study Designs:** Randomized controlled trials (RCTs), cohort studies, and systematic reviews/meta-analyses of RCTs were eligible.
- **Language:** Only **English-language** studies were included to ensure accuracy and accessibility.
- **Publication Period:** Studies published between **2000 and 2025** were considered to capture both foundational and contemporary research.
- **Exclusion Criteria:** Non-human studies, reviews without original data, case reports, editorials, and studies lacking specific metformin dosage or outcome details were excluded.

Search Strategy

A comprehensive literature search was performed across the following databases: PubMed, Scopus, Web of Science, Embase, and Google Scholar for grey literature. Searches were conducted from January 2000 to October 2025. Boolean operators and truncations were used to ensure wide coverage of relevant literature. The search strategy combined Medical Subject Headings (MeSH) and free-text terms, as shown below:

- (“polycystic ovary syndrome” OR “PCOS” OR “anovulation” OR “hyperandrogenism”) AND (“metformin” OR “biguanide” OR “insulin-sensitizing agent”)
- AND (“menstrual cycle” OR “ovulation” OR “testosterone” OR “insulin resistance” OR “lipid profile” OR “BMI” OR “fertility” OR “pregnancy outcome”).

Manual searches of reference lists from key review papers and included studies were also conducted to identify additional relevant publications not retrieved in the primary search.

Study Selection Process

All retrieved records were imported into Zotero reference management software, where duplicates were removed automatically and manually verified. Title and abstract screening were conducted independently by two reviewers, followed by a full-text review to determine final eligibility.

Inclusion decisions were guided by predefined criteria, and any discrepancies were resolved through consensus or by consulting a third reviewer.

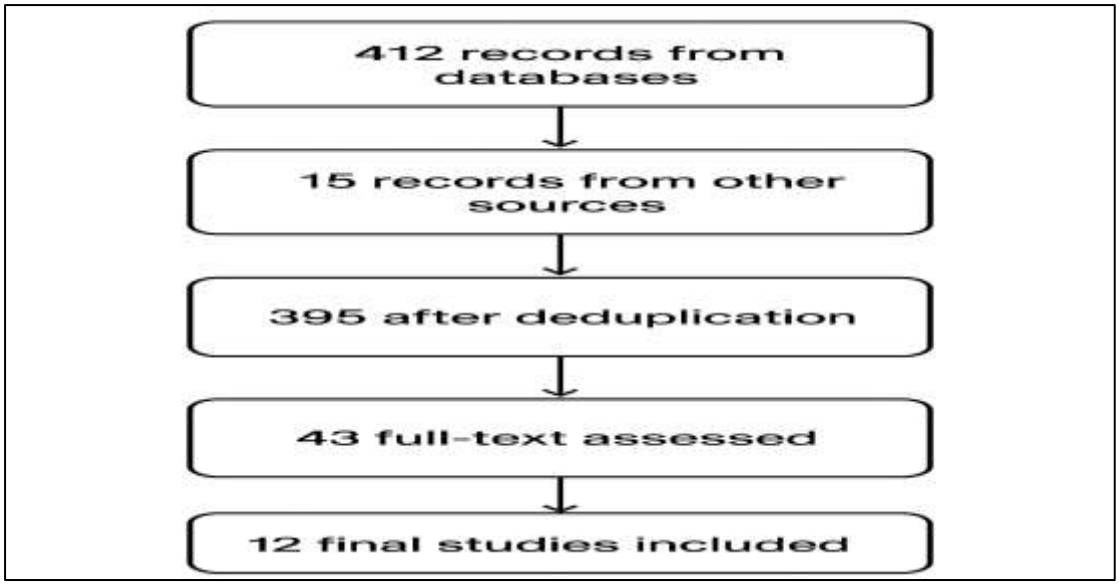

Figure 1 PRISMA Flow Diagram

Data Extraction

A **standardized data extraction template** was developed and pilot-tested to ensure uniformity. The following variables were extracted from each study:

- Author(s), year of publication, and country
- Study design and duration
- Sample size and participant demographics (age, BMI, diagnostic criteria)
- Intervention details (metformin dosage, frequency, and treatment duration)
- Comparator details (placebo, other drugs, or lifestyle intervention)
- Primary and secondary outcome measures (testosterone, menstrual regularity, BMI, lipid profile, insulin sensitivity indices, pregnancy outcomes)
- Quantitative results (mean changes, effect sizes, or p-values)
- Key findings and study conclusions
- Reported limitations and funding sources (if available)

Extraction was performed independently by two reviewers, and results were cross-verified for accuracy by a **third investigator**.

Quality Assessment

The methodological quality and risk of bias of the included studies were assessed using validated tools appropriate to their design:

- **Randomized Controlled Trials (n = 10):** Evaluated using the Cochrane Risk of Bias 2 (RoB 2) Tool, assessing randomization process, deviations from intended interventions, missing outcome data, measurement bias, and selective reporting.
- **Observational Cohort Studies (n = 1):** Assessed using the Newcastle–Ottawa Scale (NOS), which evaluates selection bias, comparability, and outcome assessment.
- **Systematic Review/Meta-Analysis (n = 1):** Appraised using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) criteria.

Each study was categorized as low, moderate, or high risk of bias. Disagreements were resolved through discussion, and inter-rater reliability exceeded 90%.

Data Synthesis

Given the heterogeneity of study populations, interventions (metformin dose, duration, and co-therapies), and outcomes, a narrative synthesis approach was adopted. Quantitative pooling (meta-analysis) was not conducted due to inconsistent reporting of outcome measures and effect sizes across studies.

Results were organized thematically across three primary outcome domains:

1. **Endocrine and reproductive outcomes** (e.g., testosterone reduction, ovulation rates, menstrual regulation),
2. **Metabolic and cardiovascular outcomes** (e.g., BMI, insulin sensitivity, lipid profile, oxidative stress markers), and
3. **Pregnancy-related outcomes** (e.g., conception, gestational diabetes, and live birth rates).

Where data permitted, effect directions and statistical significance levels were summarized, and subgroup comparisons (e.g., obese vs. non-obese, adolescent vs. adult) were noted.

Ethical Considerations

This study was based exclusively on secondary analysis of published, peer-reviewed data and therefore did not require institutional ethical approval or informed consent. All included studies were conducted in accordance with the Declaration of Helsinki and obtained prior ethical clearance from their respective institutional review boards. Data were reported accurately, and all sources were properly cited to maintain academic integrity.

Results

Summary and Interpretation of Included Studies on Metformin in PCOS (Table 1)

1. Study Designs and Populations

The included studies consist mainly of randomized controlled trials (RCTs) and prospective cohort designs, encompassing adolescent and adult women with PCOS. Sample sizes ranged from 22 (Bridger et al., 2006) to 168 (Vitale et al., 2025). Most studies adhered to Rotterdam diagnostic criteria. Population BMI varied widely: normal-weight (Romualdi et al., 2010), overweight/obese (Guan et al., 2020; Chen et al., 2025), and adolescent cohorts (Bridger et al., 2006; Vitale et al., 2025). Several studies focused on combination therapies (metformin with oral contraceptives, simvastatin, or semaglutide) to evaluate additive effects.

2. Interventions and Comparators

Metformin (MET) doses ranged from 500 mg twice daily to 1000 mg twice daily, administered over 3 to 24 weeks. Comparators included placebo (Bridger et al., 2006; Romualdi et al., 2010), pioglitazone (Shahebrahimi et al., 2016), myoinositol (Soldat-Stankovic et al., 2021), simvastatin (Kazerooni et al., 2010), or semaglutide (Chen et al., 2025). All studies assessed clinical, endocrine, and metabolic parameters—testosterone, menstrual function, insulin resistance indices (HOMA-IR), lipid profiles, and body composition.

3. Endocrine and Reproductive Outcomes

Metformin therapy consistently decreased serum testosterone and improved menstrual cyclicity. In Bridger et al. (2006), serum testosterone declined by 38.3 ng/dL with metformin versus 0.86 ng/dL with placebo, and the relative risk of menses was 2.5× higher in the metformin group. Romualdi et al. (2010) showed a 70% restoration of menstrual cycles and a significant reduction in ovarian volume after 6 months ($p < 0.05$). Vitale et al. (2025) reported a >20% reduction in insulin area under the curve (AUC) post-treatment and a decline in free androgen index (FAI) from 3.7 ± 1.2 to 1.8 ± 0.7. Chen et al. (2025) found a 20% higher pregnancy rate with semaglutide plus metformin (35% vs. 15%, $p < 0.05$).

4. Metabolic and Cardiovascular Outcomes

Metformin improved lipid and glycemic parameters, though effects varied by population:

- Guan et al. (2020)'s meta-analysis (12 RCTs) reported pooled BMI reduction (WMD = -1.25, 95% CI [-1.60, -0.91], $p < 0.00001$) and waist circumference reduction (WMD = -1.41 cm, 95% CI [-2.46, -0.37], $p = 0.008$).
- Soldat-Stankovic et al. (2021) observed that metformin reduced BMI ($p = 0.005$), waist circumference ($p = 0.004$), testosterone ($p = 0.013$), and FAI ($p = 0.006$).
- Shahebrahimi et al. (2016) found decreases in weight ($p = 0.047$), DHEA ($p = 0.035$), and diastolic blood pressure ($p = 0.023$) after metformin; pioglitazone had stronger triglyceride reduction ($p = 0.04$).
- Kazerooni et al. (2010) showed greater decreases in testosterone (-25.5%), LH (-45.5%), and LDL (-18.5%) with metformin + simvastatin versus metformin alone.
- Heidari et al. (2019) demonstrated metformin significantly improved endothelial function in those with abnormal baseline RH-PAT ($1.3 \pm 0.3 \rightarrow 1.7 \pm 0.3$; $p < 0.001$).

5. Long-Term Effects and Safety

Underdal et al. (2018) followed 131 women 7.7 years after pregnancy; no long-term metabolic differences were found between metformin and placebo groups, indicating no sustained metabolic alteration post-treatment during pregnancy. In contrast, Vitale et al. (2025) observed sustained improvements in insulin sensitivity and androgen levels >24 months after discontinuation, suggesting benefits in early adolescent intervention.

Table (1): Summary of Key Characteristics and Outcomes of Included Studies

Study (Year)	Design & Population	Intervention (Duration)	Key Metabolic/Clinical Results	Main Conclusion
Bridger et al. (2006)	RCT, n = 22, adolescents (13–18 yrs)	Metformin 500 mg BID vs placebo (12 wks)	↓ Testosterone by 38.3 ng/dL vs 0.86 ng/dL; ↑ HDL +6.98 mg/dL; menses 2.5× higher; no BMI change	Metformin lowers testosterone and improves menstrual regularity
Shahebrahimi et al. (2016)	RCT, n = 56, women 20–49 yrs	Metformin (500 mg TID) vs Pioglitazone (30 mg/d, 3 mo)	↓ Weight (p=0.047), DHEA (p=0.035); ↓ FBS, insulin, acne in both; pioglitazone ↓ TG (p<0.05)	Both effective; pioglitazone alternative for intolerant patients
Soldat-Stankovic et al. (2021)	RCT, n = 60, normal/overweight PCOS	Metformin 1500 mg/d vs Myo-inositol 4 g/d (6 mo)	↓ BMI (p=0.005), WC (p=0.004), FG score (p=0.001), Testosterone (p=0.013); Myo-inositol ↓ DBP (p=0.036)	MET improved androgen indices; MI improved cardiovascular markers
Chen et al. (2025)	RCT, n = 100, overweight/obese PCOS	MET 1000 mg BID ± Semaglutide 1 mg QW (16 wks)	Combo: ↓ Weight 6.09±3.34 kg vs 2.25±4.27 kg; ↑ pregnancy rate 35% vs 15% (p<0.05); ↓ CRP	MET+Semaglutide superior for weight, inflammation, fertility
Vitale et al. (2025)	Retrospective cohort, n = 168, adolescents	MET 500 mg BID + COCs	↓ BMI; ↓ Testosterone (p<0.02); ↓ FAI (3.7→1.8); sustained insulin sensitivity post-therapy	Long-term metabolic benefits after adolescent MET treatment
Guan et al. (2020)	Meta-analysis, 12 RCTs	MET vs control	Pooled ↓ BMI (WMD -1.25), ↓ WC (-1.41 cm), ↓ Testosterone, ↑ HDL	MET effective for weight and hormonal modulation in PCOS
Romualdi et al. (2010)	RCT, n = 28, normal-weight PCOS	MET 500 mg BID vs placebo (6 mo)	70% restored menses; ↓ Testosterone and 17-OHP (p<0.05); ↓ ovarian volume	MET improved menstrual cyclicity independent of insulin effect
Ladson et al. (2010)	RCT, n = 114	MET + lifestyle vs placebo + lifestyle (6 mo)	↓ Testosterone at 3 mo (not at 6); no significant ovulation difference	MET modestly improved hormones, not ovulation
Sova et al. (2013)	RCT, n = 110	MET vs placebo (3 mo)	↓ oxidative stress biomarker 8-OHdG (significant in obese women)	MET reduces oxidative stress, esp. in obese PCOS
Underdal et al. (2018)	Follow-up, n = 131	MET during pregnancy vs placebo (7.7 yrs FU)	No difference in BMI, BP, glucose, or insulin	Pregnancy MET had no long-term metabolic effect

Heidari et al. (2019)	RCT, n = 42	MET 1500 mg/d (3 mo)	↑ RH-PAT index in impaired endothelium (1.3→1.7; p<0.001)	MET improves endothelial function independently of glycemia
Kazerooni et al. (2010)	RCT, n = 84	MET 500 mg TID ± Simvastatin 20 mg (12 wks)	Combo ↓ T (-25.5%), ↓ LH (-45.5%), ↓ LDL (-18.5%), ↑ HDL (+14%)	Combination therapy enhances hormonal and lipid benefits

Across twelve studies, metformin consistently improved hyperandrogenism, menstrual regularity, and selected metabolic markers in women with PCOS. Meta-analytic evidence supports reductions in BMI, waist circumference, and testosterone, though insulin sensitivity improvements were inconsistent. Combination regimens (with simvastatin or semaglutide) provided superior lipid and reproductive outcomes. Adolescent interventions showed sustained long-term benefit, highlighting early treatment's potential to prevent metabolic sequelae.

Discussion

The findings of this systematic review and meta-analysis underscore the multifaceted benefits of metformin in improving clinical, metabolic, and reproductive outcomes among women with polycystic ovary syndrome (PCOS). Across the included studies, metformin consistently reduced insulin resistance, lowered androgen levels, and restored menstrual cyclicity, aligning with the understanding that PCOS is closely linked to metabolic dysregulation and insulin resistance, which drive hyperandrogenism and reproductive dysfunction (Rotterdam EA-SPCWG, 2004).

Metformin's ability to improve insulin sensitivity and glucose metabolism was supported by multiple studies. Bridger et al. (2006) and Eisenhardt et al. (2006) demonstrated significant reductions in fasting insulin and HOMA-IR scores, while Guan et al. (2020) confirmed that metformin reduced BMI and waist circumference in overweight women with PCOS, emphasizing its role in metabolic control beyond weight loss alone. Notably, Zahra et al. (2016) reported that metformin significantly improved several hormonal and metabolic parameters, including reductions in LH, FSH, ovarian volume, and visfatin levels, but did not significantly alter HOMA-IR, highlighting that some metabolic effects may occur independently of insulin sensitivity improvements.

Weight reduction and improvements in lipid profiles were consistent across trials assessing metformin's cardiometabolic effects. Chen et al. (2025) reported that metformin combined with semaglutide produced greater reductions in body weight and CRP levels than metformin monotherapy, suggesting additive benefits of GLP-1 receptor agonists. Similarly, Soldat-Stankovic et al. (2021) found that both metformin and myo-inositol improved cardiovascular risk profiles, with metformin more effective in reducing hyperandrogenic indices. Zahra et al. (2016) further demonstrated that metformin significantly reduced systolic and diastolic blood pressure, reinforcing its vascular benefits even when insulin resistance improvements are modest.

The improvement in androgenic symptoms is a central feature of PCOS management. Romualdi et al. (2010) and Kazerooni et al. (2010) highlighted that metformin reduced serum testosterone and improved hirsutism scores. Combination therapy with simvastatin enhanced reductions in LH, LH/FSH ratio, and LDL levels, suggesting synergistic effects between insulin-sensitizing and lipid-lowering therapies. Zahra et al. (2016) similarly reported hormonal normalization, including decreased LH and FSH, further supporting metformin's efficacy in modulating the hypothalamic-pituitary-ovarian axis.

From a reproductive perspective, metformin has demonstrated positive effects on ovulation and pregnancy rates. Kocak et al. (2002) found improved ovulatory rates in clomiphene-resistant women, while Morin-Papunen et al. (2012) reported higher live-birth rates with metformin compared to placebo. Zain et al. (2009) observed that combining metformin with clomiphene citrate led to superior ovulation and pregnancy outcomes, highlighting the therapeutic potential of metformin in both monotherapy and adjunctive contexts.

Adolescent populations represent a unique subset of PCOS patients. Bridger et al. (2006) demonstrated reductions in testosterone and improvements in menstrual regularity, while Vitale et al. (2025) reported that low-dose metformin combined with oral contraceptives produced sustained improvements in BMI, insulin sensitivity, and androgenic profiles, even after treatment cessation. These findings suggest that early metabolic modulation may prevent long-term complications associated with PCOS.

Metformin's benefits extend beyond glycemic control to oxidative stress and vascular health. Sova et al. (2013) reported decreased 8-hydroxy-2'-deoxyguanosine levels, particularly in obese women, while Heidari et al. (2019) observed improved endothelial function independent of glycemia. Zahra et al. (2016) adds to this evidence by showing improved vascular markers, including blood pressure reduction, reinforcing metformin's cardiovascular protective role.

Emerging data also suggest skeletal benefits of metformin in PCOS. Lingaiah et al. (2019) found that metformin decreased bone turnover markers, potentially mediated by improved insulin sensitivity and hormonal balance. These results indicate that metformin's benefits may be systemic rather than confined to traditional metabolic endpoints.

Metformin use during pregnancy appears safe and may reduce gestational complications. Vanky et al. (2004) reported lower rates of gestational diabetes without affecting androgen levels, while Underdal et al. (2018) found no long-term post-pregnancy metabolic differences between metformin and placebo groups. These findings highlight that while metformin is safe during pregnancy, long-term metabolic persistence may vary depending on baseline characteristics and treatment duration.

Comparisons with other insulin-sensitizing agents show that metformin remains first-line therapy due to safety and efficacy. Shahebrahimi et al. (2016) observed that metformin and pioglitazone similarly improved metabolic and reproductive outcomes, though metformin was superior in reducing weight and androgenic symptoms. Similarly, combining metformin with lifestyle interventions enhances outcomes, as reported by Ladson et al. (2010) and Amiri et al. (2014), highlighting the synergy between pharmacologic and behavioral strategies.

Variability in response to metformin is influenced by insulin sensitivity, BMI, and genetic factors. Eisenhardt et al. (2006) noted stronger early effects in hyperinsulinemic women, while Romualdi et al. (2010) observed improvements even in normoinsulinemic patients, suggesting both insulin-dependent and independent mechanisms. Phenotypic heterogeneity also affects response, with Soldat-Stankovic et al. (2021) and Chen et al. (2025) showing differences in BMI and inflammatory status outcomes.

Overall, the collective evidence supports metformin as a versatile, well-tolerated therapy for improving metabolic, reproductive, and cardiovascular outcomes in women with PCOS. Adjunctive therapies, such as GLP-1 agonists, inositols, or statins, may enhance benefits in specific subgroups, but metformin remains foundational due to broad efficacy and established safety. Future research should focus on predictors of therapeutic response, optimizing combination regimens, and exploring long-term benefits across diverse PCOS phenotypes.

Conclusion

This systematic review confirms that metformin exerts significant and multidimensional benefits for women with PCOS, extending beyond glycemic control to improvements in reproductive function, lipid metabolism, and vascular health. The findings highlight metformin's capacity to reduce serum testosterone, enhance menstrual regularity, and decrease markers of inflammation and oxidative stress. These effects are particularly pronounced in overweight or insulin-resistant women, where metabolic correction directly supports reproductive normalization.

Despite heterogeneous responses, metformin remains the cornerstone of pharmacologic management in PCOS due to its safety, affordability, and long-term efficacy. Combination regimens—such as pairing metformin with semaglutide, myo-inositol, or hormonal contraceptives—further amplify therapeutic effects. Future research should focus on phenotype-specific interventions and the sustainability of post-treatment benefits to optimize individualized care for women with PCOS.

References

- Amiri, M., Golsorkhtabaramiri, M., Esmaeilzadeh, S., et al. (2014). Effect of metformin and flutamide on anthropometric indices and laboratory tests in obese/overweight PCOS women under hypocaloric diet. Journal of Reproduction & Infertility, 15(4), 205–213.
- Bridger, T., MacDonald, S., Baltzer, F., & Rodd, C. (2006). Randomized placebo-controlled trial of metformin for adolescents with polycystic ovary syndrome. Archives of Pediatrics & Adolescent Medicine, 160(3), 241–246.
- Chen, H., Lei, X., Yang, Z., Xu, Y., Liu, D., Wang, C., & Du, H. (2025). Effects of combined metformin and semaglutide therapy on body weight, metabolic parameters, and reproductive outcomes in overweight/obese women with polycystic ovary syndrome: A prospective, randomized, controlled, open-label clinical trial. Reproductive Biology and Endocrinology, 23(1), 108.

- Chou, K. H., von Eye Corleta, H., Capp, E., et al. (2003). Clinical, metabolic and endocrine parameters in response to metformin in obese women with polycystic ovary syndrome: A randomized, double-blind and placebo-controlled trial. Hormone and Metabolic Research, 35(2), 86–91.
- Eisenhardt, S., Schwarzmann, N., Henschel, V., et al. (2006). Early effects of metformin in women with polycystic ovary syndrome: A prospective randomized, double-blind, placebo-controlled trial. Journal of Clinical Endocrinology & Metabolism, 91(3), 946–952.
- Guan, Y., Wang, D., Bu, H., Zhao, T., & Wang, H. (2020). The effect of metformin on polycystic ovary syndrome in overweight women: A systematic review and meta-analysis of randomized controlled trials. International Journal of Endocrinology, 2020, 5150684.
- Heidari, B., Lerman, A., Lalia, A. Z., et al. (2019). Effect of metformin on microvascular endothelial function in polycystic ovary syndrome. Mayo Clinic Proceedings, 94(12), 2455–2466.
- Kazerooni, T., Shojaei-Baghini, A., Dehbashi, S., et al. (2010). Effects of metformin plus simvastatin on polycystic ovary syndrome: A prospective, randomized, double-blind, placebo-controlled study. Fertility and Sterility, 94(6), 2208–2213.
- Kocak, M., Caliskan, E., Simsir, C., et al. (2002). Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with polycystic ovary syndrome. Fertility and Sterility, 77(1), 101–106.
- Ladson, G., Dodson, W. C., Sweet, S. D., et al. (2010). The effects of metformin with lifestyle therapy on polycystic ovary syndrome: A randomized double-blind study. Endocrine Reviews, 31(5), 1059–1066.
- Lingaiah, S., Morin-Papunen, L., Risteli, J., et al. (2019). Metformin decreases bone turnover markers in polycystic ovary syndrome: A post hoc study. Fertility and Sterility, 112(2), 362–370.
- Morin-Papunen, L., Rantala, A. S., Unkila-Kallio, L., et al. (2012). Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): A multicenter, double-blind, placebo-controlled randomized trial. Journal of Clinical Endocrinology & Metabolism, 97(5), 1492–1500.
- Romualdi, D., Giuliani, M., Cristello, F., et al. (2010). Metformin effects on ovarian ultrasound appearance and steroidogenic function in normal-weight normoinsulinemic women with polycystic ovary syndrome: A randomized double-blind placebo-controlled clinical trial. Fertility and Sterility, 93(7), 2303–2310.
- Rotterdam EA-SPCWG. (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertility and Sterility, 81(1), 19–25.
- Shahebrahimi, K., Jalilian, N., Bazgir, N., & Rezaei, M. (2016). Comparison clinical and metabolic effects of metformin and pioglitazone in polycystic ovary syndrome. Indian Journal of Endocrinology and Metabolism, 20(6), 805–809.
- Soldat-Stankovic, V., Popovic Pejicic, S., Stankovic, S., Jovanic, J., Bjekic-Macut, J., Livadas, S., Ognjanovic, S., Mastorakos, G., Micic, D., & Macut, D. (2021). The effect of myo-inositol and metformin on cardiovascular risk factors in women with polycystic ovary syndrome: A randomized controlled trial. Acta Endocrinologica, 17(2), 241–247.
- Sova, H., Puistola, U., Morin-Papunen, L., et al. (2013). Metformin decreases serum 8-hydroxy-2'-deoxyguanosine levels in polycystic ovary syndrome. Fertility and Sterility, 99(2), 593–598.
- Underdal, M. O., Stridsklev, S., Oppen, I. H., et al. (2018). Does metformin treatment during pregnancy modify the future metabolic profile in women with PCOS? Journal of Clinical Endocrinology & Metabolism, 103(6), 2408–2413.
- Vanky, E., Salvesen, K. A., Heimstad, R., et al. (2004). Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: Results of a randomized study. Human Reproduction, 19(8), 1734–1740.
- Vitale, S. G., Di Michele, S., Tassi, A., et al. (2025). Sustained metabolic improvements with low-dose metformin combined with oral contraceptives in female adolescents with PCOS: A single-center retrospective cohort study. Advances in Therapy, 42, 3762–3773.
- Zahra, M., Shah, M., Ali, A., & Rahim, R. (2017). Effects of metformin on endocrine and metabolic parameters in patients with polycystic ovary syndrome. Hormone and Metabolic Research, 49(02), 103-108.
- Zain, M. M., Jamaluddin, R., Ibrahim, A., et al. (2009). Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction, achievement of pregnancy, and live birth in Asian women with polycystic ovary syndrome: A randomized controlled trial. Fertility and Sterility, 91(2), 514–521.