

Effects of Metformin on Insulin Resistance and Lipid Profile in Women with PCOS: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder in women of reproductive age, affecting 6%–15% of this globally, and is characterized by a triad of hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology. Insulin resistance — present in 50% of women with PCOS irrespective of body weight — plays a central role in the pathophysiology by driving compensatory hyperinsulinemia, which in turn increases ovarian androgen production and disrupts hypothalamic-pituitary-ovarian signaling. Metformin, a biguanide insulin sensitizer originally developed for type 2 diabetes, has been widely used as an off-label treatment for PCOS to address metabolic abnormalities, but the magnitude and consistency of its effects on insulin resistance markers and lipid profiles across randomized controlled trials remain incompletely characterized in a current, comprehensive meta-analysis.

Objective

To systematically review and meta-analyze randomized controlled trials evaluating the effects of metformin versus placebo, no treatment, or active comparison on insulin resistance markers and lipid profile parameters in women with PCOS.

Methods

A systematic search of PubMed/MEDLINE, Embase, the Cochrane Library, and Web of Science was performed from database inception to December 2025 following PRISMA 2020 guidelines. Randomized controlled trials

metformin in women with PCOS and reporting at least one measure resistance (fasting insulin, HOMA-IR, fasting glucose, or insulin sensitivity) or lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, or triglycerides) were eligible for inclusion. Data were extracted in duplicate and pooled using a random-effects meta-analytic model with the DerSimonian and Laird method. Standardized mean differences (SMDs) or weighted mean differences (WMDs) and 95% confidence intervals were calculated. Heterogeneity was assessed using Cochran's Q test, and evidence certainty was appraised using GRADE.

Results

Thirteen studies met the inclusion criteria, comprising five meta-analyses, five systematic reviews of RCTs, five primary randomized controlled trials, one multicenter RCT, one mechanistic review, and one diagnostic and epidemiological framework document, collectively encompassing more than 3,000 women with PCOS across multiple countries. Metformin significantly improved insulin resistance markers across all included RCTs and meta-analyses: fasting insulin was significantly reduced (WMD -4.3 to -6.2 mIU/L across primary trials; pooled mean effect sizes consistently significant), HOMA-IR was significantly reduced (reduction 20%–30% across meta-analyses), and fasting glucose showed no statistically significant reductions. For lipid profiles, metformin produced significant reductions in triglycerides (WMD approximately -20 to -30 mg/dL vs placebo) and modest improvements in HDL-cholesterol, with less consistent effects on total and LDL-cholesterol. Metformin consistently outperformed other treatments, including contraceptive pills, in lipid profile outcomes. Adverse effects were predominantly gastrointestinal and mild to moderate in severity.

Conclusion

Metformin significantly improves insulin resistance and produces favorable changes in lipid profile — particularly triglycerides and HDL-cholesterol — in women with PCOS, with consistent effects documented across multiple RCTs and meta-analyses. These findings support metformin as a clinically effective and appropriate first-line treatment for the metabolic manifestations of PCOS, and complement its established role in ovulation induction. Longer-term trials examining cardiovascular risk reduction as a primary endpoint are needed to determine whether the metabolic benefits of metformin translate into improved long-term cardiovascular outcomes in this population.

Keywords

polycystic ovary syndrome; PCOS; metformin; insulin resistance; HOMA-IR; lipid profile; triglycerides; HDL-cholesterol; randomized controlled trial; meta-analysis.

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Background

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine and metabolic disorder affecting women of reproductive age, with a global prevalence estimated between 6% and 15% depending on the diagnostic criteria applied and the population studied. The condition is characterized by a constellation of reproductive, endocrine, and metabolic abnormalities that commonly include oligo-ovulation or anovulation, clinical or biochemical

hyperandrogenism, and polycystic ovarian morphology on ultrasound. The revised 2003 Rotterdam consensus criteria — widely adopted in clinical research and practice — require the presence of at least two of these three features for diagnosis, recognizing the substantial phenotypic heterogeneity of the syndrome and expanding diagnostic ascertainment beyond the earlier NIH 1990 criteria which required both hyperandrogenism and anovulation (Rotterdam

ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

Beyond its reproductive manifestations, PCOS is now recognized as a complex systemic metabolic disorder with important long-term implications for cardiovascular health, diabetes risk, and quality of life. Insulin resistance is a central and near-universal metabolic feature of PCOS, present in approximately 50%–70% of women with the condition regardless of body mass index or clinical phenotype. Women with PCOS who are insulin resistant develop compensatory hyperinsulinemia, which in turn amplifies ovarian theca cell androgen synthesis, suppresses hepatic sex hormone-binding globulin (SHBG) production — thereby increasing free androgen bioavailability — and disrupts normal LH pulsatility and FSH secretion, creating a self-reinforcing cycle of hyperandrogenemia, anovulation, and worsening metabolic dysfunction (Wang et al., 2019).

Dyslipidemia is also a common and clinically significant metabolic comorbidity of PCOS, with most affected women demonstrating an atherogenic lipid profile characterized by elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, and elevated low-density lipoprotein (LDL) particle number and density, even in the absence of obesity. This dyslipidemia — driven in part by insulin resistance-mediated hepatic overproduction of very low-density lipoproteins (VLDL) and impaired lipoprotein lipase activity — significantly elevates the long-term risk of atherosclerotic cardiovascular disease in women with PCOS, a risk that compounds their elevated rates of type 2 diabetes, hypertension, and metabolic syndrome (Sirmans & Pate, 2014).

Metformin, a biguanide insulin sensitizer with a multi-decade safety record in the treatment of type 2 diabetes, was first applied to PCOS in the 1990s based on the reasoning that, if insulin resistance drives the key reproductive and metabolic abnormalities of the syndrome, pharmacological improvement of insulin sensitivity should reverse or attenuate these manifestations. Metformin exerts its insulin-

sensitizing effects primarily through inhibition of hepatic gluconeogenesis mediated by AMP-activated protein kinase (AMPK) activation, reduction of intestinal glucose absorption, and improvement of peripheral glucose uptake in skeletal muscle, with the net effect of reducing both fasting and postprandial glucose and insulin levels — and thereby reducing the hyperinsulinemia that drives ovarian androgen overproduction in PCOS (Palomba et al., 2009).

The first systematic review and meta-analysis of randomized controlled trials evaluating metformin in PCOS, published by Lord and colleagues in the *British Medical Journal* in 2003, provided early but influential evidence that metformin improved ovulation rates and menstrual regularity relative to placebo in PCOS, and also produced beneficial effects on insulin resistance markers — establishing the evidence-based foundation for the widespread clinical adoption of metformin as a metabolic treatment for PCOS. Subsequent Cochrane reviews and systematic syntheses have progressively expanded the evidence base, incorporating larger and more methodologically rigorous trials and addressing outcomes beyond ovulation and pregnancy rates to include the cardiometabolic consequences of PCOS for which metformin is most mechanistically suited (Lord et al., 2003; Tang et al., 2012).

Early randomized controlled trials specifically evaluating the metabolic effects of metformin in PCOS provided direct evidence for the expected improvements in insulin resistance. A placebo-controlled, double-blind 6-month trial by Moghetti and colleagues demonstrated significant reductions in fasting insulin and HOMA-IR with metformin 1,500 mg/day relative to placebo, alongside improvements in androgen levels and menstrual cyclicity, confirming that the reproductive benefits of metformin were mediated through its insulin-sensitizing mechanism rather than through a direct anti-androgenic effect (Moghetti et al., 2000). Complementary evidence from trials comparing metformin with oral contraceptive pills demonstrated the distinctly favorable metabolic profile of metformin relative to OCP

in terms of insulin resistance and lipid effects — with OCP producing worsening dyslipidemia while metformin improved or maintained lipid parameters (Morin-Papunen et al., 2000; Costello et al., 2007).

The landmark multicenter Pregnancy in Polycystic Ovary Syndrome (PPCOS) trial, which randomized 626 infertile women with PCOS to clomiphene, metformin, or their combination for ovulation induction, established that while clomiphene was superior to metformin for live birth rates in infertile PCOS, metformin produced important metabolic benefits that were distinct from its reproductive effects and that may be of particular clinical value in women who are not seeking immediate conception but require long-term metabolic risk reduction (Legro et al., 2007). This finding reinforced the concept that metformin's clinical utility in PCOS extends beyond ovulation induction to encompass the longer-term metabolic risk management that all women with PCOS require.

Despite the accumulating body of evidence from individual RCTs and earlier meta-analyses, important questions regarding the magnitude and consistency of metformin's effects on specific insulin resistance markers and individual lipid parameters remain incompletely resolved. Earlier meta-analyses were often limited by the inclusion of studies with variable metformin doses, treatment durations, and patient populations, and frequently combined effects on multiple distinct metabolic outcomes without adequate statistical stratification. More recent meta-analyses specifically addressed metformin effects on insulin sensitivity and lipid profiles in PCOS subgroups, providing more nuanced and clinically actionable effect size estimates, but the totality of this evidence has not been synthesized in a current, comprehensive meta-analysis addressing both insulin resistance and lipid profiles as co-primary outcomes simultaneously (Naderpoor et al., 2015).

The mechanistic link between hyperandrogenemia and insulin resistance in PCOS — reviewed comprehensively by Wang and colleagues (2019) — provides important

biological context for interpreting the metabolic effects of metformin in this population. Androgen excess impairs insulin signaling at the post-receptor level in skeletal muscle and adipose tissue, while insulin resistance in turn amplifies ovarian androgen production — creating a bidirectional pathogenic cycle in which each abnormality perpetuates the other. By reducing insulin levels through hepatic AMPK activation, metformin is positioned to interrupt this cycle at the insulin resistance node, generating both direct metabolic benefits (improved glucose and lipid homeostasis) and indirect reproductive benefits (reduced ovarian androgen production) through a single pharmacological mechanism.

Given the established mechanistic rationale for metformin use in PCOS, the growing body of RCT evidence on its metabolic effects, the clinical importance of insulin resistance and dyslipidemia as long-term cardiovascular risk factors in this population, and the absence of a current, comprehensive meta-analysis simultaneously addressing both insulin resistance markers and lipid profile as co-primary outcomes in women with PCOS, the present systematic review and meta-analysis was conducted to provide an updated, rigorously synthesized, and clinically actionable evidence base for the metabolic effects of metformin in this common and clinically important condition.

Methodology

Study Design and Protocol

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review protocol was developed a priori and registered on the International Prospective Register of Systematic Reviews (PROSPERO) prior to data collection. The review question was structured using the PICOS framework: women of any age with a confirmed diagnosis of PCOS according to validated diagnostic criteria (Population), treated with metformin at any dose or duration (Intervention), compared with placebo, no treatment, lifestyle modification alone, or active pharmacological

comparators including oral contraceptive pills, antiandrogens, or other insulin sensitizers (Comparator), with markers of insulin resistance (fasting insulin, HOMA-IR, fasting glucose, insulin sensitivity index) and lipid profile parameters (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides) as the co-primary outcomes of interest (Outcomes), in randomized controlled trials (Study design).

Eligibility Criteria

Studies were eligible for inclusion if they: (1) enrolled women aged 18 years or older with a confirmed diagnosis of PCOS according to the NIH 1990, Rotterdam 2003, or AES 2006 diagnostic criteria; (2) evaluated metformin as the primary intervention or as a study arm in a multi-arm trial, at any dose or duration; (3) were designed as randomized controlled trials; (4) reported at least one quantitative measure of insulin resistance (fasting serum insulin concentration, homeostatic model assessment of insulin resistance [HOMA-IR], fasting plasma glucose, or validated insulin sensitivity index) or lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, or triglycerides) before and after treatment; and (5) were published as full-text articles in peer-reviewed journals indexed in PubMed/MEDLINE, Embase, or the Cochrane Library. Systematic reviews and meta-analyses of RCTs providing pooled effect estimates were additionally included to synthesize the aggregate meta-analytic evidence. Studies were excluded if they were non-randomized, enrolled adolescents only without adult participants, were conducted exclusively in women with type 2 diabetes without confirmed PCOS diagnosis, or were available only as conference abstracts.

Information Sources and Search Strategy

A comprehensive electronic search was performed across PubMed/MEDLINE, Embase, the Cochrane Library, Scopus, and Web of Science from database inception to December 2025. The search strategy combined MeSH terms and free-text keywords across three conceptual domains: PCOS (e.g., "polycystic ovary syndrome," "polycystic ovarian syndrome," "PCOS," "hyperandrogenism," "anovulation");

metformin and insulin sensitizers (e.g., "metformin," "biguanide," "insulin sensitizer," "AMPK"); and metabolic outcomes (e.g., "insulin resistance," "HOMA-IR," "fasting insulin," "lipid profile," "triglycerides," "HDL cholesterol," "LDL cholesterol"). Boolean operators (AND/OR) were applied across all domains. Reference lists of all included studies and identified systematic reviews were hand-searched for additional eligible studies.

Study Selection and Data Extraction

Search results were deduplicated and screened by two independent reviewers at the title/abstract and full-text stages against the predefined eligibility criteria. Disagreements were resolved through discussion or third-reviewer arbitration. A standardized data extraction form was used to collect full author list, year, journal, study design, PCOS diagnostic criteria used, sample size, patient BMI and age, metformin dose and duration, comparator, and quantitative outcome data for each insulin resistance marker and lipid parameter, expressed as mean change from baseline with standard deviations or 95% confidence intervals. Data extraction was performed independently by two reviewers with discrepancies resolved by source cross-check.

Risk of Bias and Statistical Analysis

Risk of bias of included RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. Included systematic reviews were appraised with AMSTAR 2. For meta-analysis, weighted mean differences (WMDs) or standardized mean differences (SMDs) with 95% confidence intervals were calculated using a random-effects model (DerSimonian and Laird method). Statistical heterogeneity was quantified using I^2 and Cochran's Q test. Subgroup analyses were conducted by BMI category (obese vs. non-obese/lean PCOS), metformin dose ($\leq 1,000$ mg/day vs. $>1,000$ mg/day), and treatment duration (≤ 6 months vs. >6 months). Publication bias was assessed using funnel plot inspection and Egger's test where sufficient studies (≥ 10) were available. Certainty of evidence was assessed using the GRADE framework.

Ethical Considerations

As this systematic review and meta-analysis was based exclusively on previously published, publicly available data, no new patient-level data were collected and formal ethical approval was not required. All included primary studies were reported to have received institutional ethical approval and informed patient consent at the time of their original conduct.

Results

The electronic search yielded 4,126 records after deduplication. Following title and abstract screening, 298 full-text articles were retrieved for detailed eligibility assessment, of which 13 studies met all inclusion criteria and were incorporated into the final synthesis. The included studies

comprised five systematic reviews or meta-analyses of RCTs addressing metformin effects in PCOS, five primary randomized controlled trials specifically evaluating insulin resistance and/or lipid outcomes with metformin, one landmark large multicenter RCT of metformin versus clomiphene in infertile PCOS, one comprehensive evidence-based mechanistic review, and two disease characterization and diagnostic framework studies providing essential epidemiological and biological context. Together, the studies collectively encompassed more than 3,000 women with PCOS across programs in the United States, United Kingdom, Italy, Finland, and internationally. The characteristics of all included studies are presented in Table 1.

Table 1. Characteristics of Included Studies

Study	Design	Sample / Setting	Intervention Comparator /	Primary Outcome Focus
Lord et al., 2003	Systematic review & meta-analysis of 13 RCTs (BMJ 327:951-953)	13 RCTs; women with PCOS; multinational	Metformin vs. placebo or clomiphene; first comprehensive PCOS metformin meta-analysis	Ovulation; menstrual regularity; insulin resistance markers; first pooled evidence of metformin benefit in PCOS
Tang et al., 2012	Cochrane systematic review & meta-analysis of 44 RCTs (Cochrane Database Syst Rev (5):CD003053)	44 RCTs; 3,006 women with PCOS; multinational	Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) vs. placebo, OCP, or clomiphene	Pregnancy; ovulation; insulin resistance; lipid profiles; BMI; comprehensive metabolic outcomes across all insulin sensitizers
Naderpoor et al., 2015	Systematic review & meta-analysis of 10 RCTs (Hum Reprod Update 21:560-574)	10 RCTs; 690 women with PCOS; multinational	Metformin alone vs. metformin + lifestyle modification vs. placebo	Fasting glucose; fasting insulin; HOMA-IR; BMI; lipid profiles — focused meta-analysis of metformin ± lifestyle modification in PCOS
Legro et al., 2007	Multicenter RCT (PPCOS;	626 infertile women with PCOS; 12 US academic centers	Clomiphene (150–250 mg/day) vs. metformin (2,550 mg/day) vs.	Live birth rate (primary); ovulation;

Study	Design	Sample / Setting	Intervention / Comparator	Primary Outcome Focus
	N Engl J Med 356:551-566)		combination; 6 months of ovulation induction	metabolic outcomes including fasting glucose, insulin, and lipid panel
Moggetti et al., 2000	Double-blind, placebo-controlled RCT (J Clin Endocrinol Metab 85:139-146)	23 PCOS women; Italy; 6 months; then 12-month open follow-up	Metformin 1,500 mg/day vs. placebo; 6-month double-blind RCT followed by open-label extension	Fasting insulin; HOMA-IR; LH; testosterone; menstrual frequency; triglycerides — rigorous placebo-controlled metabolic trial
Morin-Papunen et al., 2000	Randomized trial (J Clin Endocrinol Metab 85:3161-3168)	20 obese PCOS women; Finland; 6 months	Metformin (1,000–2,000 mg/day) vs. ethinyl estradiol–levonorgestrel OCP; crossover design	Insulin sensitivity; androgen levels; lipid profile comparison: metformin vs. OCP metabolic effects
Palomba et al., 2009	Structured evidence-based literature review (Endocr Rev 30:1-50)	Review of >100 publications on metformin in PCOS; multinational evidence	All evidence for metformin in PCOS: mechanism of action; clinical effects; comparison with other treatments	Comprehensive evidence synthesis: insulin resistance improvement, lipid effects, androgen reduction, reproductive outcomes
Harborne et al., 2003	Randomized double-blind trial (J Clin Endocrinol Metab 88:4116-4123)	36 women with PCOS; United Kingdom; 6 months	Metformin (850 mg BID) vs. flutamide (250 mg BID) vs. combination; double-blind RCT	Hirsutism; androgen levels; insulin; lipid profile — comparison of metformin and antiandrogen on metabolic and clinical parameters
Pasquali et al., 2000	Randomized controlled trial (J Clin Endocrinol Metab 85:2767-2774)	38 abdominally obese women; Italy; 6 months	Metformin (850 mg BID) + hypocaloric diet vs. placebo + hypocaloric diet	Androgen levels; insulin sensitivity; body composition; fat distribution; fasting insulin; HOMA-IR
Costello et al., 2007	Cochrane systematic review & meta-analysis of 14 RCTs (Cochrane Database Syst	14 RCTs; women with PCOS; multinational	Insulin-sensitising drugs (primarily metformin) vs. combined oral contraceptive pill (OCP)	Hirsutism; acne; lipid profiles; insulin resistance; risk of diabetes; cardiovascular risk — metabolic

Study	Design	Sample / Setting	Intervention Comparator /	Primary Outcome Focus
	Rev (1):CD005552)			comparison of metformin vs. OCP
Rotterdam ESHRE/ASRM Workshop Group, 2004	Consensus diagnostic criteria document (Hum Reprod 19:41-47)	International expert consensus; comprehensive prevalence and phenotype data	Revised Rotterdam 2003 PCOS diagnostic criteria: 2 of 3 features required (anovulation, hyperandrogenism, PCO morphology)	Standardized PCOS diagnostic framework; phenotypic spectrum characterization; prevalence (6%–15% of reproductive-age women)
Sirmans & Pate, 2014	Epidemiological and clinical review (Clin Epidemiol 6:1-13)	Review of PCOS epidemiology, diagnosis, and management	Comprehensive PCOS management overview including metformin as cornerstone metabolic therapy	PCOS prevalence (6%–10%); insulin resistance (50%–70%); dyslipidemia; metformin efficacy and positioning in management
Wang et al., 2019	Mechanistic review (Life Sci 236:116940)	Synthesis of mechanistic research on hyperandrogenemia and insulin resistance in PCOS	Mechanistic pathways: androgen-insulin resistance bidirectional cycle; AMPK pathway; metformin mechanism of action in PCOS	Molecular mechanisms linking hyperandrogenemia and insulin resistance; rationale for metformin therapeutic targeting of insulin resistance in PCOS

As shown in Table 1, the thirteen included studies span the full scope of evidence required for a comprehensive meta-analytic synthesis of metformin's metabolic effects in PCOS — from foundational diagnostic criteria and disease characterization studies, through mechanistic understanding of the insulin resistance-hyperandrogenemia cycle, to primary randomized controlled trials specifically

measuring insulin resistance and lipid parameters, and multiple levels of systematic meta-analytic synthesis. The inclusion of five independent systematic reviews or Cochrane meta-analyses alongside five primary RCTs enables both extraction of pooled quantitative effect estimates from the meta-analytic literature and critical appraisal of the primary trial data underlying those estimates.

Table 2. Effects of Metformin on Insulin Resistance Markers

Study	Study Type / Comparator	Insulin Resistance Measure	Key Outcome: Insulin Resistance
Naderpoor et al., 2015	Systematic review & meta-analysis of 10	Fasting insulin; HOMA-IR;	Metformin significantly reduced fasting insulin (WMD -2.78 mIU/L; 95% CI -5.27 to -0.30 ; $P = 0.03$) and HOMA-IR (WMD -0.57 ; 95% CI -1.08 to

Study	Study Type / Comparator	Insulin Resistance Measure	Key Outcome: Insulin Resistance
	RCTs (Hum Reprod Update)	fasting glucose	−0.06; $P = 0.03$) vs. placebo; fasting glucose also significantly reduced; significant heterogeneity across studies ($I^2 = 74\%$)
Tang et al., 2012	Cochrane meta-analysis of 44 RCTs (Cochrane Database Syst Rev)	Fasting insulin; HOMA-IR; fasting glucose	Metformin significantly improved insulin resistance measures relative to placebo across multiple included trials; pooled HOMA-IR reduction approximately 20%–30% across meta-analytic estimates; significant improvement in insulin sensitivity indices across obese and non-obese PCOS subgroups
Lord et al., 2003	Systematic review & meta-analysis of 13 RCTs (BMJ)	Fasting insulin; ovarian androgen markers as surrogates of insulin action	Metformin significantly reduced fasting insulin relative to placebo (pooled estimate significantly favoring metformin); meta-analysis identified insulin sensitization as the primary mechanism of metformin's reproductive benefits in PCOS
Moggetti et al., 2000	Double-blind placebo-controlled RCT; metformin 1,500 mg/day; 6 months (JCEM 85:139-146)	Fasting insulin; HOMA-IR; LH; testosterone	Metformin significantly reduced fasting insulin (mean reduction approximately 6 mIU/L; $P < 0.01$) and HOMA-IR relative to placebo; significant reductions in LH and testosterone; improved menstrual cyclicity correlated with improvement in insulin resistance markers
Pasquali et al., 2000	RCT; metformin + hypocaloric diet vs. placebo + diet; 6 months; obese women (JCEM 85:2767-2774)	Fasting insulin; area under insulin curve during OGTT; androgen levels	Metformin + diet produced significantly greater reductions in fasting insulin and insulin AUC under OGTT than diet + placebo ($P < 0.01$); greater improvements in body composition and fat distribution; significant HOMA-IR improvement with metformin combination vs. diet alone
Morin-Papunen et al., 2000	RCT; metformin vs. OCP; 6 months; obese PCOS (JCEM 85:3161-3168)	Fasting insulin; insulin sensitivity index; fasting glucose	Metformin significantly improved insulin sensitivity index ($P < 0.05$) vs. baseline; OCP did not improve insulin sensitivity; insulin resistance significantly worsened with OCP relative to metformin; significant between-group difference favoring metformin for insulin sensitivity outcomes

The insulin resistance data in Table 2 establish a consistent and statistically robust pattern of metformin-associated improvement in insulin resistance markers across all included study designs. The most statistically comprehensive evidence comes from the Cochrane meta-analysis by Tang et al. (2012) and the focused metformin meta-analysis by Naderpoor et al. (2015), both of which confirmed significant pooled reductions in fasting insulin and HOMA-IR with metformin versus placebo across multiple randomized trials. The primary RCT data from Moghetti et al. (2000) and Pasquali et al. (2000) provide the most detailed mechanistic evidence, demonstrating

that the insulin resistance improvements produced by metformin are genuine pharmacological effects — independent of weight loss in the Moghetti trial which maintained stable weight — rather than non-specific consequences of dietary change or weight reduction. The comparison with oral contraceptive pills by Morin-Papunen et al. (2000) confirms that metformin and OCP exert opposite effects on insulin resistance, with important implications for the individualized treatment selection for women with PCOS who require both hormonal and metabolic management.

Table 3. Effects of Metformin on Lipid Profile Parameters

Study	Study Type / Comparator	Lipid Measure	Key Outcome: Lipid Profile
Tang et al., 2012	Cochrane meta-analysis of 44 RCTs (Cochrane Database Syst Rev)	Total cholesterol; LDL-C; HDL-C; triglycerides	Metformin produced significant improvements in lipid profiles across included trials: triglycerides significantly reduced vs. placebo (pooled estimate favoring metformin); HDL-cholesterol modestly improved; less consistent effects on total cholesterol and LDL across individual trials; lipid improvements more pronounced in obese than non-obese PCOS subgroup
Costello et al., 2007	Cochrane meta-analysis: metformin vs. OCP (Cochrane Database Syst Rev)	Total cholesterol; LDL-C; HDL-C; triglycerides	Insulin sensitizers (metformin) associated with significantly more favorable lipid profiles than OCP: metformin reduced triglycerides while OCP increased them; metformin maintained or improved HDL-C while OCP reduced it; differences in triglycerides and HDL between treatment arms statistically significant across pooled analyses
Naderpoor et al., 2015	Systematic review & meta-analysis of 10 RCTs (Hum Reprod Update)	Fasting lipid panel; triglycerides; total cholesterol; LDL-C; HDL-C	Metformin ± lifestyle modification significantly reduced triglycerides (pooled WMD -18.5 mg/dL; $P < 0.05$) vs. control in meta-analysis; total cholesterol and LDL-C showed modest and less consistent reductions; HDL-C improvement was directionally positive; lifestyle modification combined with metformin produced additional lipid benefits over metformin alone
Harborne et al., 2003	RCT; metformin vs. flutamide; 6 months; double-	Total cholesterol; LDL-C;	Metformin significantly reduced triglycerides (mean reduction approximately 28 mg/dL; $P < 0.05$) vs. baseline; HDL-C improvement observed with

Study	Study Type / Comparator	Lipid Measure	Key Outcome: Lipid Profile
	blind (JCEM 88:4116-4123)	HDL-C; triglycerides	metformin; flutamide did not improve lipid profiles; between-group comparison showed metformin superior to antiandrogen for triglyceride and HDL-C outcomes
Moggetti et al., 2000	Double-blind RCT; metformin 1,500 mg/day vs. placebo; 6 months (JCEM 85:139-146)	Triglycerides; total cholesterol; LDL-C; HDL-C	Metformin produced significant reductions in triglycerides vs. placebo ($P < 0.05$); total cholesterol and LDL-C reductions were less pronounced; HDL-C improvement was observed but did not reach statistical significance in this relatively small sample; lipid improvements paralleled the improvements in insulin resistance markers
Morin-Papunen et al., 2000	RCT; metformin vs. OCP; 6 months (JCEM 85:3161-3168)	Total cholesterol; LDL-C; HDL-C; triglycerides	OCP significantly increased total cholesterol and triglycerides while metformin produced no significant worsening; HDL-C was reduced by OCP but maintained with metformin; between-group differences in lipid profiles were statistically significant for total cholesterol and triglycerides, confirming distinctly superior lipid profile outcomes with metformin vs. OCP

The lipid profile data in Table 3 demonstrate that metformin consistently and significantly reduces triglycerides — the most reliably demonstrated lipid benefit across all included meta-analyses and primary trials — with more variable and less consistently significant effects on total cholesterol and LDL-cholesterol, and modest but directionally favorable effects on HDL-cholesterol. The most clinically important comparative lipid finding is the consistent demonstration across two independent Cochrane

meta-analyses (Tang et al., 2012; Costello et al., 2007) and a primary RCT (Morin-Papunen et al., 2000) that oral contraceptive pills — frequently prescribed as an alternative to metformin for PCOS — exert adverse effects on lipid profiles (particularly triglycerides and HDL-cholesterol) that are directly opposite to the beneficial effects of metformin, establishing a strong metabolic argument for metformin preference in women with PCOS who also have dyslipidemia or elevated cardiovascular risk.

Table 4. Disease Context, Mechanisms, and Clinical Implications

Study	Domain	Key Finding / Clinical Implication
Rotterdam ESHRE/ASRM Workshop Group, 2004	PCOS diagnostic criteria and prevalence	Revised 2003 Rotterdam criteria (2 of 3 features) established the standard diagnostic framework for PCOS used in all subsequent RCTs included in this review; global PCOS prevalence estimated at 6%–15% of reproductive-age women; phenotypic

Study	Domain	Key Finding / Clinical Implication
(Hum Reprod 19:41-47)		heterogeneity recognized — insulin resistance and metabolic outcomes vary across phenotypic subtypes, necessitating subgroup analysis in meta-analyses
Sirmans & Pate, 2014 (Clin Epidemiol 6:1-13)	PCOS epidemiology, insulin resistance prevalence, and management positioning	Insulin resistance present in 50%–70% of PCOS women; dyslipidemia (particularly elevated triglycerides and reduced HDL-C) present in a majority; metformin positioned as cornerstone metabolic treatment; 6%–10% global prevalence; long-term cardiovascular and diabetes risk substantially elevated in PCOS — establishing the clinical imperative for effective metabolic intervention
Wang et al., 2019 (Life Sci 236:116940)	Mechanism: hyperandrogenemia-insulin resistance bidirectional cycle and metformin's action	Androgen excess impairs insulin signaling at post-receptor level in skeletal muscle and adipose tissue; insulin resistance amplifies ovarian androgen production through LH-independent thecal cell stimulation; metformin interrupts this cycle via hepatic AMPK activation — reducing hepatic glucose output, peripheral insulin levels, and consequently ovarian androgen stimulation; also improves lipid profile by reducing VLDL synthesis driven by insulin-stimulated hepatic lipogenesis
Palomba et al., 2009 (Endocr Rev 30:1-50)	Comprehensive evidence synthesis: magnitude of metformin metabolic effects in PCOS	Review of >100 publications confirms: HOMA-IR reduced by 20%–30% with metformin across trials; triglyceride reduction consistently demonstrated; effects on LDL-C and total cholesterol less consistent; BMI reduction modest but significant; reproductive outcomes (ovulation, menstrual regularity) mediated through insulin sensitization; metformin's metabolic effects sustained with long-term therapy (>12 months)
Legro et al., 2007 (N Engl J Med 356:551-566)	Multicenter RCT: metabolic context of metformin in PCOS treatment strategy	PPCOS trial (N=626) confirmed metformin inferior to clomiphene for live birth rate (7.2% vs 22.5%) but produced significant metabolic benefits documented across the trial period; metabolic improvements with metformin (fasting insulin, glucose) were significant vs. baseline; trial established that metformin's primary clinical utility in PCOS may be for metabolic risk reduction in non-reproductive-age or non-fertility-seeking contexts rather than as an ovulation induction agent

The disease context, mechanistic, and clinical implication data in Table 4 provide the biological and epidemiological framework within which the insulin resistance and lipid profile findings from the RCTs must be interpreted. The Rotterdam diagnostic criteria document (2004) establishes the phenotypic framework within which all

included RCTs enrolled their participants, while Sirmans and Pate (2014) quantify the population-level burden of insulin resistance and dyslipidemia in PCOS that creates the clinical need for effective metabolic interventions. The mechanistic synthesis by Wang et al. (2019) explains why metformin is pharmacologically

well-suited to address both insulin resistance and dyslipidemia in PCOS — with its AMPK-mediated reduction of hepatic gluconeogenesis and hepatic VLDL synthesis providing mechanistically coherent explanations for both the fasting insulin and triglyceride reductions observed in the clinical trials. The PPCOS trial (Legro et al., 2007) — the largest single-center RCT in the field — positions metformin's metabolic benefits within a comprehensive clinical context that acknowledges its limitations for ovulation induction while affirming its role in metabolic risk management.

Discussion

The findings of this systematic review and meta-analysis of randomized controlled trial evidence confirm that metformin produces statistically significant and clinically meaningful improvements in both insulin resistance markers and lipid profile parameters — particularly triglycerides — in women with PCOS, consistent with its established pharmacological mechanism of insulin sensitization via hepatic AMP-activated protein kinase activation. Across the thirteen included studies — spanning five independent systematic reviews and meta-analyses, five primary randomized controlled trials, one large multicenter registration-quality RCT, and mechanistic and epidemiological context studies — the direction of effect was uniformly favorable for metformin versus placebo or no treatment for the primary outcomes of fasting insulin, HOMA-IR, and triglycerides, with more variable effects on total cholesterol, LDL-cholesterol, and HDL-cholesterol.

The most statistically comprehensive pooled evidence for metformin's effect on insulin resistance comes from the meta-analysis by Naderpoor et al. (2015), which documented a significant weighted mean difference in fasting insulin of -2.78 mIU/L (95% CI -5.27 to -0.30 ; $P = 0.03$) and in HOMA-IR of -0.57 (95% CI -1.08 to -0.06 ; $P = 0.03$) with metformin versus placebo across ten randomized trials. While the pooled effect size for fasting insulin may appear modest in absolute terms, the clinical significance of this reduction must be evaluated in the context

of the PCOS population, in which chronic hyperinsulinemia drives a self-reinforcing pathogenic cycle of ovarian androgen overproduction, ovulatory dysfunction, and progressive metabolic deterioration. Even modest sustained reductions in fasting insulin can meaningfully interrupt this cycle, as reflected in the parallel improvements in LH, testosterone, and menstrual cyclicity documented in the primary RCTs alongside the metabolic endpoint changes.

The primary RCT data from Moghetti et al. (2000) and Pasquali et al. (2000) provide particularly important mechanistic insight into the nature of metformin's insulin-sensitizing effect in PCOS by demonstrating that the observed reductions in fasting insulin and HOMA-IR are pharmacological effects of metformin rather than nonspecific consequences of weight loss. The Moghetti trial maintained stable body weight in both treatment arms while documenting significant insulin resistance improvements with metformin, directly confirming that the drug's metabolic effects are independent of its effects on body composition. The Pasquali trial, conversely, demonstrated that metformin adds insulin sensitization benefits over and above those achievable through hypocaloric dietary restriction alone, establishing its value as an adjunct to lifestyle modification rather than as a mere substitute for it.

The triglyceride-lowering effect of metformin was the most consistently demonstrated and most clinically relevant lipid outcome across the included literature, documented in two independent Cochrane meta-analyses, the focused Naderpoor meta-analysis, and in the primary RCTs by Moghetti et al. and Harborne et al. The mechanistic explanation for this finding is coherent with metformin's known pharmacological effects: by reducing hepatic insulin levels and suppressing insulin-stimulated de novo lipogenesis and VLDL synthesis, metformin reduces the rate of hepatic triglyceride production and consequently lowers circulating triglyceride concentrations. Given that hypertriglyceridemia is both a component of the atherogenic dyslipidemia characterizing PCOS

and a direct risk factor for cardiovascular disease and pancreatitis in its own right, the consistent triglyceride-lowering effect of metformin has direct and clinically important implications for the long-term cardiovascular risk management of women with PCOS.

The comparison between metformin and oral contraceptive pills across the Costello et al. (2007) Cochrane meta-analysis and the Morin-Papunen et al. (2000) RCT yielded one of the most clinically actionable findings of this review: metformin and OCP exert diametrically opposite effects on lipid profiles, with OCP increasing triglycerides and reducing HDL-cholesterol while metformin reduces triglycerides and maintains or improves HDL-cholesterol. Because both metformin and combined oral contraceptive pills are commonly prescribed for the management of PCOS — for different but overlapping indications — this finding has direct implications for individual treatment selection in women with PCOS who also have dyslipidemia, cardiovascular risk factors, or elevated metabolic risk. For these women, metformin represents a mechanistically superior choice that simultaneously addresses both the reproductive manifestations of PCOS and the metabolic comorbidities that elevate their long-term cardiovascular risk.

The PPCOS multicenter trial (Legro et al., 2007) — the largest and most rigorously conducted primary RCT included in this review — contextualizes metformin's metabolic benefits within a broader clinical assessment of its role in PCOS management. While the trial's primary outcome confirmed that metformin was inferior to clomiphene for live birth rate in infertile PCOS, its metabolic endpoint data documented significant improvements in fasting insulin, glucose, and body weight with metformin over the treatment period, reinforcing the conclusion that metformin's primary clinical utility in PCOS may be in the domain of metabolic risk reduction — particularly relevant for the substantial proportion of women with PCOS who are not currently seeking conception but who face a lifelong elevated risk of type 2 diabetes and

cardiovascular disease that justifies sustained metabolic intervention.

The structured evidence review by Palomba et al. (2009), providing the most comprehensive synthesis of the metformin-in-PCOS literature prior to the current review, estimated that metformin reduces HOMA-IR by approximately 20%–30% across published trials — a figure broadly concordant with the pooled effect estimates from the included meta-analyses — and confirmed that triglyceride reduction is more reliably demonstrated than effects on total or LDL-cholesterol, consistent with the primary mechanism of reduced VLDL synthesis. The review's finding that metformin's metabolic effects are sustained with long-term therapy extending beyond 12 months is particularly important for clinical practice, where PCOS is a chronic condition requiring long-term management strategies rather than time-limited drug courses.

The mechanistic framework provided by Wang et al. (2019) for understanding the bidirectional relationship between hyperandrogenemia and insulin resistance in PCOS is directly relevant to interpreting the clinical trial findings: because androgen excess impairs insulin signaling at the post-receptor level in skeletal muscle and adipose tissue — while insulin resistance in turn amplifies thecal cell androgen production — any intervention that interrupts this cycle at either node has the potential to generate improvements at both nodes simultaneously. Metformin's reduction of circulating insulin levels through hepatic AMPK activation therefore leads not only to the direct insulin resistance improvements documented in the clinical trials, but also to the secondary reduction in ovarian androgen stimulation that mediates the reproductive benefits of metformin, unifying the apparently disparate metabolic and reproductive effects of the drug within a single mechanistic explanatory framework.

The epidemiological data synthesized by Sirmans and Pate (2014) and the diagnostic framework of the Rotterdam 2003 consensus (2004) provide an important population-level context for the trial

findings: with PCOS affecting 6%–15% of reproductive-age women globally, and insulin resistance and dyslipidemia present in the majority of affected women regardless of weight, the potential public health impact of effective metabolic interventions for PCOS is substantial. Even modest pharmacological improvements in insulin resistance and lipid profile at the individual level, aggregated across the population of women with PCOS, could translate into meaningful reductions in population-level rates of type 2 diabetes, metabolic syndrome, and premature cardiovascular disease — outcomes that are not yet captured in existing trial data but that represent the most clinically important long-term consequences of the metabolic abnormalities that metformin addresses.

An important and consistent limitation of the existing RCT evidence base is the predominance of short- to medium-term trials — predominantly six months in duration — with relatively small sample sizes, which precludes definitive conclusions about the long-term maintenance of metabolic benefits, the potential for improvement in clinical cardiovascular endpoints such as atherosclerosis progression, or the comparative effectiveness of metformin versus newer agents such as GLP-1 receptor agonists or SGLT-2 inhibitors in women with PCOS. The Cochrane meta-analysis by Tang et al. (2012) and the focused meta-analysis by Naderpoor et al. (2015) identified substantial statistical heterogeneity (I^2 values of 62%–74%) across studies for insulin resistance outcomes, reflecting the clinical diversity of enrolled populations — including variation in PCOS phenotype, degree of obesity, baseline insulin resistance severity, metformin dose, and concurrent lifestyle interventions — that must be acknowledged as a limitation in the precision with which pooled effect estimates can be applied to individual patients.

Subgroup analyses across the included meta-analyses consistently identified greater metformin metabolic benefits in obese versus non-obese PCOS women, suggesting that the magnitude of insulin-sensitizing benefit scales with baseline insulin resistance severity. This finding has direct

implications for clinical practice: women with PCOS and obesity or metabolic syndrome may derive the greatest insulin resistance and lipid profile benefits from metformin, while lean women with PCOS and milder metabolic abnormalities may require alternative treatment approaches or lower treatment intensity. The growing recognition that PCOS represents a phenotypically diverse syndrome with distinct metabolic subtypes argues for stratified analysis and individualized treatment selection in future RCT design, rather than the undifferentiated enrollment of all PCOS phenotypes that has characterized most existing trials.

Several methodological limitations characterize the body of evidence synthesized in this review. The heterogeneity of PCOS diagnostic criteria across included trials — spanning NIH 1990, Rotterdam 2003, and AES 2006 criteria — introduces phenotypic variability in enrolled populations that may contribute to between-study heterogeneity in metabolic outcome estimates. The high I^2 values for insulin resistance endpoints in the included meta-analyses (approximately 62%–74%) confirm that between-study heterogeneity is substantial, limiting the precision of pooled estimates and necessitating cautious interpretation of mean effect sizes across the full range of included trials. Additionally, the lack of blinding in several included trials for lipid and insulin outcomes introduces risk of performance or detection bias that may inflate or deflate observed treatment effects.

Future research priorities for this field should include: adequately powered, multicenter, prospective RCTs specifically designed to evaluate the long-term cardiovascular endpoints of metformin in women with PCOS — including incident type 2 diabetes, atherosclerosis progression measured by carotid intima-media thickness, and major adverse cardiovascular events — as primary endpoints rather than the surrogate metabolic markers that dominate existing evidence; head-to-head comparative RCTs evaluating metformin versus GLP-1 receptor agonists, SGLT-2 inhibitors, and inositol compounds for metabolic endpoints in

PCOS, to inform evidence-based pharmacological selection; stratified trials enrolling PCOS phenotypic subgroups — particularly lean versus obese, and insulin-resistant versus insulin-sensitive PCOS — to determine whether metformin's metabolic benefits are uniformly distributed across phenotypic subtypes or concentrated in specific high-risk subgroups; and systematic long-term follow-up studies of PCOS cohorts to determine whether sustained metformin therapy translates the observed surrogate metabolic improvements into reduction of clinically relevant events including incident diabetes, cardiovascular disease, and endometrial cancer.

Conclusion

This systematic review and meta-analysis of randomized controlled trial evidence demonstrates that metformin produces statistically significant and clinically meaningful improvements in insulin resistance markers — particularly fasting insulin and HOMA-IR, reduced by approximately 20%–30% across meta-analytic estimates — and in lipid profile parameters, most consistently reducing triglycerides and producing modest improvements in HDL-cholesterol, in women with polycystic ovary syndrome. The insulin

resistance and triglyceride-lowering benefits of metformin are consistent across multiple independent meta-analyses, primary RCTs, and disease-specific subgroup analyses, and are mechanistically coherent with metformin's established pharmacological action through hepatic AMPK activation. Metformin consistently and significantly outperforms oral contraceptive pills in metabolic profile outcomes, with particular advantages for triglycerides and HDL-cholesterol, establishing a strong evidence-based preference for metformin in women with PCOS who also have dyslipidemia or elevated cardiovascular risk. These findings confirm metformin as an effective and appropriate pharmacological intervention for the metabolic manifestations of PCOS, complementary to its established — though more limited — reproductive applications, and support its continued use in the long-term metabolic risk management of this common and clinically important endocrine disorder. Future research should prioritize prospective trials with long-term cardiovascular endpoints, comparative effectiveness studies against newer metabolic agents, and phenotype-stratified analyses to maximize the precision and clinical applicability of evidence on metformin's metabolic role in PCOS.

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