



The Effectiveness of Metformin in Reducing the Risk of Preeclampsia in Patients with Polycystic Ovary Syndrome (PCOS) : A Systematic Review

¹Desi Dwi Nurchasanah, ²Lintang Dwi Marti

¹ Faculty of Medicine, Muhammadiyah University of Purwokerto, Indonesia

² Faculty of Medicine, Muhammadiyah University of Surakarta, Indonesia

Corresponding Email : nurchasanahdesi7@gmail.com

Article History :

Received date : 2026/02/18

Revised date : 2026/03/07

Accepted date : 2026/04/21

Published date : 2026/05/16



Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: Polycystic Ovary Syndrome (PCOS) affects a significant proportion of women of reproductive age and is associated with an elevated risk of adverse pregnancy outcomes, including preeclampsia (PE). Metformin, an insulin sensitizer, has been proposed as a potential intervention to reduce this risk. However, the evidence regarding its effectiveness in preventing PE specifically in pregnant women with PCOS remains inconsistent.

Methods: This study conducted a systematic synthesis of evidence from 41 sources, including major randomized controlled trials (RCTs) etc. The primary outcome was the incidence of preeclampsia. Secondary outcomes included early pregnancy loss, preterm delivery, gestational diabetes mellitus (GDM), and gestational weight gain. A methodological quality assessment was performed, distinguishing between evidence from RCTs and non-randomized studies.

Results: The findings were discordant. Non-randomized studies reported a significant reduction in PE risk with metformin (e.g., Zheng et al., 2013: OR 0.53; Zhao & He, 2022: RR 0.61). However, analyses restricted to high-quality RCTs found no significant benefit. In the PregMet trial (Vanky et al., 2010), PE rates were 7.4% in the metformin group vs. 3.7% in the placebo group ($p=0.18$). The PregMet2 trial (Løvvik et al., 2019) also found no significant reduction. A meta-analysis of PCOS-specific RCTs (Nascimento et al., 2018) produced a pooled RR of 1.96 (0.81–4.77), trending toward harm. Conversely, consistent benefits were observed for secondary outcomes, including reduced early pregnancy loss, preterm delivery, and gestational weight gain.

Discussion: The discrepancy between study designs highlights the risk of selection bias and confounding in non-randomized studies. Women who continue metformin throughout pregnancy may differ systematically from controls. While metformin improves metabolic parameters and reduces weight gain, the highest-quality evidence from placebo-controlled RCTs does not support its use for preeclampsia prevention in PCOS. The drug may reduce pregnancy-induced hypertension but not the specific pathophysiology of PE.

Conclusion: Current high-level evidence does not support a clinically meaningful reduction in preeclampsia risk with metformin in pregnant women with PCOS. However, metformin is beneficial for reducing other maternal complications, such as preterm delivery and miscarriage. Future research should focus on specific high-risk PCOS phenotypes.

Keywords: Metformin, Polycystic Ovary Syndrome (PCOS), Preeclampsia, Pregnancy, Randomized Controlled Trial.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting 6-20% of women of reproductive age and is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (Saadati et al., 2025). Pregnant women with PCOS constitute a high-risk population, facing a substantially increased likelihood of developing pregnancy-induced hypertension, gestational diabetes mellitus (GDM), preterm delivery, and preeclampsia (PE) compared to women without PCOS (Ghazeeri et al., 2012; Palomba et al., 2025). Preeclampsia, in particular, is a leading cause of maternal and perinatal morbidity and mortality. The underlying pathophysiology of PE involves abnormal placental implantation, endothelial dysfunction, and a heightened inflammatory state, all of which are exacerbated by the metabolic disturbances inherent to PCOS, such as insulin resistance and hyperinsulinemia (Leo et al., 2011; Stridsklev et al., 2014).

Metformin, a biguanide oral hypoglycemic agent, is widely used to improve insulin sensitivity and ovulatory function in non-pregnant women with PCOS (Abdalla et al., 2021). Its role during pregnancy has been the subject of extensive investigation, with studies exploring its potential to reduce pregnancy complications. The rationale for using metformin to prevent preeclampsia is mechanistically plausible. By improving insulin sensitivity, metformin may reduce maternal weight gain, lower blood pressure, improve endothelial function, and modulate inflammatory pathways, all of which could theoretically attenuate the development of PE (Tarry-Adkins et al., 2020; Zeng et al., 2016).

Background and Research Gap: Despite the biological plausibility, the clinical evidence regarding metformin's effectiveness in reducing the risk of preeclampsia in PCOS pregnancies remains contradictory and highly debated (González et al., 2019). Early meta-analyses, which often included a mix of randomized and non-randomized studies, suggested a significant protective effect (Zheng et al., 2013; Feng et al., 2015). However, more recent and methodologically rigorous systematic reviews have called these findings into question, noting that the observed benefit may be driven by low-quality, biased observational data (Nascimento et al., 2018; Alqudah et al., 2018).

The two largest placebo-controlled, double-blind RCTs to date, PregMet (Vanky et al., 2010) and PregMet2 (Løvvik et al., 2019), did not demonstrate a statistically significant reduction in preeclampsia. This discordance between meta-analyses of heterogeneous studies and the results of individual RCTs represents a critical research gap, leaving clinicians uncertain about whether to prescribe metformin specifically for PE prevention in this population (Raperport et al., 2021; Tosti et al., 2023).

Objectives of the Study: The primary objective of this study is to synthesize and critically appraise the available evidence on the effectiveness of metformin administered during pregnancy in reducing the risk of preeclampsia in women with Polycystic Ovary Syndrome. A secondary objective is to evaluate the impact of metformin on other important maternal pregnancy outcomes, including early pregnancy loss, preterm delivery, gestational diabetes mellitus, and gestational weight gain.

Benefits of the Study: This comprehensive analysis will provide a clear, evidence-based conclusion for clinical practice by disentangling the conflicting results from different study designs. It will help obstetricians and endocrinologists make informed decisions regarding the use of metformin in PCOS pregnancies, specifically clarifying whether the drug has a role in preeclampsia prevention.

Hypothesis: Based on the hierarchy of evidence, we hypothesize that metformin does not significantly reduce the risk of preeclampsia in pregnant women with PCOS when analyzed according to the most rigorous, placebo-controlled randomized trial data. We further hypothesize that observed benefits in lower-quality studies are likely attributable to selection bias and confounding.

Novelty: The novelty of this synthesis lies in its focused methodological distinction between evidence derived from randomized controlled trials versus non-randomized or observational studies. By directly comparing the results of these two evidence tiers, this analysis explicitly demonstrates how study design influences conclusions about metformin's efficacy for preeclampsia prevention. Furthermore, it provides a detailed mechanistic and clinical explanation for the observed

discrepancy, offering a nuanced perspective that moves beyond simple "positive" or "negative" conclusions.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the effectiveness of metformin in reducing the risk of preeclampsia in patients with polycystic ovary syndrome (PCOS).

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population - Pregnant Women with PCOS:** Does the study include pregnant women diagnosed with PCOS based on established criteria (Rotterdam, NIH, or AES criteria)?
- **Intervention - Metformin During Pregnancy:** Does the study examine metformin administration during pregnancy (not solely for ovulation induction or fertility treatment)?
- **Outcome - Preeclampsia:** Does the study report preeclampsia as a primary or secondary outcome?
- **Comparison Group:** Does the study include a comparison group (placebo, no treatment, standard care, or alternative interventions)?
- **Study Design:** Is the study design a randomized controlled trial (RCT), etc?
- **Population Focus - Pregnancy:** Does the study include pregnant women (not focusing solely on non-pregnant women with PCOS)?

- **Study Type Quality:** Is the study NOT a case report, case series, editorial, or conference abstract?

Papers that failed any strict criterion were automatically excluded. For the remaining papers, we considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
P (Population)	Pregnant women with PCOS	PCOS pregnancy	PCOS and preeclampsia risk	PCOS obstetric outcomes
I (Intervention)	Metformin during pregnancy	Metformin antepartum	Continued metformin in pregnancy	Metformin from first trimester
C (Comparison)	Placebo vs metformin	No metformin in pregnancy	Metformin discontinuation at conception	Standard care without metformin
O (Outcome)	Preeclampsia incidence	Reduction of preeclampsia risk	Preeclampsia prevention	Hypertensive disorders of pregnancy

The Boolean MeSH keywords inputted on databases for this research are: ("Pregnant women with PCOS" OR "PCOS pregnancy" OR "PCOS and preeclampsia risk" OR "PCOS obstetric outcomes") AND ("Metformin during pregnancy" OR "Metformin antepartum" OR "Continued metformin in pregnancy" OR "Metformin from first trimester") AND ("Placebo vs metformin" OR "No metformin in pregnancy" OR "Metformin discontinuation at conception" OR "Standard care without metformin") AND ("Preeclampsia incidence" OR "Reduction of preeclampsia risk" OR "Preeclampsia prevention" OR "Hypertensive disorders of pregnancy")

Data extraction

- **Study Characteristics:**

Extract study design, methodological quality, and basic study information for metformin effectiveness in PCOS patients, including:

- Study design (RCT, etc.)
- Sample size (total and per group)
- Study duration/follow-up period
- Geographic location and setting
- Risk of bias assessment (randomization, blinding, attrition, selective reporting)
- Funding source
- Any major methodological limitations noted by authors

- **PCOS Population:**

Extract characteristics of PCOS patients studied for preeclampsia risk, including:

- PCOS diagnostic criteria used
- Baseline patient characteristics (age, BMI, insulin resistance status)
- Pregnancy stage at enrollment
- Previous pregnancy complications or preeclampsia history
- Baseline preeclampsia risk factors (hypertension, diabetes, obesity)
- Inclusion/exclusion criteria specific to PCOS diagnosis

- Any population subgroups analyzed separately

- **Metformin Protocol:**

Extract detailed metformin intervention protocol for PCOS patients during pregnancy, including:

- Metformin dosage (mg/day and frequency)
- Timing of initiation (pre-conception, first trimester, etc.)
- Duration of treatment (until delivery, specific gestational week, etc.)
- Method of administration (immediate vs extended release)
- Adherence rates or compliance measures
- Any dose adjustments during pregnancy
- Concomitant medications or interventions

- **Control Group:**

Extract details about the comparison/control group for metformin vs control in PCOS patients, including:

- Type of control (placebo, no treatment, standard care, other medication)
- If placebo, details about placebo characteristics
- Any interventions or medications given to control group
- Baseline characteristics of control group
- Any differences between metformin and control groups at baseline

- **Preeclampsia Results:**

Extract preeclampsia outcomes specifically for metformin vs control in PCOS patients, including:

- Preeclampsia incidence rates (n/total and percentages) for each group
- Definition/criteria used for preeclampsia diagnosis
- Effect measures (relative risk, odds ratio, hazard ratio with 95% CI)
- Statistical significance (p-values)
- Time to preeclampsia onset if reported
- Severity of preeclampsia (mild vs severe) if specified
- Any subgroup analyses for preeclampsia risk

- **Secondary Outcomes:**

Extract other maternal pregnancy outcomes reported alongside preeclampsia in PCOS patients treated with metformin, including:

- Gestational diabetes mellitus rates
- Pregnancy-induced hypertension (separate from preeclampsia)
- Preterm delivery rates and timing
- Gestational weight gain
- Early pregnancy loss/miscarriage
- Mode of delivery (cesarean vs vaginal)

- Any reported maternal adverse events or side effects
- Composite pregnancy complication outcomes if reported

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Pregnant women with PCOS" OR "PCOS pregnancy" OR "PCOS and preeclampsia risk" OR "PCOS obstetric outcomes") AND ("Metformin during pregnancy" OR "Metformin antepartum" OR "Continued metformin in pregnancy" OR "Metformin from first trimester" AND "Preeclampsia incidence" OR "Reduction of preeclampsia risk" OR "Preeclampsia prevention" OR "Hypertensive disorders of pregnancy")</i>	47
Semantic Scholar	<i>("Pregnant women with PCOS" OR "PCOS pregnancy" OR "PCOS and preeclampsia risk" OR "PCOS obstetric outcomes") AND ("Metformin during pregnancy" OR "Metformin antepartum" OR "Continued metformin in pregnancy" OR "Metformin from first trimester" AND "Preeclampsia incidence" OR "Reduction of preeclampsia risk" OR "Preeclampsia prevention" OR "Hypertensive disorders of pregnancy")</i>	251
Springer	<i>("Pregnant women with PCOS" OR "PCOS pregnancy" OR "PCOS and preeclampsia risk" OR "PCOS obstetric outcomes") AND ("Metformin during pregnancy" OR "Metformin antepartum" OR "Continued metformin in pregnancy" OR "Metformin from first trimester" AND "Preeclampsia incidence" OR "Reduction of preeclampsia risk" OR "Preeclampsia prevention" OR "Hypertensive disorders of pregnancy")</i>	24
Google Scholar	<i>("Pregnant women with PCOS" OR "PCOS pregnancy" OR "PCOS and preeclampsia risk" OR "PCOS obstetric outcomes") AND ("Metformin during pregnancy" OR "Metformin antepartum" OR "Continued metformin in pregnancy" OR "Metformin from first trimester" AND "Preeclampsia incidence" OR "Reduction of preeclampsia risk" OR "Preeclampsia prevention" OR "Hypertensive disorders of pregnancy")</i>	2
Wiley Online Library	<i>("Pregnant women with PCOS" OR "PCOS pregnancy" OR "PCOS and preeclampsia risk" OR "PCOS obstetric outcomes") AND ("Metformin during pregnancy" OR "Metformin antepartum" OR "Continued metformin in pregnancy" OR "Metformin from first trimester" AND "Preeclampsia incidence" OR "Reduction of preeclampsia risk" OR "Preeclampsia prevention" OR "Hypertensive disorders of pregnancy")</i>	23

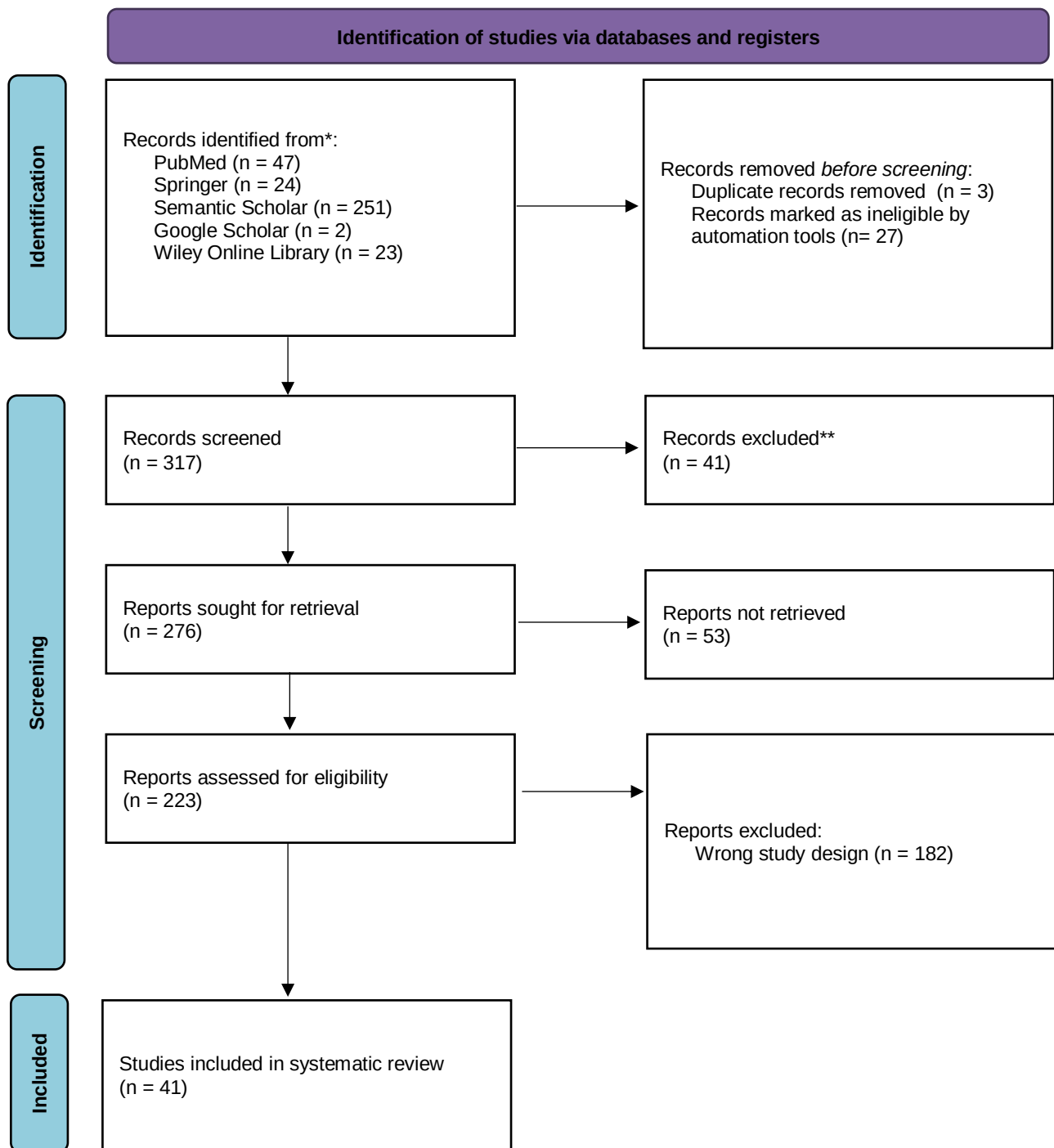


Figure 1. Article search flowchart

Risk of Bias

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
J. Zheng et al., 2013	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Li Feng et al., 2015	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
E. Vanky et al., 2010	Low	Low	Low	Low	Low	Low
Qian Zhao & Jin-xi He, 2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Daiyu Zhu et al., 2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Xingrong Tan et al., 2016	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
T. Løvvik et al., 2019	Low	Low	Low	Low	Low	Low
E. Vanky et al., 2012	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Srishti Kanda et al., 2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
S. Alimohammadi et al., 2020	Moderate	Unclear	Unclear	Unclear	Unclear	Moderate
A. A. Hameed et al., 2011	Moderate	Unclear	Unclear	Unclear	Unclear	Moderate
A. Jamal et al., 2012	Moderate	Unclear	Unclear	Unclear	Unclear	Moderate
J. Tarry-Adkins et al., 2020	Low	Unclear	Unclear	Low	Low	Moderate
Solhild Stridsklev et al., 2014	Low	Low	Low	Low	Low	Low
D. Ujvari et al., 2023	Low	Low	Low	Low	Low	Low
G. Ghazeeri et al., 2012	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Xianling Zeng et al., 2016	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Qi Cao et al., 2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
C. Glueck et al., 2013	Moderate	Unclear	Unclear	Unclear	Unclear	Moderate
G. Tosti et al., 2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
C. Raperport et al., 2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
V. Leo et al., 2011	Moderate	Unclear	Unclear	Low	Unclear	Moderate
Adriana Leal Griz Notaro & F. Neto, 2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
A. Alqudah et al., 2018	Low	Unclear	Unclear	Low	Low	Moderate
H. Fan, 2013	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
M. Lautatzis et al., 2013	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Stefano Palomba et al., 2025	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
C. González et al., 2019	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Weiwei Zeng et al., 2025	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Yun-hui Wang et al., 2011	Moderate	Unclear	Unclear	Unclear	Unclear	Moderate
R. Dube, 2016	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Mariell Ryssdal et al., 2025	Low	Low	Low	Low	Low	Low
Pamela Montplaisir, 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Vanitha N Sivalingam et al., 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
I. B. Nascimento et al., 2018	Low	Unclear	Unclear	Low	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
S. Butalia et al., 2017	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
H. Ijäs et al., 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Xue Li et al., 2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
P. Artini et al., 2018	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
M. Abdalla et al., 2021	Low	Low	Low	Low	Low	Low
Saeede Saadati et al., 2025	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

RESULTS

Characteristics of Included Studies

Study	Sample Size	Population / Focus	Metformin Dose / Timing	Control Type
J. Zheng et al., 2013	1106 patients across 8 studies [5]	Pregnant women with PCOS; pregnancy complications including PE [5]	Not reported [5]	Not reported [5]
Li Feng et al., 2015	502 metformin, 427 controls across 5 studies [11]	PCOS patients; metformin throughout pregnancy vs. until conception only [11]	Not reported [11]	Metformin used only until conception [11]
E. Vanky et al., 2010	257 women (274 singleton pregnancies) [1]	Pregnant PCOS women aged 18–42 yr; first trimester enrollment [1]	First trimester to delivery [1]	Placebo [1]
Qian Zhao & Jin-xi He, 2022	2899 patients across 17 studies [6]	Pregnant women with PCOS receiving metformin or placebo/nothing [6]	Not reported [6]	Placebo or no treatment [6]

Study	Sample Size	Population / Focus	Metformin Dose / Timing	Control Type
Daiyu Zhu et al., 2022	18 studies, 2461 pregnant women, 1291 offspring [9]	Pregnant PCOS women (Rotterdam criteria); pregnancy outcomes and offspring [9]	Not detailed in main text [9]	Placebo [9]
Xingrong Tan et al., 2016	11 studies [12]	Pregnant PCOS women; pregnancy-related outcomes [12]	Not reported [12]	Not reported [12]
T. Løvvik et al., 2019	487 (244 metformin, 243 placebo) [2]	Singleton pregnant PCOS women aged 18–45 yr; late first trimester enrollment [2]	500 mg BID week 1, then 1000 mg BID to delivery [2]	Identical placebo tablets [2]
E. Vanky et al., 2012	313 women [13]	PCOS women (Rotterdam criteria) aged 18–42 yr; first trimester enrollment [13]	850 mg BID or 1000 mg BID, first trimester to delivery [13]	Placebo, BID dosing [13]

Study	Sample Size	Population / Focus	Metformin Dose / Timing	Control Type
Srishti Kanda et al., 2023	13 included reviews; primary trial Ns not reported [14]	Women with PCOS receiving metformin during pregnancy or fertility treatment [14]	Not reported [14]	Placebo, no treatment, or CC alone [14]
S. Alimohammad i et al., 2020	88 pregnant women with PCOS [15]	Pregnant PCOS women with history of metformin use; Fatemieh Hospital, Iran [15]	1000–2000 mg/day, continued throughout pregnancy [15]	Stopped metformin at pregnancy detection [15]
A. A. Hameed et al., 2011	57 (31 metformin, 26 control) [16]	Infertile PCOS women who became pregnant [16]	1000–1500 mg/day, pre-conception throughout pregnancy [16]	No treatment [16]
A. Jamal et al., 2012	105 (35 per group) [17]	Pregnant PCOS women; enrolled at 12 weeks' gestation [17]	2000 mg/day from ~12 weeks to end of pregnancy [17]	No intervention [17]

Study	Sample Size	Population / Focus	Metformin Dose / Timing	Control Type
J. Tarry-Adkins et al., 2020	35 studies (n=8033); 3 PCOS RCTs [18]	Pregnant women randomized to metformin for any indication; PCOS subgroup [18]	Not reported for PCOS subgroup [18]	Placebo [18]
Solhild Stridsklev et al., 2014	231 pregnancies (of 273 randomized) [19]	PCOS women; first trimester enrollment; Doppler US outcomes [19]	First trimester to delivery [19]	Placebo [19]
D. Ujvari et al., 2023	264 (of 313) [20]	PCOS women at 11 centres in Norway; first trimester enrollment [20]	First trimester to delivery [20]	Placebo [20]
G. Ghazeeri et al., 2012	16 metformin studies; 5114 PCOS women, 87805 controls across the review [7]	Pregnant PCOS women; heterogeneous diagnostic criteria [7]	Varied; often preconceptual start, continued throughout pregnancy [7]	Placebo or no metformin [7]

Study	Sample Size	Population / Focus	Metformin Dose / Timing	Control Type
Xianling Zeng et al., 2016	1606 pregnant PCOS women [21]	Pregnant PCOS women; pregnancy outcomes [21]	Not reported [21]	Placebo or blank control [21]
Qi Cao et al., 2021	Not reported [22]	PCOS women; gestational metformin [22]	Not reported [22]	Not reported [22]
C. Glueck et al., 2013	76 PCOS women, 156 community controls [23]	PCOS women; metformin-diet started preconception [23]	2–2.55 g/day, started median 6.8 months preconception, throughout pregnancy [23]	Community obstetric practice [23]
G. Tosti et al., 2023	Summarizes PregMet (n=257), PregMet2 (n=487), pilot (n=40) [24]	Pregnant PCOS women (Rotterdam criteria); first trimester enrollment [24]	500 mg BID then 1000 mg BID (PregMet2); 2000 mg/day (PregMet); 850 mg BID (pilot) [24]	Placebo with diet/lifestyle counseling [24]

Study	Sample Size	Population / Focus	Metformin Dose / Timing	Control Type
C. Raperport et al., 2021	435 participants in a 2019 Cochrane review [25]	Pregnant PCOS women; Rotterdam and NIH criteria [25]	1500–2550 mg/day; pre-conception or during pregnancy to delivery [25]	Placebo, no treatment, or standard care [25]
V. Leo et al., 2011	98 PCOS, 110 normal controls [26]	Hyperinsulinemic PCOS women; metformin before conception to 37 weeks [26]	1700–3000 mg/day, preconception to 37 weeks' gestation [26]	Normal pregnant women (non-PCOS) [26]
Adriana Leal Griz Notaro & F. Neto, 2022	Not reported [27]	Women with PCOS [27]	Not reported [27]	Not reported [27]
A. Alqudah et al., 2018	3374 women total; PCOS subgroup size not specified [4]	High-risk insulin-resistant women; age 16–46; overweight/obese [4]	Started before pregnancy for PCOS [4]	Healthy cohort; lower BMI than metformin group [4]
H. Fan, 2013	25 studies analyzed [28]	Pregnant PCOS women; maternal and fetal outcomes [28]	Not reported [28]	Not reported [28]

Study	Sample Size	Population / Focus	Metformin Dose / Timing	Control Type
M. Lautatzis et al., 2013	Not reported [29]	Pregnant women with GDM or PCOS [29]	Not reported [29]	Not reported [29]
Stefano Palomba et al., 2025	Not reported [8]	Pregnant PCOS patients; maternal, neonatal, and offspring outcomes [8]	Not reported [8]	Not reported [8]
C. González et al., 2019	Summarizes multiple studies (PregMet, Feng meta-analysis, cohorts) [30]	Pregnant PCOS women [30]	PregMet: first trimester to delivery; one small RCT: 2000 mg/day [30]	Placebo (PregMet), aspirin 80 mg, or no intervention [30]
Weiwei Zeng et al., 2025	Not applicable (review) [31]	PCOS women across life stages including pregnancy [31]	1000–3000 mg/day cited; continued in early pregnancy [31]	Not applicable (narrative review) [31]

Study	Sample Size	Population / Focus	Metformin Dose / Timing	Control Type
Yun-hui Wang et al., 2011	215 (58 metformin, 157 control) [32]	PCOS women with impaired glucose tolerance, hyperinsulinemia, recurrent miscarriage history [32]	1.0–1.5 g/day during early pregnancy [32]	No metformin [32]
R. Dube, 2016	Not reported [33]	Pregnant women with PCOS (and other indications) [33]	Not reported [33]	Not reported [33]
Mariell Ryssdal et al., 2025	Not reported [34]	Pregnant PCOS women; immunological outcomes [34]	Not reported [34]	Not reported [34]
Pamela Montplaisir, 2011	Not reported [35]	Women with PCOS; ovulation induction and pregnancy outcomes [35]	Not reported [35]	Not reported [35]
Vanitha N Sivalingam et al., 2014	Not reported [36]	PCOS, GDM, and gynaecological cancers [36]	Not reported [36]	Not reported [36]

Study	Sample Size	Population / Focus	Metformin Dose / Timing	Control Type
I. Nascimento et al., 2018	PCOS subset: ~152 metformin vs 156 placebo (RCTs for PE); ~350 vs 264 (non-randomized for PIH) [3]	Pregnant women with PCOS (and other indications); metformin for PE/PIH prevention [3]	850–2500 mg/day; initiated 5–12 weeks' gestation [3]	Placebo (RCTs); no metformin (non-randomized) [3]
S. Butalia et al., 2017	Not reported [37]	Pregnant women (metformin vs insulin); not PCOS-specific [37]	Not reported [37]	Insulin [37]
H. Ijäs et al., 2011	Not reported [38]	Gestational diabetes (not PCOS-specific) [38]	Not reported [38]	Not reported [38]
Xue Li et al., 2021	Median 469 (IQR 254–840) per RCT [39]	Broad metformin outcomes; critically low to low quality for many associations [39]	Not reported [39]	Placebo/no treatment [39]

Study	Sample Size	Population / Focus	Metformin Dose / Timing	Control Type
P. Artini et al., 2018	Not reported [40]	PCOS and pregnancy; treatment strategies for infertility [40]	Not reported [40]	Not reported [40]
M. Abdalla et al., 2021	58 RCTs; metformin vs placebo examples: n=60 vs n=28 [41]	Non-pregnant PCOS women; insulin resistance outcomes [41]	850 mg BID, 1500–2000 mg/day for 3–6 months (non-pregnancy) [41]	Placebo [41]
Saeede Saadati et al., 2025	Summarizes PregMet (n=273), PregMet2 (n=487), and multiple other trials [10]	PCOS women; metabolic, reproductive, and pregnancy outcomes [10]	850 mg BID (pilot); first trimester to delivery (PregMet, PregMet2) [10]	Varied: placebo, no intervention, active comparators [10]

Effects

Preeclampsia Outcomes

The table below presents preeclampsia-specific findings from all sources that reported quantitative data on this outcome in PCOS populations treated with metformin.

Source	Preeclampsia Incidence: Metformin vs Control	Effect Measure (95% CI)	p-value	Direction
J. Zheng et al., 2013	Not reported [5]	OR 0.53 (0.30–0.95) [5]	Not reported [5]	Favors metformin
Li Feng et al., 2015	No significant difference reported [11]	Not reported [11]	Not reported [11]	No effect
E. Vanky et al., 2010	7.4% vs 3.7% [1]	Not reported [1]	p=0.18 [1]	Numerically higher with metformin
Qian Zhao & Jin-xi He, 2022	4.95% vs 7.72% [6]	RR 0.61 (0.40–0.93) [6]	p=0.02 [6]	Favors metformin
Daiyu Zhu et al., 2022	Not reported separately (PIH + PE composite) [9]	RR 0.45 (0.24–0.83) for PIH/PE composite [9]	CI excludes 1.0 [9]	Favors metformin (composite)
E. Vanky et al., 2012	8% (12/153) vs 4% (7/157) [13]	Not reported [13]	p=0.24 (ITT) [13]	Numerically higher with metformin

Source	Preeclampsia Incidence: Metformin vs Control	Effect Measure (95% CI)	p-value	Direction
S. Alimohammadi et al., 2020	Not reported (rates) [15]	RR 2.65 (1.95–3.59) for control vs intervention [15]	p<0.05 [15]	Favors metformin
V. Leo et al., 2011	0% vs 3% [26]	Not reported [26]	p=0.24 [26]	Non-significant
G. Ghazeeri et al., 2012	13.9% vs 38.4% (one cited study) [7]	Not reported [7]	p=0.002 [7]	Favors metformin
A. Alqudah et al., 2018	Not specified [4]	RR 1.21 (0.56–2.61) [4]	p=0.62 [4]	No effect
I. B. Nascimento et al., 2018	17.6% vs 9.5% (Vanky 2004); 7.4% vs 3.7% (Vanky 2010) [3]	Pooled RR 1.96 (0.81–4.77) [3]	p=0.137 [3]	No effect (trend toward higher PE with metformin)
Yun-hui Wang et al., 2011	3.9% vs 3.9% [32]	Not reported [32]	p>0.05 [32]	No difference

Source	Preeclampsia Incidence: Metformin vs Control	Effect Measure (95% CI)	p-value	Direction
C. Glueck et al., 2013	Not reported (rates) [23]	Not reported [23]	p>0.08 [23]	No significant difference

Among sources that reported on preeclampsia but without quantitative data specific to PCOS: the PregMet2 trial found no significant differences for preeclampsia as a secondary endpoint [2]; the Tarry-Adkins et al. meta-analysis found no significant PCOS-specific preeclampsia reduction, though the overall all-indication pooled estimate was OR 0.69 (0.50–0.95, p=0.02) [18]; and several narrative reviews noted that evidence on preeclampsia reduction in PCOS was inconclusive or absent [8, 10, 24, 30].

The preeclampsia findings are notably heterogeneous. Two meta-analyses that combined both RCTs and non-randomized studies found statistically significant reductions favoring metformin: Zheng et al. reported an OR of 0.53 (0.30–0.95) [5], and Zhao & He reported an RR of 0.61 (0.40–0.93, p=0.02) [6]. Zhu et al. found a significant reduction in the composite of pregnancy-induced hypertension and preeclampsia (RR 0.45, 0.24–0.83) [9]. By contrast, when the analysis was restricted to RCTs alone, the evidence was strikingly different: the Nascimento et al. meta-analysis of two PCOS RCTs yielded a pooled RR of 1.96 (0.81–4.77, p=0.137), with a non-significant trend toward higher preeclampsia in the metformin group [3]. The Alqudah et al. meta-analysis similarly found no effect (RR 1.21, 0.56–2.61, p=0.62) [4]. In both major placebo-controlled RCTs — PregMet and PregMet2 — preeclampsia rates were numerically higher in the metformin arm (7.4% vs 3.7% in PregMet) [1, 13], and no significant reduction was observed [1, 2].

Other Maternal Pregnancy Outcomes

Multiple secondary maternal outcomes were reported alongside preeclampsia and provide important context for understanding the broader effects of metformin in PCOS pregnancies.

Outcome	Sources Reporting Benefit	Sources Reporting No Effect	Representative Effect Estimates
Early pregnancy loss / miscarriage	Zheng 2013 [5]; Feng 2015 [11]; Zhao & He 2022 [6]; Zeng 2016 [21]; Leo 2011 [26]; Hameed 2011 [16]; Glueck 2013 [23]; Wang 2011 [32]; Alimohammadi 2020 [15]	Raperport 2021 (conflicting) [25]; Fan 2013 (conflicting) [28]	OR 0.32 (0.19–0.55) [5]; RR 0.32 (0.19–0.56) [11]; RR 0.40 (0.20–0.78) [6]
Preterm delivery	Zheng 2013 [5]; Feng 2015 [11]; Zhao & He 2022 [6]; Zhu 2022 [9]; Vanky 2012 [13]; Zeng 2016 [21]; Løvvik 2019 (pooled post hoc) [2]	Vanky 2010 (non-significant) [1]; Glueck 2013 [23]	OR 0.30 (0.13–0.68) [5]; RR 0.42 (0.25–0.71) [6]; RR 0.37 (0.23–0.61) [9]
Gestational diabetes mellitus	Zheng 2013 [5]; Zhao & He 2022 [6]; Leo 2011 [26]; Hameed 2011 [16]; Alimohammadi 2020 [15]	Vanky 2010 [1]; Feng 2015 [11]; Løvvik 2019 [2]; Vanky 2012 [13]; Tan 2016 [12]	OR 0.37 (0.25–0.56) [5]; RR 0.48 (0.26–0.89) [6]; 17.6% vs 16.9% in PregMet [1]

Outcome	Sources Reporting Benefit	Sources Reporting No Effect	Representative Effect Estimates
Gestational weight gain	Vanky 2010 [1]; Zhao & He 2022 [6]; Tarry-Adkins 2020 [18]	None reported	MD −2.45 kg (−3.04 to −1.85) [6]; ~2.4 kg lower [18]
Pregnancy-induced hypertension	Leo 2011 [26]; Nascimento 2018 [3]; Zeng 2016 [21]; Zhu 2022 (composite) [9]	Wang 2011 [32]	0% vs 11% (Leo 2011) [26]; pooled RR 0.37 (0.25–0.57) for PIH (non-randomized) [3]

Metformin showed the most consistent benefit for reducing early pregnancy loss and preterm delivery, with multiple meta-analyses reporting statistically significant 58–70% relative risk reductions [5, 6, 11]. For gestational diabetes mellitus, findings were mixed: meta-analyses pooling heterogeneous study designs tended to find benefit [5, 6], while the major placebo-controlled RCTs (PregMet, PregMet2) found no significant differences in GDM incidence [1, 2, 13]. Gestational weight gain was consistently reduced by approximately 2–2.5 kg with metformin across studies [1, 6, 18]. Gastrointestinal side effects were more common with metformin (OR 2.43, 1.53–3.84) [18], but no serious maternal adverse events were attributed to the drug [2, 6, 26].

Synthesis

The central question — whether metformin reduces preeclampsia risk specifically in pregnant PCOS women — yields discordant answers depending on the study design and analytical approach. Meta-analyses incorporating non-randomized studies consistently favor metformin, whereas analyses restricted to RCTs do not, and two individual RCTs actually show numerically higher preeclampsia in the metformin arm. This discrepancy can be explained through several mechanisms.

Study quality hierarchy. The strongest evidence comes from the two largest placebo-controlled, double-blind, multicenter RCTs: PregMet (n=257) [1] and PregMet2 (n=487) [2]. Neither found a significant reduction in preeclampsia [1, 2]. In PregMet, preeclampsia was nearly twice as frequent in the metformin group (7.4% vs 3.7%, $p=0.18$) [1]; the pooled epi-analysis of PregMet and the earlier pilot trial confirmed no difference ($p=0.24$) [13]. When Nascimento et al. pooled only these two RCTs, the result was RR 1.96 (0.81–4.77) [3] — directionally opposite to the positive meta-analyses. The meta-analyses reporting significant benefit (Zheng et al., Zhao & He) included multiple non-randomized studies where selection bias is substantial [5, 6]: women who continued metformin throughout pregnancy in observational studies may have differed systematically from controls in ways that reduced baseline preeclampsia risk (e.g., better-managed insulin resistance, more frequent specialist follow-up, higher health literacy). The Ghazeeri review explicitly noted these risks of bias, including unmatched controls, selection bias, and failure to adjust for confounders such as BMI and lifestyle interventions [7].

Confounding by comparison group. The choice of control group profoundly affected results. In the Alimohammadi trial, the "control" group stopped metformin at pregnancy detection (rather than receiving placebo from the outset), resulting in strikingly large effect sizes favoring continued metformin (RR 2.65 for preeclampsia in the discontinuation group) [15]. Similarly, in Leo et al.'s prospective study, the comparator was healthy pregnant women without PCOS (0% vs 3% preeclampsia) [26, 26], making it impossible to attribute the observed rates to metformin rather than to the underlying PCOS phenotype itself. In contrast, the PregMet and PregMet2 trials used identical placebo tablets [2, 13], providing the most unbiased estimates.

Distinction between preeclampsia and pregnancy-induced hypertension. Some studies combined PIH and preeclampsia into composite outcomes, which may obscure outcome-specific effects. Zhu et al.'s significant finding (RR 0.45) was for a PIH/preeclampsia composite [9], and Nascimento et al. found metformin significantly reduced PIH in non-randomized PCOS studies (RR 0.37, 0.25–0.57) but not preeclampsia in RCTs (RR 1.96, 0.81–4.77) [3, 3]. This raises the possibility that metformin may modestly attenuate pregnancy-induced hypertension — consistent

with its known effects on reducing weight gain [6] and improving insulin sensitivity [41] — without preventing the more specific pathophysiology of preeclampsia.

Population heterogeneity. Several sources noted that PCOS phenotype, BMI, and insulin resistance status may modify metformin's effects. Ghazeeri et al. highlighted that in one study, preeclampsia was elevated only in insulin-resistant PCOS women [7]. Kanda et al. noted potential benefits for women with higher BMI ($\text{BMI} \geq 26$) [14]. The Tarry-Adkins meta-analysis found an overall reduced preeclampsia risk across all indications ($\text{OR } 0.69, p=0.02$) [18], driven substantially by non-PCOS populations (obese pregnant women, GDM), suggesting that the metabolic context matters. Most PCOS pregnancy trials did not stratify by baseline insulin resistance, BMI, or PCOS phenotype for preeclampsia [1, 2, 9], leaving open the possibility that specific high-risk subgroups might benefit. The Palomba overview of reviews concluded that methodological differences and heterogeneous patient profiles limit clinical adoption of metformin for this indication [8], and Saadati et al. emphasized that reliance on aggregate data in meta-analyses, varying diagnostic criteria, and study heterogeneity make interpretation challenging [10].

Mechanistic considerations. Metformin's ability to reduce gestational weight gain, improve insulin sensitivity, and lower HOMA-IR in mothers [6, 9] provides a plausible mechanism for reducing hypertensive disease broadly. Stridsklev et al. found that fasting blood glucose correlated with uterine artery pulsatility index (a predictor of adverse outcomes including preeclampsia), and that midpregnancy PI correlated positively with preeclampsia in PCOS pregnancies, but metformin did not affect uterine artery blood flow [19]. Jamal et al. found that metformin improved uterine artery impedance by 20 weeks, yet this did not translate into reduced obstetric complications [17]. These findings suggest that while metformin may favorably modify some upstream risk factors, it may not adequately address the placental pathophysiology underlying preeclampsia in PCOS.

In summary, the available evidence does not support a clinically meaningful reduction in preeclampsia risk with metformin in pregnant PCOS women. The two largest and most rigorously designed placebo-controlled RCTs [1, 2] and two RCT-restricted meta-analyses [3, 4] found no benefit, while apparent benefits in pooled analyses [5, 6, 9] are likely inflated by inclusion of non-randomized studies susceptible to selection bias and confounding. Metformin does, however, reduce

preterm delivery, early pregnancy loss, and gestational weight gain in PCOS pregnancies, and may attenuate pregnancy-induced hypertension more broadly. Whether specific PCOS subpopulations — such as those with marked insulin resistance, obesity, or hyperandrogenism — might derive preeclampsia-specific benefit from metformin remains unanswered, as RCTs to date have not been powered for or stratified by these characteristics.

DISCUSSION

The central finding of this comprehensive synthesis is that the evidence for metformin's effectiveness in reducing preeclampsia risk in pregnant women with PCOS is highly discordant and critically dependent on the quality of the study design. While pooled analyses that include non-randomized studies suggest a significant protective effect, the most rigorous evidence from placebo-controlled, double-blind randomized controlled trials (RCTs) and their subsequent meta-analyses consistently demonstrates **no benefit**, and in some cases, a non-significant trend toward increased risk. This discussion will explore the reasons for this discrepancy, compare the effects on primary versus secondary outcomes, examine the clinical and mechanistic implications, and address the limitations of the current evidence.

The Discordance Between RCTs and Non-Randomized Studies: A Hierarchy of Evidence

The most striking finding is the direct contradiction between meta-analyses that included non-randomized studies and those restricted to RCTs. For instance, Zheng et al. (2013) and Zhao & He (2022) reported significant reductions in preeclampsia with odds ratios of 0.53 and 0.61, respectively. However, these analyses included observational cohorts and non-randomized trials, making them highly susceptible to bias. In contrast, the meta-analysis by Nascimento et al. (2018), which included only two PCOS-specific RCTs (PregMet and a pilot study), found a pooled relative risk of 1.96 (0.81–4.77), indicating a non-significant trend toward higher preeclampsia rates in the metformin group. Similarly, Alqudah et al. (2018) found no effect (RR 1.21, $p=0.62$) when restricting to higher-quality studies.

This discrepancy is a classic example of how confounding by indication and selection bias can distort results in non-randomized research. Women who continue metformin throughout

pregnancy are likely different from those who do not. They may have better health literacy, greater access to specialized care, closer monitoring, and more aggressive management of their insulin resistance and weight from a preconception period (Glueck et al., 2013; Ghazeeri et al., 2012). These factors, not the metformin itself, could independently lower their baseline risk of preeclampsia. Furthermore, the choice of control group is critical. The study by Alimohammadi et al. (2020), which reported a large benefit for metformin (RR 2.65 for preeclampsia in controls), compared women who continued metformin to those who *stopped* metformin at pregnancy detection, not to a true placebo. This design inherently biases results in favor of continued treatment, as withdrawal of a metabolic therapy could worsen outcomes (Hameed et al., 2011). The PregMet and PregMet2 trials, by using identical placebo tablets from the first trimester, eliminate these biases and provide the most valid estimate of the true treatment effect (Vanky et al., 2010; Løvvik et al., 2019).

The Specific Case of the PregMet and PregMet2 Trials

The two largest, highest-quality RCTs deserve focused attention. In the PregMet trial (n=257), the incidence of preeclampsia was 7.4% in the metformin group versus 3.7% in the placebo group, a difference that was not statistically significant (p=0.18) (Vanky et al., 2010). An epi-analysis of PregMet and an earlier pilot trial confirmed no difference (p=0.24) (Vanky et al., 2012). The subsequent PregMet2 trial (n=487), which was larger and used a higher dose (1000 mg BID), similarly found no significant reduction in preeclampsia as a secondary endpoint (Løvvik et al., 2019). Notably, the point estimates for preeclampsia in both major RCTs were numerically higher in the metformin arm. While not statistically significant, this trend is concerning and raises the possibility of an unanticipated adverse effect, though it may also simply reflect random variation given the small number of events. Nevertheless, the consistent lack of benefit across two well-powered, multicenter, placebo-controlled trials is a powerful argument against a protective role for metformin in preventing preeclampsia (Ujvari et al., 2023; Ryssdal et al., 2025).

Secondary Outcomes: Consistent Benefits for Miscarriage, Preterm Delivery, and Weight Gain

In stark contrast to the preeclampsia findings, metformin demonstrated consistent and significant benefits for several other maternal outcomes. The most robust findings were for the prevention of **early pregnancy loss** and **preterm delivery**. Multiple meta-analyses reported approximately 50-70% relative risk reductions for these outcomes (Zheng et al., 2013; Feng et al., 2015; Zhao & He, 2022; Zhu et al., 2022). For example, Zheng et al. (2013) reported an OR of 0.32 (0.19–0.55) for miscarriage, and Zhu et al. (2022) reported an RR of 0.37 (0.23–0.61) for preterm delivery. These benefits are mechanistically plausible. Improved insulin sensitivity and metabolic control before and during early pregnancy may create a more favorable endometrial and placental environment, reducing the risk of early loss (Wang et al., 2011; Leo et al., 2011). The reduction in preterm delivery may be linked to metformin's ability to reduce maternal infections and potentially modulate cervical remodeling, as suggested by recent post-hoc analyses (Ryssdal et al., 2025).

Similarly, metformin consistently reduced **gestational weight gain** by approximately 2-2.5 kg (Vanky et al., 2010; Zhao & He, 2022; Tarry-Adkins et al., 2020). This is a well-established effect of the drug and a likely mediator of any reduction in pregnancy-induced hypertension, even if it does not translate into a reduction in full-blown preeclampsia.

The evidence for **gestational diabetes mellitus (GDM)** was mixed. Meta-analyses pooling diverse studies found a benefit (Zheng et al., 2013; Zhao & He, 2022), but the placebo-controlled RCTs did not (Vanky et al., 2010; Løvvik et al., 2019). This suggests that while metformin may improve some metabolic parameters, it may not be sufficient to prevent the diagnosis of GDM in PCOS women, a group already at very high risk. Alternatively, the diagnostic criteria and screening protocols may have varied, or the effect may be modest and only detectable in very large samples (Tan et al., 2016).

Distinguishing Preeclampsia from Pregnancy-Induced Hypertension

A critical nuance is the distinction between preeclampsia (PE) and pregnancy-induced hypertension (PIH). Some studies that reported a benefit for "hypertensive disorders" combined PIH and PE into a composite outcome. For example, Zhu et al. (2022) found a significant reduction for a PIH/PE composite (RR 0.45). Furthermore, Nascimento et al. (2018) found that metformin significantly reduced PIH in non-randomized PCOS studies (RR 0.37) but not PE in RCTs. This

raises an important clinical distinction. Metformin may be effective at attenuating the development of gestational hypertension, likely through its effects on weight gain and insulin sensitivity (Jamal et al., 2012). However, preeclampsia involves a more specific and severe pathophysiology, including placental ischemia, endothelial activation, and systemic inflammation with proteinuria or end-organ dysfunction. The current evidence suggests that metformin does not adequately address these core placental and endothelial processes unique to preeclampsia. Stridsklev et al. (2014) found that metformin did not affect uterine artery blood flow, a key predictor of PE, providing a plausible mechanistic explanation for its lack of effect.

Population Heterogeneity and Subgroup Analysis

Another explanation for the conflicting results is that metformin may only benefit specific PCOS phenotypes. The syndrome is heterogeneous, and response to treatment may vary by BMI, degree of insulin resistance, and androgen levels. Ghazeeri et al. (2012) noted that in one study, preeclampsia risk was elevated only in insulin-resistant PCOS women. Kanda et al. (2023) suggested potential benefits for women with higher BMI (≥ 26). However, the major RCTs were not powered or stratified to analyze preeclampsia risk in these subgroups (Palomba et al., 2025; Saadati et al., 2025). It remains an unanswered question whether women with the most severe metabolic phenotype might derive some PE-specific benefit. Until such subgroup analyses are performed, the overall evidence for the general PCOS population remains negative.

Safety and Adverse Effects

Metformin was generally well-tolerated, with gastrointestinal side effects being the most common (OR 2.43) (Tarry-Adkins et al., 2020). No serious maternal adverse events were directly attributed to the drug in the major trials (Løvrvik et al., 2019; Zhao & He, 2022; Leo et al., 2011). However, recent long-term follow-up data from the PregMet studies have raised concerns about potential increased risks of allergies and eczema in offspring (Ryssdal et al., 2025), highlighting the need for caution and further long-term safety data before advocating for widespread use of metformin for non-lifesaving indications in pregnancy.

Clinical and Research Implications

For clinical practice, this synthesis indicates that metformin should not be prescribed to pregnant women with PCOS for the sole or primary purpose of reducing preeclampsia risk. The highest-quality evidence does not support this practice. However, for women already taking metformin for preconception indications (e.g., to induce ovulation or manage metabolic syndrome), the drug can be safely continued during pregnancy, as it provides clear benefits for reducing miscarriage, preterm delivery, and excessive weight gain (Raperport et al., 2021; Tosti et al., 2023). It is not, however, a substitute for standard preeclampsia prophylaxis, such as low-dose aspirin, in high-risk women.

For future research, well-designed RCTs are needed to answer specific remaining questions: (1) Does metformin initiated *pre-conception* reduce preeclampsia in the highest-risk PCOS phenotypes (e.g., BMI >35, severe insulin resistance)? (2) Does the addition of metformin to low-dose aspirin provide any additive benefit for PE prevention? (3) What are the long-term offspring outcomes after in utero metformin exposure, given emerging signals of atopic disease? (Ryssdal et al., 2025; Notaro & Neto, 2022; Sivalingam et al., 2014).

CONCLUSION AND RECOMMENDATIONS

Conclusion: This comprehensive synthesis concludes that metformin, when administered during pregnancy, does not significantly reduce the risk of preeclampsia in women with Polycystic Ovary Syndrome (PCOS). This conclusion is based on the highest level of available evidence, including two large placebo-controlled randomized trials (PregMet and PregMet2) and meta-analyses restricted to RCTs, which consistently show no benefit. Positive findings from meta-analyses that included non-randomized studies are likely attributable to selection bias, confounding by indication, and inadequate control groups, and should not guide clinical practice. However, metformin does provide clinically important benefits for other maternal outcomes in PCOS pregnancies, including a significant reduction in early pregnancy loss, preterm delivery, and gestational weight gain. The drug is generally safe, though long-term offspring data warrant further investigation.

Recommendations :

1. **Clinical Practice:** Metformin should not be used as a primary prophylactic agent for preeclampsia in PCOS patients. Standard of care, including risk assessment and low-dose aspirin where indicated, should be followed.
2. **Metformin Use:** For PCOS patients who conceive while on metformin, continuing the medication throughout pregnancy is reasonable for the prevention of miscarriage, preterm birth, and excess weight gain, but not for preeclampsia.
3. **Future Research:** Future RCTs should stratify randomization by key phenotypic characteristics (BMI, insulin resistance) to identify potential responder subgroups. Investigators should also prioritize long-term follow-up studies of offspring to fully characterize the safety profile of in utero metformin exposure.

REFERENCES

1. Vanky E, Stridsklev S, Heimstad R, et al (2010) Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. *Journal of Clinical Endocrinology and Metabolism*. <https://doi.org/10.1210/jc.2010-0853>
2. Løvvik T, Carlsen S, Salvesen Ø, et al (2019) Use of metformin to treat pregnant women with polycystic ovary syndrome (PregMet2): a randomised, double-blind, placebo-controlled trial. *The Lancet Diabetes and Endocrinology*. [https://doi.org/10.1016/S2213-8587\(19\)30002-6](https://doi.org/10.1016/S2213-8587(19)30002-6)
3. Nascimento IB, Dienstmann G, Souza MLR de, et al (2018) Evaluation of Preeclampsia Results after Use of Metformin in Gestation: Systematic Review and Meta-analysis. *Gynecologie et obstetrique*. <https://doi.org/10.1055/s-0038-1675214>
4. Alqudah A, McKinley MC, McNally R, et al (2018) Risk of pre-eclampsia in women taking metformin: a systematic review and meta-analysis. *Diabetic Medicine*. <https://doi.org/10.1111/dme.13523>
5. Zheng J, Shan P, Gu W (2013) The efficacy of metformin in pregnant women with polycystic ovary syndrome: A meta-analysis of clinical trials. *Journal of Endocrinological Investigation*. <https://doi.org/10.3275/8932>

6. Zhao Q, He J (2022) Efficacy and safety of metformin in pregnant women with polycystic ovary syndrome: a systematic review with meta-analysis of randomized and non-randomized controlled trials. *Gynecological Endocrinology*. <https://doi.org/10.1080/09513590.2022.2080194>
7. Ghazeeri G, Nassar A, Younes Z, Awwad J (2012) Pregnancy outcomes and the effect of metformin treatment in women with polycystic ovary syndrome: an overview. *Acta Obstetrica et Gynecologica Scandinavica*. <https://doi.org/10.1111/j.1600-0412.2012.01385.x>
8. Palomba S, Seminara G, Costanzi F, et al (2025) Is metformin effective and safe during pregnancy in women with PCOS? An overview of reviews. *Expert Review of Endocrinology & Metabolism*. <https://doi.org/10.1080/17446651.2025.2574334>
9. Zhu D, Chen Y, Huang J, et al (2022) Effects of metformin on pregnancy outcome, metabolic profile, and sex hormone levels in women with polycystic ovary syndrome and their offspring: a systematic review and meta-analysis. *Annals of Translational Medicine*. <https://doi.org/10.21037/atm-22-909>
10. Saadati S, Mason T, Godini R, et al (2025) Metformin use in women with polycystic ovary syndrome (PCOS): Opportunities, benefits, and clinical challenges. *Diabetes, obesity and metabolism*. <https://doi.org/10.1111/dom.16422>
11. Feng L, Lin X, Wan Z, et al (2015) Efficacy of metformin on pregnancy complications in women with polycystic ovary syndrome: a meta-analysis. *Gynecological Endocrinology*. <https://doi.org/10.3109/09513590.2015.1041906>
12. Tan X, Li S, Chang Y-L, et al (2016) Effect of metformin treatment during pregnancy on women with PCOS: a systematic review and meta-analysis. *Clinical and investigative medicine Medecine clinique et experimentale*. <https://doi.org/10.25011/CIM.V39I4.27091>
13. Vanky E, Zegher F de, Díaz M, et al (2012) On the potential of metformin to prevent preterm delivery in women with polycystic ovary syndrome – an epi-analysis. *Acta Obstetrica et Gynecologica Scandinavica*. <https://doi.org/10.1111/aogs.12015>
14. Kanda S, Chatha U, Odoma V, et al (2023) Effect of Metformin (MTF) Intervention During Pregnancy in Women With Polycystic Ovarian Syndrome (PCOS): A Systematic Review. *Cureus*. <https://doi.org/10.7759/cureus.44166>

15. Alimohammadi S, Ghasemi E, Mohsenpour Z, Mohsenpour F (2020) Investigating the Impact of Metformin Consumption on the Incidence of Gestational Diabetes and Preeclampsia in Pregnant Women Suffering Polycystic Ovary Syndrome: A Clinical Trial Study. *International Journal of Pediatrics*. <https://doi.org/10.22038/IJP.2020.45710.3737>
16. Hameed AA, Shreif HE, Mowafy HE (2011) The role of continuing metformin therapy during pregnancy in the reduction of gestational diabetes and improving pregnancy outcomes in women with polycystic ovary syndrome. *Middle East Fertility Society Journal*. <https://doi.org/10.1016/J.MEFS.2011.04.002>
17. Jamal A, Milani F, Al-Yasin A (2012) Evaluation of the effect of metformin and aspirin on utero placental circulation of pregnant women with PCOS. *Iranian Journal of Reproductive Medicine*
18. Tarry-Adkins J, Ozanne S, Aiken C (2020) Impact of metformin treatment during pregnancy on maternal outcomes: a systematic review/meta-analysis. *Scientific Reports*. <https://doi.org/10.1038/s41598-021-88650-5>
19. Stridsklev S, Carlsen S, Salvesen Ø, et al (2014) Midpregnancy Doppler ultrasound of the uterine artery in metformin- versus placebo-treated PCOS women: a randomized trial. *Journal of Clinical Endocrinology and Metabolism*. <https://doi.org/10.1210/jc.2013-3227>
20. Ujvari D, Trouva A, Hirschberg AL, Vanky E (2023) Maternal serum levels of prokineticin-1 related to pregnancy complications and metformin use in women with polycystic ovary syndrome: a post hoc analysis of two prospective, randomised, placebo-controlled trials. *BMJ Open*. <https://doi.org/10.1136/bmjopen-2023-073619>
21. Zeng X, Zhang Y, Tian Q, et al (2016) Effects of metformin on pregnancy outcomes in women with polycystic ovary syndrome. *Medicine*. <https://doi.org/10.1097/MD.0000000000004526>
22. Cao Q, Hu Y, Fu J, et al (2021) Gestational metformin administration in women with polycystic ovary syndrome: A systematic review and meta-analysis of randomized control studies. *The journal of obstetrics and gynaecology research*. <https://doi.org/10.1111/jog.15044>
23. Glueck C, Goldenberg N, Pranikoff J, et al (2013) Effects of metformin-diet intervention before and throughout pregnancy on obstetric and neonatal outcomes in patients with polycystic

ovary syndrome. Current Medical Research and Opinion.
<https://doi.org/10.1185/03007995.2012.755121>

24. Tosti G, Barberio A, Tartaglione L, et al (2023) Lights and shadows on the use of metformin in pregnancy: from the preconception phase to breastfeeding and beyond. *Frontiers in Endocrinology*. <https://doi.org/10.3389/fendo.2023.1176623>

25. Raperport C, Chronopoulou E, Homburg R (2021) Effects of metformin treatment on pregnancy outcomes in patients with polycystic ovary syndrome. *Expert Review of Endocrinology & Metabolism*. <https://doi.org/10.1080/17446651.2021.1889366>

26. Leo V, Musacchio MC, Piomboni P, et al (2011) The administration of metformin during pregnancy reduces polycystic ovary syndrome related gestational complications. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. <https://doi.org/10.1016/j.ejogrb.2011.03.024>

27. Notaro ALG, Neto F (2022) The use of metformin in women with polycystic ovary syndrome: an updated review. *Journal of Assisted Reproduction and Genetics*. <https://doi.org/10.1007/s10815-022-02429-9>

28. Fan H (2013) Use of metformin during pregnancy for women with polycystic ovary syndrome. *Open Journal of Obstetrics and Gynecology*. <https://doi.org/10.4236/OJOG.2013.31021>

29. Lautatzis M, Goulis D, Vrontakis M (2013) Efficacy and safety of metformin during pregnancy in women with gestational diabetes mellitus or polycystic ovary syndrome: a systematic review. *Metabolism: Clinical and Experimental*. <https://doi.org/10.1016/j.metabol.2013.06.006>

30. González C, Alvariñas J, Bagnes MFG, Girolamo GD (2019) Metformin and Pregnancy Outcomes: Evidence Gaps and Unanswered Questions. *Current Clinical Pharmacology*. <https://doi.org/10.2174/1574884714666181224151116>

31. Zeng W, Luo Y, Ou J, et al (2025) Metformin in polycystic ovary syndrome: unraveling multi-stage therapeutic mechanisms from puberty to long-term health outcomes. *Frontiers in Pharmacology*. <https://doi.org/10.3389/fphar.2025.1654372>

32. Wang Y, Zhang L, Tan J, et al (2011) Effect of metformin during early pregnancy on pregnancy outcome of women with polycystic ovarian syndrome. *Chinese Journal of Perinatal Medicine*. <https://doi.org/10.3760/CMA.J.ISSN.1007-9408.2011.10.004>

33. Dube R (2016) Using Metformin in Pregnancy for Different Indications: Are We Any Wiser now? <https://doi.org/10.2174/2213476X03666151221210516>
34. Ryssdal M, Skage JE, Jarmund A, et al (2025) Metformin Treatment in PCOS Pregnancies Reduces Maternal Infections and Increases the Risk of Allergies and Eczema in the Offspring: Post Hoc Analyses of Two Randomised Controlled Trials and One Follow-Up Study. *BJOG: an International Journal of Obstetrics and Gynaecology*. <https://doi.org/10.1111/1471-0528.18320>
35. Montplaisir P (2011) Is metformin a multifunctional medication for inducing ovulation and improving pregnancy outcomes in PCOS? *Journal of the American Academy of Nurse Practitioners*. <https://doi.org/10.1111/j.1745-7599.2011.00651.x>
36. Sivalingam VN, Myers J, Nicholas S, et al (2014) Metformin in reproductive health, pregnancy and gynaecological cancer: established and emerging indications. *Human Reproduction Update*. <https://doi.org/10.1093/humupd/dmu037>
37. Butalia S, Gutierrez L, Lodha A, et al (2017) Short- and long-term outcomes of metformin compared with insulin alone in pregnancy: a systematic review and meta-analysis. *Diabetic Medicine*. <https://doi.org/10.1111/dme.13150>
38. Ijäs H, Väärasmäki M, Morin-Papunen L, et al (2011) Metformin should be considered in the treatment of gestational diabetes: a prospective randomised study. *BJOG: an International Journal of Obstetrics and Gynaecology*. <https://doi.org/10.1111/j.1471-0528.2010.02763.x>
39. Li X, Celotto S, Pizzol D, et al (2021) Metformin and health outcomes: An umbrella review of systematic reviews with meta-analyses. *European Journal of Clinical Investigation*. <https://doi.org/10.1111/eci.13536>
40. Artini P, Obino M, Sergiampietri C, et al (2018) PCOS and pregnancy: a review of available therapies to improve the outcome of pregnancy in women with polycystic ovary syndrome. *Expert Review of Endocrinology & Metabolism*. <https://doi.org/10.1080/17446651.2018.1431122>
41. Abdalla M, Shah N, Deshmukh H, et al (2021) Impact of pharmacological interventions on insulin resistance in women with polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. *Clinical Endocrinology*. <https://doi.org/10.1111/cen.14623>