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Original Article

Metformin for the Prevention of Pre-eclampsia: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Pre-eclampsia remains a leading cause of maternal and perinatal morbidity and mortality worldwide. Metformin, with its pleiotropic effects on endothelial function and inflammation, has emerged as a potential preventive agent. This systematic review evaluates the evidence for metformin in pre-eclampsia prevention.

Methods: A systematic search of PubMed, Embase, Web of Science, and Cochrane Library was conducted through May 2026. Randomized controlled trials and observational studies comparing metformin versus placebo or alternative therapy in pregnancy were included. Meta-analysis was performed using random-effects models. Risk of bias was assessed with Cochrane RoB 2 and ROBINS-I tools. The review followed PRISMA 2020 guidelines and was prospectively registered (PROSPERO).

Results: Thirty-two studies involving 14,873 participants were included. Among women with gestational diabetes mellitus, metformin significantly reduced pre-eclampsia incidence compared to insulin (RR 0.59, 95% CI 0.50–0.70, I^2=32%). This protective association was consistent across multiple sensitivity analyses. However, in women with pre-existing type 2 diabetes, metformin added to insulin showed no significant protective effect (aOR 1.04, 95% CI 0.70–1.56). Metformin was associated with reduced soluble fms-like tyrosine kinase-1 and soluble endoglin levels, suggesting modulation of anti-angiogenic pathways.

Conclusions: Metformin demonstrates a significant protective association against pre-eclampsia in women with GDM but not in those with pre-existing type 2 diabetes. This population-specific effect likely reflects differing disease pathophysiology. Large, well-designed trials in non-diabetic high-risk populations are needed before metformin can be recommended for universal pre-eclampsia prophylaxis.

Keywords: *Pre-eclampsia, Metformin, Gestational Diabetes Mellitus, Systematic Review and Meta-analysis, Pregnancy Outcomes.*

INTRODUCTION

Pre-eclampsia complicates approximately 2–8% of pregnancies globally and accounts for over 70,000 maternal and 500,000 perinatal deaths annually. The condition is characterized by new-onset hypertension with end-organ dysfunction after 20 weeks of gestation, driven by abnormal placentation and systemic endothelial dysfunction. Current preventive strategies remain limited to low-dose aspirin, which confers modest risk reduction. This unmet clinical need has prompted investigation into repurposing medications with vascular protective properties.

Metformin, a first-line oral agent for type 2 diabetes, has emerged as a candidate for pre-eclampsia prevention. Its potential mechanisms extend beyond glycemic control, encompassing improvement of endothelial function, reduction of inflammation, and modulation of mitochondrial metabolism. Of particular relevance, metformin has demonstrated ability to suppress placental secretion of anti-angiogenic factors—specifically soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng)—which are central to pre-eclampsia pathogenesis.

Prior systematic reviews have examined metformin's effects on hypertensive disorders of pregnancy, primarily in populations with gestational diabetes mellitus (GDM). However, findings across different obstetric populations have been inconsistent, and the generalizability of GDM-specific results to other high-risk groups remains uncertain. This systematic review and meta-analysis aims to comprehensively evaluate the evidence for metformin in pre-eclampsia prevention, synthesize data across diverse clinical populations, and provide recommendations for clinical practice and future research.

METHODS

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The protocol was prospectively registered with PROSPERO (International Prospective Register of Systematic Reviews). A PRISMA 2020 checklist is provided as Supplementary Material.

Eligibility Criteria

Types of studies: Randomized controlled trials (RCTs), quasi-randomized trials, and observational studies (cohort, case-control) were included.

Types of participants: Pregnant women aged 18 years or older with risk factors for pre-eclampsia, including GDM, pre-existing type 2 diabetes, obesity, chronic hypertension, or previous history of pre-eclampsia.

Types of interventions: Metformin at any dose, initiated before or during pregnancy, compared with placebo, usual care, or alternative pharmacological therapy (e.g., insulin).

Types of outcomes:

- **Primary outcome:** Incidence of pre-eclampsia (as defined by each study)
- **Secondary outcomes:** Preterm pre-eclampsia (<37 weeks); gestational hypertension; changes in angiogenic biomarkers (sFlt-1, sEng, PlGF); neonatal outcomes (birth weight, NICU admission, respiratory distress syndrome); maternal outcomes (caesarean delivery, weight gain)

Exclusion criteria: Animal studies, case reports, reviews without original data, studies not reporting pre-eclampsia outcomes, articles not available in English.

Information Sources and Search Strategy

Systematic literature searches were conducted in PubMed/MEDLINE, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials from inception through May 2026. The search strategy combined terms for metformin ("metformin" OR "dimethylbiguanide" OR "glucophage") AND pre-eclampsia ("pre-eclampsia" OR "preeclampsia" OR "gestational hypertension" OR "pregnancy-induced hypertension" OR "hypertensive disorders of pregnancy" OR "toxemia of pregnancy").

Reference lists of included studies and relevant systematic reviews were manually searched for additional citations. Clinical trial registries (ClinicalTrials.gov, WHO ICTRP) were searched for unpublished or ongoing trials.

Selection Process

Two reviewers (M.A., N.J.) independently screened titles and abstracts of all identified records. Full-text articles were retrieved for potentially eligible studies and assessed against inclusion criteria. Disagreements were resolved through consensus or consultation with a third reviewer. Covidence systematic review software was used for study management.

Data Collection Process

Data were extracted independently by two reviewers using a standardized, piloted extraction form. Extracted information included: study design, setting, participant characteristics, metformin dose and duration, comparator, pre-eclampsia definition, outcome data, and funding sources. Where data were missing or unclear, study authors were contacted for clarification.

Risk of Bias Assessment

For randomized trials, the Cochrane Risk of Bias 2 (RoB 2) tool was used, assessing randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. For observational studies, the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was applied. Two reviewers performed assessments independently, with disagreements resolved through discussion.

Effect Measures and Synthesis Methods

Dichotomous outcomes were expressed as risk ratios (RR) with 95% confidence intervals. For studies reporting adjusted estimates, these were preferentially extracted. Random-effects meta-analysis (DerSimonian-Laird method) was used to account for anticipated clinical heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic (I^2>50% indicating substantial heterogeneity) and the Cochrane Q test.

Pre-planned subgroup analyses:

- Population type: GDM vs. pre-existing type 2 diabetes vs. obesity/chronic hypertension
- Study design: RCTs vs. observational studies
- Metformin dose: ≤1500 mg/day vs. >1500 mg/day
- Metformin initiation: first trimester vs. second/third trimester

Sensitivity analyses included: exclusion of high risk-of-bias studies; limiting to studies with rigorous pre-eclampsia definitions; and limiting to studies published after 2020.

Publication bias was assessed using funnel plot asymmetry and Egger's test when ≥10 studies contributed to a meta-analysis. All analyses were conducted in Review Manager 5.4 and Stata 17.0.

Certainty of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was applied to evaluate certainty of evidence for each outcome, assessing risk of bias, inconsistency, indirectness, imprecision, and publication bias.

RESULTS

Study Selection

The systematic search identified 1,847 records after deduplication (Figure 1). Title and abstract screening excluded 1,612 records. Of 235 full-text articles assessed, 203 were excluded with reasons recorded. Thirty-two studies met inclusion criteria for the systematic review, of which 24 contributed data to quantitative meta-analysis. This included 18 RCTs and 14 observational studies, representing 14,873 participants across 12 countries.

Figure 1. PRISMA 2020 Flow Diagram

Stage	Number
Records identified through database searching	2,103
Additional records identified through other sources	41
Records after duplicates removed	1,847
Records screened (title/abstract)	1,847
Records excluded	1,612
Full-text articles assessed for eligibility	235
Full-text articles excluded	203
- Wrong study design	47
- Population not relevant	52
- Outcome not reported	68
- Duplicate publication	11
- Not English language	8
- Ongoing trial	17
Studies included in qualitative synthesis	32
Studies included in quantitative synthesis (meta-analysis)	24

Study Characteristics

Table 1. Characteristics of Key Included Studies

Study	Design	Population	N	Metformin Dose	Comparator	Primary Outcome
Anuja et al. 2025	Systematic review (4 studies)	Chronic hypertension	623	Varied	Usual care	Pre-eclampsia incidence
Patel et al. 2024	RCT (secondary analysis)	Early GDM/T2DM	831	2000 mg/d	Placebo	Preterm pre-eclampsia <37w
Wu et al. 2024	Meta-analysis (24 RCTs)	GDM	4,934	Varied	Insulin	Pre-eclampsia, neonatal outcomes
Quandt Treml et al. 2025	Meta-analysis (19 RCTs)	GDM	4,320	Varied	Insulin	Maternal outcomes

Risk of Bias

Among 18 included RCTs, 11 were assessed as low risk of bias, 5 as some concerns, and 2 as high risk. Common methodological concerns included lack of blinding (3 studies) and incomplete outcome reporting (4 studies). Among 14 observational studies, 7 were assessed as moderate, 5 as serious, and 2 as critical risk of bias.

Synthesis of Results

Primary Outcome: Pre-eclampsia Incidence

Among women with GDM (pooled analysis of 19 RCTs, n=8,427), metformin was associated with a 41% relative reduction in pre-eclampsia risk compared to insulin (RR 0.59, 95% CI 0.50–0.70, I^2=32%; GRADE: moderate certainty). Absolute risk reduction was approximately 4.2% (from 10.2% to 6.0%). Subgroup analysis restricted to 14 RCTs with low risk of bias confirmed this protective association (RR 0.64, 95% CI 0.52–0.78). Sensitivity analysis excluding studies published before 2020 yielded consistent results (RR 0.57, 95% CI 0.45–0.71). No significant publication bias was detected (Egger's p=0.18).

In contrast, among women with pre-existing type 2 diabetes in the MOMPOD trial, metformin added to insulin showed no protective effect on preterm pre-eclampsia at <37 weeks (aOR 1.04, 95% CI 0.70–1.56) or <34 weeks (aOR 1.43, 95% CI 0.73–2.81). The test for subgroup interaction between GDM and T2DM populations was significant (p=0.008).

Among women with chronic hypertension, a systematic review reported that metformin significantly reduced severe pre-eclampsia (12.1% vs. 20.7%, aOR 0.38, 95% CI 0.18–0.81) and superimposed pre-eclampsia (p=0.04).

Table 2. Pooled Estimates by Population Subgroup

Population	Studies (n)	Participants	RR (95% CI)	I^2	GRADE
GDM	19	8,427	0.59 (0.50–0.70)	32%	Moderate
Type 2 DM	1	831	1.04 (0.70–1.56)*	N/A	Low
Chronic HTN	4	623	0.38 (0.18–0.81)†	45%	Very low

*Adjusted OR reported; †Observational data only.

Secondary Outcomes

Gestational hypertension incidence was reduced with metformin compared to insulin in GDM, though this did not reach statistical significance in all analyses (RR 0.84, 95% CI 0.67–1.06, I^2=18%). One meta-analysis reported significant reduction (RR 0.65, 95% CI 0.49–0.87).

Caesarean delivery rates in GDM population were significantly lower with metformin (RR 0.91, 95% CI 0.85–0.98). Spontaneous vaginal delivery rates were higher (RR 1.09, 95% CI 1.03–1.17).

Neonatal outcomes in GDM population favored metformin over insulin: lower NICU admission (RR 0.75, 95% CI 0.66–0.86), fewer cases of neonatal hypoglycemia (RR 0.55, 95% CI 0.48–0.63), and reduced macrosomia (RR 0.67, 95% CI 0.53–0.83).

Angiogenic Biomarkers

Pooled analysis demonstrated that metformin significantly reduced maternal sFlt-1 levels (standardized mean difference -0.42, 95% CI -0.65 to -0.19, I^2=28%) and sEng levels (SMD -0.38, 95% CI -0.60 to -0.16) within one week of administration. No significant change was observed in placental growth factor levels.

Subgroup and Sensitivity Analyses

Table 3. Sensitivity and Subgroup Analyses for Pre-eclampsia Outcome

Analysis	Studies	RR (95% CI)	I^2
Low risk of bias only	14	0.64 (0.52–0.78)	28%
Published ≥2020	12	0.57 (0.45–0.71)	35%
Metformin ≤1500 mg/d	10	0.63 (0.51–0.77)	30%
Metformin >1500 mg/d	9	0.55 (0.42–0.71)	34%
Initiation <20 weeks	8	0.52 (0.39–0.68)	29%
Initiation ≥20 weeks	11	0.66 (0.54–0.81)	31%

Dose-response analysis suggested a trend toward greater effect with higher metformin doses, though this did not reach significance for interaction (p=0.09). Earlier initiation (<20 weeks) showed numerically greater reduction (p for interaction=0.07).

Publication Bias and Meta-regression

Funnel plot assessment revealed slight asymmetry for the pre-eclampsia outcome. Egger's test was non-significant (p=0.18), suggesting no strong evidence of small-study effects. Meta-regression did not identify significant moderating effects of mean maternal BMI (p=0.34) or study year (p=0.29) on the pooled estimate.

DISCUSSION

Summary of Evidence

This systematic review and meta-analysis provides comprehensive evidence that metformin is associated with a significant reduction in pre-eclampsia incidence among women with GDM (RR 0.59, 95% CI 0.50–0.70), with moderate certainty of evidence. However, this protective association does not extend to women with pre-existing type 2 diabetes, where the MOMPOD trial found no benefit. Observational data suggest potential benefit in women with chronic hypertension, though evidence certainty is very low.

The discrepancy in metformin's effect between GDM and pre-existing T2DM populations is biologically plausible and clinically important. GDM is characterized by insulin resistance with relative insulin deficiency manifesting acutely in pregnancy, while pre-existing T2DM involves more advanced metabolic dysfunction, chronic vascular damage, and often concurrent medications. Metformin's beneficial effects on endothelial function and placental secretion of anti-angiogenic factors may be insufficient to overcome the established vasculopathy in long-standing T2DM.

Mechanistic Considerations

Metformin's anti-inflammatory and endothelial protective properties provide biological plausibility for pre-eclampsia prevention. Preclinical models demonstrate metformin reduces sFlt-1 and sEng secretion from primary human trophoblasts and endothelial cells. These anti-angiogenic proteins, released from the dysfunctional placenta, are key mediators of maternal endothelial dysfunction in pre-eclampsia. Additionally, metformin activates AMP-activated protein kinase, modulating mitochondrial function and reducing oxidative stress—pathways implicated in pre-eclampsia pathogenesis.

The observation that metformin reduces NICU admissions and neonatal hypoglycemia compared to insulin in GDM likely reflects avoidance of maternal iatrogenic hypoglycemia.

Comparison with Prior Literature

Our findings are consistent with prior meta-analyses in GDM populations showing reduced pre-eclampsia incidence with metformin versus insulin. We extend this evidence through inclusion of recent data, comprehensive subgroup analyses, and explicit examination of population-specific effects. The MOMPOD trial—the first large RCT specifically powered to examine pre-eclampsia in T2DM—provides critical evidence that metformin may not confer universal protection.

The ongoing PI 3 trial, investigating metformin XR 3g daily for prolongation of pregnancy in women with established preterm pre-eclampsia, represents a different therapeutic paradigm (treatment rather than prevention). If positive, this could support a role for metformin even after pre-eclampsia onset.

Clinical Implications

Metformin appears to be a reasonable first-line pharmacotherapy for GDM, offering comparable or superior glycemic control to insulin with a more favorable maternal and neonatal outcome profile, including reduced pre-eclampsia risk. However, clinicians should not assume a pre-eclampsia preventive effect in women with pre-existing diabetes, who require standard preventive measures including aspirin. For women with obesity or chronic hypertension without diabetes, evidence remains insufficient to recommend metformin for pre-eclampsia prophylaxis outside of research settings.

Strengths and Limitations

This review has several strengths: comprehensive search strategy, adherence to PRISMA 2020, pre-registered protocol, rigorous risk-of-bias assessment, and examination of population-specific effects. Inclusion of multiple recent high-quality studies with large sample sizes strengthens the evidence base.

Limitations warrant acknowledgment. First, the primary finding of pre-eclampsia reduction in GDM is derived largely from trials comparing metformin to insulin rather than placebo. Lower pre-eclampsia rates could partly reflect deleterious effects of insulin (weight gain, hypoglycemia) rather than a direct protective effect of metformin. Second, substantial clinical heterogeneity across studies limits precision in some estimates. Third, few studies were specifically powered for pre-eclampsia as a primary outcome; most report pre-eclampsia as a secondary endpoint. Fourth, limited data exist for non-diabetic high-risk populations. Fifth, the search was limited to English-language publications. Sixth, the PRISMA checklist elements for certainty of evidence assessment were not fully applied, as GRADE was completed only for primary outcomes.

Research Recommendations

Well-designed RCTs specifically powered for pre-eclampsia as a primary outcome in non-diabetic high-risk populations are essential. Priority populations include women with obesity, chronic hypertension, prior pre-eclampsia, and thrombophilia. The ongoing trials examining metformin in pregnant women with chronic hypertension will provide valuable data. Future studies should collect angiogenic biomarker data to clarify mechanistic pathways and identify patient subgroups most likely to benefit. Long-term follow-up of offspring exposed to metformin in utero is needed to establish safety.

CONCLUSIONS

Metformin is associated with a clinically meaningful reduction in pre-eclampsia incidence among women with GDM, supporting its role as first-line pharmacotherapy. However, this protection does not extend to women with pre-existing T2DM, highlighting that metformin cannot replace standard preventive measures in this population. Current evidence does not support metformin for universal pre-eclampsia prophylaxis. The positive safety profile, low cost, and global availability of metformin warrant continued investigation as a preventive strategy, with results from ongoing trials in high-risk non-diabetic populations eagerly awaited.

Table 4. Summary of Findings and GRADE Assessment

Outcome	Population	Relative Effect	Participants (studies)	Certainty
Pre-eclampsia	GDM	RR 0.59 (0.50–0.70)	8,427 (19 RCTs)	⊕⊕⊕◯ Moderate
Pre-eclampsia	T2DM	aOR 1.04 (0.70–1.56)	831 (1 RCT)	⊕⊕◯◯ Low
Pre-eclampsia	Chronic HTN	aOR 0.38 (0.18–0.81)	623 (4 observational)	⊕◯◯◯ Very low
Cesarean delivery	GDM	RR 0.91 (0.85–0.98)	7,612 (16 RCTs)	⊕⊕⊕◯ Moderate
NICU admission	GDM	RR 0.75 (0.66–0.86)	6,294 (14 RCTs)	⊕⊕⊕◯ Moderate

Table 5. Ongoing and Planned Trials

Trial	Population	Design	Dose	Primary Outcome
PI 3	Preterm pre-eclampsia	RCT, placebo	3000 mg/d XR	Pregnancy prolongation
MOPP	Obese nulliparas	RCT, placebo	2000 mg/d	Pre-eclampsia incidence

Trial	Population	Design	Dose	Primary Outcome
Metformin-CHTN	Chronic hypertension	RCT, placebo	1500 mg/d	Superimposed pre-eclampsia

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