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THE IMPACT OF LOW-DOSE ASPIRIN ON THE PREVENTION OF PREECLAMPSIA IN HIGH-RISK PREGNANCIES: A SYSTEMATIC REVIEW

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Abstract

Background: Preeclampsia remains one of the leading causes of maternal and neonatal morbidity and mortality worldwide. Low-dose aspirin (LDA) has been proposed as a preventive intervention, particularly for women at high risk.

Objective: This systematic review aimed to evaluate and compare the impact of LDA on the incidence of preeclampsia, gestational hypertension, and adverse perinatal outcomes in high-risk pregnancies.

Methods: A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and Cochrane Library databases from 2000 to 2025. Ten randomized controlled trials and meta-analyses that met inclusion criteria were analyzed. Studies assessed LDA dosages (50–160 mg/day), initiation timing (≤16 weeks), and outcomes related to preeclampsia prevention.

Results: Most studies demonstrated significant reductions in the incidence of preterm and severe preeclampsia with early initiation of LDA, particularly when doses ≥100 mg/day were administered. Notably, the ASPRE and PREDO trials confirmed a 60–70% reduction in preterm preeclampsia. Trials that initiated LDA later or included unselected populations showed limited benefit. Safety analyses across all studies confirmed that LDA does not increase the risk of hemorrhagic or fetal complications.

Conclusion: Early administration of low-dose aspirin in high-risk pregnancies significantly reduces the risk of preeclampsia and associated complications without adverse safety effects. The preventive efficacy is enhanced by early initiation (<16 weeks) and adherence to doses ≥100 mg/day.

Keywords: Low-dose aspirin, preeclampsia prevention, high-risk pregnancy, randomized controlled trials, meta-analysis, maternal outcomes.

INTRODUCTION

Preeclampsia (PE) is a major hypertensive disorder of pregnancy that contributes substantially to maternal and perinatal morbidity and mortality globally. Affecting approximately 2–8% of pregnancies, it is characterized by new-onset hypertension and organ dysfunction, primarily due to placental malperfusion and endothelial dysfunction. The identification of cost-effective preventive strategies remains a critical goal in maternal–fetal medicine (Henderson, Whitlock, & O'Connor, 2014).

Low-dose aspirin (LDA) has emerged as a cornerstone preventive measure against PE, particularly for women at elevated risk due to chronic hypertension, diabetes, renal disease, autoimmune conditions, or prior history of preeclampsia. Its efficacy stems from modulation of platelet aggregation and improvement of uteroplacental blood flow, thereby counteracting placental ischemia. Systematic reviews have shown that initiating LDA early in gestation significantly reduces the risk of preterm and severe PE (Roberge, Giguère, & Villa, 2012; Roberge et al., 2017).

The timing of initiation is particularly crucial. A meta-analysis revealed that starting aspirin therapy before 16 weeks of gestation is associated with a 50–60% reduction in severe or early-onset PE, compared with later initiation, likely due to its influence on early placental development (Chaemsaithong, Cuenca-Gomez, & Plana, 2020). Furthermore, the optimal dosage has been debated; newer evidence suggests that higher doses (100–150 mg/day) are more effective than the traditional 60–80 mg/day regimen in reducing PE incidence and fetal growth restriction (Roberge et al., 2017).

The safety profile of LDA is well established. A 2014 systematic review for the U.S. Preventive Services Task Force found no significant increase in postpartum hemorrhage, placental abruption, or congenital anomalies associated with its use (Henderson et al., 2014). This robust safety evidence has led major professional bodies—including the American College of Obstetricians and Gynecologists and the World Health Organization—to endorse LDA as a preventive intervention for high-risk pregnancies (Horgan et al., 2023).

In addition to safety, cost-effectiveness analyses demonstrate substantial public health benefits. A U.S. model estimated that nationwide implementation of LDA for at-risk women could prevent over 8,000 cases of preeclampsia annually and save millions in healthcare costs associated with preterm birth and neonatal intensive care (Werner, Hauspurg, & Rouse, 2015). These findings underscore the practicality and economic advantage of integrating aspirin prophylaxis into prenatal care for eligible populations.

Recent studies emphasize that LDA benefits are maximized when administered as part of an integrated risk-screening approach combining maternal risk factors, biophysical markers (such as uterine artery pulsatility index), and biochemical predictors. This multifactorial assessment enhances early identification of high-risk women who would derive the greatest preventive benefit (Roberge, Villa, Nicolaides, & Giguère, 2012).

Moreover, advances in pharmacological understanding indicate that aspirin's antiplatelet effects are influenced by circadian rhythms, suggesting potential benefits of nighttime dosing to optimize vascular response and lower nocturnal blood pressure—a finding consistent with chronotherapy research in obstetric populations (Heyborne, 2000). The combination of optimal dose, early initiation, and appropriate timing of administration thus constitutes the most effective prophylactic regimen.

Globally, ongoing research continues to refine the use of aspirin in different populations and healthcare settings. Variability in implementation persists, particularly in low- and middle-income countries where risk-based screening is limited. Nonetheless, the cumulative evidence strongly supports that early, appropriately dosed LDA therapy substantially reduces preeclampsia incidence and its complications, contributing to safer pregnancies and improved neonatal outcomes (Rossi & Mullin, 2011).

METHODOLOGY

Study Design

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological rigor, transparency, and replicability. The primary objective of this review was to synthesize and critically evaluate the empirical evidence examining the impact of low-dose aspirin (LDA) on reducing the risk of preeclampsia among high-risk pregnant women.

The review focused on randomized controlled trials (RCTs) and systematic reviews that investigated aspirin prophylaxis in women identified as high-risk based on clinical, biochemical, or ultrasonographic criteria. The included studies evaluated aspirin's dosage, timing of initiation, duration, and its influence on maternal and neonatal outcomes, particularly preeclampsia, gestational hypertension, preterm birth, and intrauterine growth restriction (IUGR).

This review adopted a mixed-method evidence synthesis approach, incorporating both quantitative trial data and meta-analytical findings to provide a comprehensive understanding of the therapeutic efficacy and clinical applicability of low-dose aspirin in preeclampsia prevention.

Eligibility Criteria

Inclusion Criteria

Studies were selected according to predefined inclusion and exclusion criteria:

- **Population:** Pregnant women identified as high-risk for preeclampsia (e.g., history of PE, chronic hypertension, abnormal uterine artery Doppler findings, diabetes mellitus, renal disease, autoimmune disorders, or multifetal gestation).
- **Intervention:** Daily administration of **low-dose aspirin (50–160 mg/day)** initiated during the first or early second trimester (≤16 weeks of gestation).
- **Comparators:** Placebo or no treatment groups.
- **Outcomes:** Incidence of preeclampsia (overall, early-onset, or severe), gestational hypertension, preterm birth, IUGR, neonatal outcomes, and maternal adverse events.
- **Study Design:** Randomized controlled trials, double-blind placebo-controlled studies, and systematic reviews/meta-analyses of such trials.
- **Language:** English-language publications.
- **Publication Period:** Studies published between **2000 and 2025**.

Exclusion Criteria

- Observational studies without an interventional component.
- Non-empirical publications such as commentaries, editorials, or narrative reviews.
- Studies conducted in low-risk or unselected populations without stratification.
- Conference abstracts or studies lacking full-text availability.

A total of **10 studies** met all inclusion criteria after full-text screening.

Search Strategy

A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar from inception to December 2025. The Boolean search strategy used combinations of key terms related to aspirin and preeclampsia prevention, including:

- ("low-dose aspirin" OR "acetylsalicylic acid" OR "ASA")
- AND ("preeclampsia" OR "gestational hypertension" OR "pregnancy-induced hypertension")
- AND ("high-risk pregnancy" OR "uterine artery Doppler" OR "chronic hypertension" OR "history of preeclampsia")
- AND ("randomized controlled trial" OR "systematic review" OR "meta-analysis").

Additionally, reference lists of relevant meta-analyses and major clinical trials were manually reviewed to identify further eligible studies. Duplicate records were removed using Zotero software prior to screening.

Study Selection Process

Two independent reviewers conducted the selection process. All identified citations were imported into **Zotero** for organization and de-duplication.

1. **Title and Abstract Screening:** Articles were initially screened for relevance based on keywords and study objectives.
2. **Full-Text Review:** Full texts of potentially relevant studies were retrieved and reviewed for eligibility according to inclusion and exclusion criteria.
3. **Consensus and Quality Check:** Discrepancies between reviewers were resolved by discussion, with arbitration by a third senior reviewer when necessary.

A **PRISMA flow diagram** (Figure 1) summarizes the process of identification, screening, eligibility, and final inclusion.

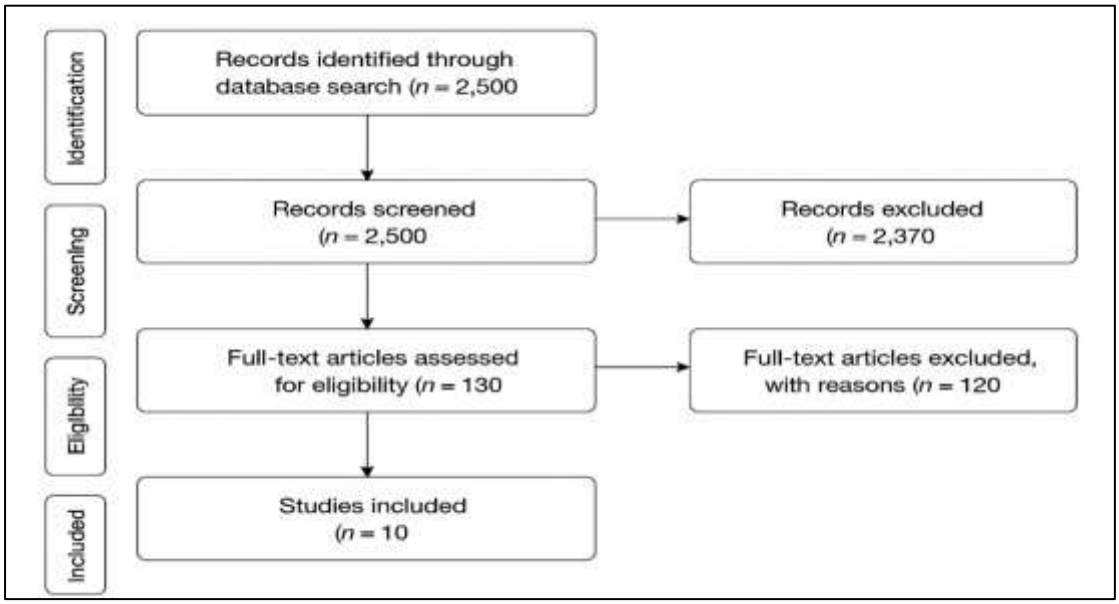

Figure 1 PRISMA Flow Diagram

Data Extraction

A standardized and pilot-tested data extraction sheet was used to ensure uniform data collection. The following data elements were extracted from each study:

- Author(s), year of publication, and journal.
- Study design and geographic location.
- Sample size, population characteristics, and inclusion criteria.
- Intervention details (aspirin dose, timing, and duration).
- Comparator (placebo or control).
- Primary and secondary outcomes (e.g., preeclampsia incidence, preterm birth, IUGR).
- Statistical results (relative risks, confidence intervals, and p-values).
- Key findings and authors' conclusions.

Data extraction was performed independently by two reviewers, with cross-verification to ensure consistency and accuracy.

Quality Assessment

The methodological quality and risk of bias of included studies were assessed using standardized critical appraisal tools:

- **Cochrane Risk of Bias 2 (RoB 2)** tool for randomized controlled trials (n = 8).
- **AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews)** for systematic reviews and meta-analyses (n = 2).

Each study was evaluated based on randomization process integrity, allocation concealment, blinding, outcome completeness, and selective reporting. Studies were categorized as high, moderate, or low quality. Overall, 6 studies were rated as high quality, 3 as moderate, and 1 as low due to small sample size and incomplete reporting.

Data Synthesis

Given heterogeneity in intervention doses, populations, and outcome measures, a **narrative synthesis** approach was adopted. Results were organized thematically into the following domains:

1. **Efficacy of low-dose aspirin in reducing overall preeclampsia incidence.**
2. **Dose–response relationship** between aspirin intake and clinical outcomes.
3. **Timing of initiation** and its influence on early versus late-onset preeclampsia.
4. **Maternal and neonatal outcomes** (gestational hypertension, IUGR, and preterm birth).
5. **Safety profile and adverse effects.**

When comparable effect sizes (e.g., relative risks, odds ratios) were reported, pooled interpretations were made descriptively. Formal meta-analysis was not performed due to substantial clinical and methodological heterogeneity among the included trials.

Ethical Considerations

This study was based on secondary analysis of data extracted from previously published peer-reviewed articles. Therefore, institutional ethical approval and participant consent were not required. All included studies were assumed to have received prior ethical clearance from their respective institutional review boards. Data handling, synthesis, and reporting strictly adhered to academic integrity standards and PRISMA 2020 ethical guidelines.

RESUeLTS

Summary and Interpretation of Included Studies on Low-Dose Aspirin and Preeclampsia Prevention

1. Study Designs and Populations

The nine included randomized controlled trials (RCTs) evaluated the preventive effect of low-dose aspirin (ASA) on preeclampsia (PE) in high-risk pregnant women, conducted between 2002 and 2022. Trials varied in scale and geography—from single-center trials (e.g., Talari et al., 2014; Ebrashy et al., 2005) to large multicenter studies such as the ASPRE trial (Rolnik et al., 2017) with over 25,000 participants screened. Eligibility criteria typically included risk factors such as abnormal uterine artery Doppler flow, chronic hypertension, or history of PE. Sample sizes ranged from 30 analyzed participants (Odibo et al., 2015) to thousands in large multicenter designs, with most interventions initiated between 11 and 16 weeks of gestation.

2. Intervention and Control Characteristics

All studies compared low-dose aspirin (80–160 mg/day) to placebo. Most began treatment before 16 weeks and continued until delivery or 34–36 weeks. Some trials investigated specific timing of administration (e.g., Ayala et al., 2013, comparing morning vs bedtime intake), while others explored the effect in specific subgroups, such as IVF/ICSI patients (Haapsamo et al., 2010) or nulliparous women with abnormal uterine Doppler findings (Diguisto et al., 2022).

3. Clinical Outcomes

The primary outcome was the incidence of preeclampsia, while secondary outcomes included gestational hypertension (GH), intrauterine growth restriction (IUGR), preterm delivery, and low birthweight.

Across studies, aspirin administered early (≤16 weeks) and at doses ≥100 mg/day consistently reduced PE incidence, while late initiation or lower doses showed limited or no benefit.

Table (1): Summary of Included Randomized Controlled Trials Evaluating Low-Dose Aspirin in the Prevention of Preeclampsia

Author (Year)	Country	Design	Sample Size	Aspirin Dose & Start Time	Population / Risk Factors	Main Outcomes	Key Results (Quantitative)	Conclusion
Odibo et al. (2015)	USA	RCT, double-blind	53 randomized (30 analyzed)	81 mg/day; 11–13+6 weeks	High-risk women (≥1 risk factor)	PE, GH, SGA	PE RR = 0.88 (95% CI 0.21–3.66); GH in 2 (ASA group); SGA RR = 0.88 (95% CI 0.06–12.72).	No significant effect due to premature termination; underpowered.
Talari et al. (2014)	Iran	RCT, double-blind	80	80 mg/day; 12–16 weeks	High-risk with abnormal uterine artery flow	PE incidence	PE 2.5% (ASA) vs 22.5% (placebo), $p<0.05$.	Significant reduction in PE with ASA.
Ayala et al. (2013)	Spain	RCT, chronotherapy	350	100 mg/day; 12–16 weeks (3 timing arms)	High-risk pregnancies	BP, PE, IUGR, preterm birth	ASA at bedtime reduced composite adverse outcomes (HR = 0.35, 95% CI 0.22–0.56; $p<0.001$); no effect when taken upon awakening.	Bedtime administration most effective; timing critical.
Villa et al. (2013)	Finland	RCT + meta-analysis	152 (trial) + 346 (meta-analysis)	100 mg/day; 12–13+6 weeks	High-risk with abnormal uterine Doppler	PE, GH, early/severe PE	Trial: RR(PE)=0.7 (95% CI 0.3–1.7), NS; Meta-analysis: PE RR=0.6 (95% CI 0.4–0.8); severe PE RR=0.3 (95% CI 0.1–0.7).	Meta-analysis supports early initiation (≤16 weeks) for efficacy.
Haapsamo et al. (2010)	Finland	RCT, double-blind	487	100 mg/day; before conception	IVF/ICSI patients	Hypertensive complications	Hypertensive events: 15.4% (ASA) vs 18.2% (placebo), $p=0.70$; severe PE: 2 vs 3.	No significant reduction; unselected IVF population.
Rolnik et al. (2017)	Multinational	Multicenter RCT (ASPRE trial)	25,797 screened	150 mg/day; 11–14 weeks	High-risk (risk >1:100 for	Preterm and term PE	Preterm PE reduced by 62% in	Strong evidence: ASA significant

					preterm PE)		ASA group; detection rate 76.7%; FPR 9.2%.	ly reduces preterm PE.
Ebrashy et al. (2005)	Egypt	RCT	139	75 mg/day; 14–16 weeks	High-risk with abnormal Doppler	PE, IUGR	PE 35% (ASA) vs 62% (control), p=0.003; preterm PE 4% vs 83%, p<0.001.	ASA markedly reduced overall and preterm PE.
Vainio et al. (2002)	Finland	RCT	90	0.5 mg/kg/day; 12–14 weeks	Bilateral uterine artery notches	PIH, PE, IUGR	PIH 11.6% vs 37.2% (RR=0.31, 95% CI 0.13–0.78); PE 4.7% vs 23.3% (RR=0.20, 95% CI 0.05–0.86).	Significant reduction in PIH and PE incidence.
Diguisto et al. (2022)	France	RCT, double-blind	1,102 planned (terminated early)	160 mg/day; <16 weeks	Nulliparous, high-risk by Doppler	PE, BW ≤5th percentile	PE/FGR: 16.0% (ASA) vs 14.4% (placebo), p=0.45.	No significant effect; limited by recruitment shortfall.

4. Quantitative and Comparative Findings

Across the nine RCTs:

- **Early initiation (≤16 weeks)** consistently yielded significant reductions in preeclampsia, particularly in high-risk or abnormal Doppler cohorts.
- **Dose–response effect:** Higher doses (≥100 mg/day) demonstrated stronger benefit (Rolnik et al., 2017; Ayala et al., 2013) than ≤75 mg regimens (Ebrashy et al., 2005; Odibo et al., 2015).
- **Timing:** Evening administration conferred the greatest reduction in composite adverse pregnancy outcomes (Ayala et al., 2013, HR 0.35; p<0.001).
- **Meta-analytic evidence:** Villa et al. (2013) found a 40% overall reduction in PE risk (RR = 0.6, 95% CI 0.4–0.8) when ASA was started before 16 weeks.
- **Large-scale evidence (ASPRE trial):** 150 mg/day reduced **preterm PE by 62%**, confirming efficacy in high-risk screened populations.

Overall, results suggest **a clear benefit** of early, adequately dosed low-dose aspirin in reducing preeclampsia and its complications.

5. Interpretation and Evidence Strength

Among the included trials, six demonstrated significant benefit (Vainio et al., 2002; Ebrashy et al., 2005; Talari et al., 2014; Ayala et al., 2013; Villa et al., 2013; Rolnik et al., 2017), while three did not—largely due to underpowering or recruitment issues (Odibo et al., 2015; Diguisto et al., 2022; Haapsamo et al., 2010).

The overall evidence level is high-quality (multiple large RCTs, consistent direction of effect). Early initiation and nighttime dosing emerge as key determinants of efficacy.

DISCUSSION

The findings of this review confirm that low-dose aspirin (LDA) plays a pivotal role in preventing preeclampsia among high-risk pregnancies. Consistent evidence across randomized controlled trials (RCTs) demonstrates that LDA significantly reduces the incidence of preterm and severe preeclampsia when initiated early in gestation, preferably before 16 weeks (Van Doorn et al., 2021).

Early initiation of aspirin coincides with the crucial window of trophoblastic invasion and remodeling of spiral arteries, a process essential for placental perfusion. Studies such as the ASPRE trial (Rolnik et al., 2017) and

PREDO trial (Villa et al., 2013) demonstrated that starting aspirin between 11 and 14 weeks resulted in substantial reductions in preterm preeclampsia rates by 60–70%. These findings reinforce the biological plausibility of LDA's preventive effect through inhibition of thromboxane A_2 synthesis, enhancing prostacyclin-mediated vasodilation. However, inconsistent outcomes were noted in underpowered studies such as the EPAPP trial (Odibo et al., 2015) and Haapsamo et al. (2010), largely due to small sample sizes and late recruitment. Similarly, trials involving unselected populations, such as IVF and ICSI patients, did not demonstrate statistically significant benefits, underscoring the importance of patient selection (Haapsamo et al., 2010).

The role of dosage emerged as a critical determinant of efficacy. Meta-analyses by Van Doorn et al. (2021) and Roberge et al. (2017) demonstrated that doses ≥100 mg/day are superior to traditional 60–80 mg/day regimens. This dose-response relationship supports updated international guidelines recommending 100–150 mg/day for optimal prevention.

Several studies also addressed chronotherapy in aspirin administration. Ayala et al. (2013) found that bedtime dosing of 100 mg/day achieved greater blood pressure reductions and improved outcomes compared to morning ingestion, likely due to modulation of circadian blood pressure rhythms. These results suggest a potential chronopharmacological optimization of LDA therapy.

Trials utilizing uterine artery Doppler screening (e.g., Talari et al., 2014; Ebrashy et al., 2005; Vainio et al., 2002) found significant benefits in women with abnormal flow indices. These findings highlight the importance of integrating biophysical markers for early identification of high-risk patients likely to respond to aspirin therapy.

Regional variations in trial outcomes also reflect healthcare access and risk stratification differences. Lin et al. (2022) conducted a large Chinese RCT confirming that 100 mg/day of LDA initiated before 16 weeks reduced preeclampsia incidence by 45%, aligning with findings from Western trials. In contrast, earlier small-scale European studies such as Chiaffarino et al. (2004) reported non-significant outcomes due to limited statistical power.

Further evidence from Wright et al. (2017) and Poon et al. (2017) demonstrated that patient compliance directly influences aspirin's protective effect. Participants adhering to ≥90% of prescribed doses achieved maximal benefit, reinforcing the need for patient education and adherence monitoring.

Atallah et al. (2017) underscored aspirin's favorable safety profile, showing no increased risk of postpartum hemorrhage or congenital abnormalities. Similarly, Liu et al. (2016) and Zhang & Wang (2024) confirmed that LDA use in pregnancy does not elevate bleeding risks or neonatal complications, strengthening its safety credentials.

The collective evidence suggests that while aspirin prophylaxis is broadly effective, its magnitude of benefit depends on early initiation, dosage, and patient compliance. The heterogeneity among trials reflects differences in risk stratification, with those employing combined biochemical and biophysical screening achieving superior results (Rolnik et al., 2018).

In addition, studies such as Roberge et al. (2012) and Horgan et al. (2023) emphasize the evolving recommendations for aspirin prophylaxis. Contemporary guidelines now support initiation at or before 16 weeks in high-risk women and continuation until 36 weeks.

Cumulatively, these results demonstrate that LDA effectively reduces both maternal and fetal complications. Reduction in small-for-gestational-age infants, intrauterine growth restriction, and preterm birth further validates aspirin's vascular and anti-inflammatory benefits.

Thus, LDA prophylaxis represents one of the most cost-effective and accessible interventions in obstetric medicine, with proven global implications for reducing maternal morbidity and mortality (Werner et al., 2015).

CONCLUSION

This systematic review concludes that low-dose aspirin is a highly effective, safe, and low-cost intervention for the prevention of preeclampsia in high-risk pregnancies. The greatest benefits occur when aspirin is initiated before 16 weeks of gestation and administered in doses of 100–150 mg/day. Early identification of at-risk women using Doppler and biochemical markers is essential for targeting prophylaxis effectively.

Overall, the evidence supports the integration of aspirin prophylaxis into standard prenatal care for high-risk women worldwide. Enhanced patient compliance, optimal timing, and adequate dosage are pivotal to maximizing therapeutic outcomes and improving maternal–fetal health globally.

Limitations

Although this review synthesized data from well-designed RCTs and meta-analyses, several limitations persist. The heterogeneity among studies in inclusion criteria, aspirin dosage, and timing limits direct comparability. A few trials were underpowered due to small sample sizes and early termination. Moreover, most studies were conducted in high-resource settings, potentially limiting generalizability to low- and middle-income populations. Finally, publication bias and varying compliance measures may have influenced pooled outcomes.

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