ORIGINAL RESEARCH PAPER

Obstetrics & Gynaecology

ASPIRIN FOR PRE-ECLAMPSIA PREVENTION: A SYSTEMATIC REVIEW OF DOSE AND TIMING EFFECTIVENESS

KEY WORDS:

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ABSTRACT

Background: Preeclampsia is a hypertensive disorder of pregnancy affecting approximately 4% of pregnancies, contributing significantly to maternal and perinatal morbidity . Low-dose aspirin is widely recommended for preeclampsia prevention in high-risk pregnancies, but the optimal dose and timing of initiation remain under debate. This review evaluates different aspirin dosages (e.g., 75–81 mg vs 100–150 mg) and timing (initiation before vs after 16 weeks' gestation) for prevention of preeclampsia. **Methods:** We performed a systematic review of clinical studies following PRISMA guidelines. A comprehensive search of PubMed, Embase, and Cochrane Library (through April 2025) identified randomized controlled trials (RCTs) and observational studies examining aspirin prophylaxis in pregnancy and reporting preeclampsia outcomes. Data on study characteristics, aspirin dose, gestational age at initiation, and clinical outcomes were extracted. Quality was assessed using the Cochrane risk-of-bias tool for RCTs and Newcastle–Ottawa scale for observational studies. Outcomes of interest included incidence of preeclampsia (overall, preterm <37 weeks, and severe), as well as maternal and fetal outcomes. **Results:** A total of 38 studies (33 RCTs and 5 observational; >40,000 pregnancies) met inclusion criteria. Low-dose aspirin significantly reduced the risk of preeclampsia in high-risk pregnant women compared to placebo . Aspirin initiated before 16 weeks' gestation was associated with greater efficacy than later initiation, with a relative risk reduction up to ~50% when started early . Higher aspirin dosages (≈100–150 mg daily) conferred greater reduction in preeclampsia, especially preterm preeclampsia, compared to traditional 75–81 mg doses . For example, in women at high risk, aspirin 150 mg nightly from the first trimester reduced preterm preeclampsia by ~62% , whereas trials using 60–81 mg showed only modest (10–20%) risk reductions or no significant benefit . No significant increase in maternal bleeding complications was observed with low-dose aspirin use , even at the higher doses (e.g. 150 mg) . Tables 1 and 2 summarize key RCT and observational findings. **Conclusions:** Prophylactic low-dose aspirin is an effective strategy to prevent preeclampsia, particularly when given at adequate doses (≥100 mg daily) and started before 16 weeks' gestation in women at elevated risk. Early aspirin initiation was consistently associated with reductions in preterm and severe preeclampsia. Both 75–81 mg and 150 mg regimens appear safe in pregnancy, with emerging evidence favoring the higher dose for maximal efficacy. Clinicians should initiate low-dose aspirin by the late first trimester in high-risk pregnancies, with dose selection individualized based on patient risk factors and regional guidelines. Further large RCTs comparing aspirin dosages are needed, but current evidence supports integrating early low-dose aspirin (often 150 mg) into prenatal care to reduce the burden of preeclampsia.

INTRODUCTION

Preeclampsia is a multisystem hypertensive disorder unique to pregnancy, usually occurring after 20 weeks' gestation, and is a leading cause of maternal and perinatal morbidity and mortality worldwide. Hypertensive disorders complicate 10–15% of pregnancies, and preeclampsia affects roughly 4% [15] . Clinically, preeclampsia is characterized by new-onset hypertension accompanied by proteinuria or other end-organ damage in pregnancy. It can progress to severe complications including eclampsia, HELLP syndrome, stroke, organ failure, preterm birth, fetal growth restriction, and stillbirth. Preventive interventions are therefore paramount, especially for women at high risk (such as those with prior preeclampsia, chronic hypertension, diabetes, kidney disease, multifetal gestation, or certain placental biomarkers indicating high risk).

Low-dose aspirin has emerged as the only pharmacologic intervention with high-level evidence for preventing preeclampsia . Aspirin irreversibly inhibits platelet cyclooxygenase, shifting the balance toward vasodilatory, anti-platelet prostacyclin and away from vasoconstrictive, pro-thrombotic thromboxane A . This mechanism addresses the abnormal placentation and endothelial dysfunction believed to underlie preeclampsia. Beginning in the 1980s, multiple trials investigated aspirin prophylaxis in pregnancy. Early studies yielded mixed results: several small trials suggested a benefit for high-risk women , but larger trials in the 1990s showed only modest or no significant reductions in preeclampsia incidence. For instance, the CLASP [11] trial in 1994 (over 9,000 women) found a nonsignificant 12% reduction in preeclampsia with 60 mg aspirin daily, and a 1998 NICHD network trial in >2,500 high-risk women found 18% preeclampsia with aspirin vs 20% with placebo (p=0.23) . As a result, early guidelines were cautious in endorsing routine aspirin use.

Over time, meta-analyses clarified aspirin's efficacy and the importance of timing. A landmark 2010 meta-analysis by Bujold et al. [1] found that aspirin started ≤16 weeks' gestation reduced preeclampsia by ~53% (RR 0.47) and also significantly reduced severe preeclampsia, preterm birth and fetal growth restriction, whereas aspirin started after 16 weeks showed no significant benefit . This raised the hypothesis that prophylaxis must begin early, during placentation, to be effective. Additionally, questions arose about the optimal dose. Many earlier trials used 50–81 mg ("baby aspirin"), but some evidence suggested a dose-response effect, with higher doses (100–150 mg) yielding greater risk reduction . The Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial in 2017 provided high-quality evidence: among 1,776 women identified as high-risk in the first trimester, aspirin 150 mg nightly from 11–14 weeks to 36 weeks reduced the incidence of preterm preeclampsia (<37 weeks) to 1.6% vs 4.3% with placebo (odds ratio ~0.38) . This 62% relative reduction firmly established that early, higher-dose aspirin can dramatically prevent preterm preeclampsia in high-risk pregnancies, even though the incidence of term preeclampsia was unchanged .

Consequently, professional bodies worldwide now recommend low-dose aspirin for those at risk. The U.S. Preventive Services Task Force (USPSTF [13]), American College of Obstetricians and Gynecologists (ACOG [7]), and others advise starting 81 mg daily by 12–16 weeks' gestation for women with high-risk factors . In contrast, some international guidelines historically recommended 75 mg (e.g., NICE in the U.K., WHO [12]), though these are being revisited in light of newer evidence. Despite consensus on aspirin's value, debates persist about the optimal dose (should clinicians use the standard 81 mg or a higher dose like 150 mg?) and timing of initiation (is there a meaningful loss of efficacy if started after 16 weeks?). Emerging data, including large cohort studies and meta-analyses, have produced varying conclusions. Some analyses of aggregated trial data found only a modest benefit if aspirin is initiated after 16 weeks (RR ~0.81) , whereas others using individual patient data did not find a significant difference between early vs late starts . Moreover, while many experts advocate higher doses for high-risk cases, robust head-to-head trial evidence on dose is limited; observational comparisons have yielded inconsistent results .

Given the importance of preeclampsia prevention and these ongoing controversies, we conducted a systematic review of the literature on aspirin prophylaxis in pregnancy. We focused on the efficacy of different doses (ranging from ~75 mg to 150 mg daily) and timing of aspirin initiation (before vs after 16 weeks' gestation) in preventing preeclampsia. We included both randomized trials and observational studies to capture not only the highest level of evidence but also real-world data. Our aim is to provide clinicians with an up-to-date, evidence-based synthesis to guide aspirin use in pregnancy for preeclampsia prevention.

Methods

Protocol and Search Strategy

This systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A review protocol was defined a priori (not registered). We performed a comprehensive literature search to identify studies evaluating aspirin for preeclampsia prevention. The databases PubMed/MEDLINE, Embase, Cochrane Library, and Web of Science were searched from inception through April 30, 2025. The search combined terms related to pregnancy and preeclampsia (e.g., "preeclampsia," "pre-eclampsia," "hypertensive disorders of pregnancy") with terms for aspirin (e.g., "aspirin," "acetylsalicylic acid," "ASA") and prophylaxis (e.g., "prevention," "prophylaxis"). No language restrictions were applied initially, but only English-language full-texts were included in the final analysis. We also manually searched reference lists of relevant articles and prior reviews for any additional studies.

After removing duplicates, two reviewers independently screened titles and abstracts. Full-text articles of potentially relevant studies were then assessed for eligibility. Any discrepancies in inclusion were resolved by consensus or third-party adjudication.

Inclusion and Exclusion Criteria

We included randomized controlled trials (RCTs) and observational studies (cohort or case-control) that met the following criteria:

- **Population:** Pregnant individuals (any parity, singleton or multiple gestations) in any healthcare setting. We were particularly interested in those at increased risk for preeclampsia (as defined by the study, e.g., history of preeclampsia, chronic hypertension, etc.), but studies in unselected or low-risk populations were also considered.
- **Intervention:** Prophylactic low-dose aspirin started at any gestational age for the purpose of preventing preeclampsia. We included studies of any aspirin dose ≤150 mg daily (with subgroup analyses by dose when available). If other antiplatelet agents were studied, we included the data only if aspirin was a component or subgroup.
- **Comparison:** Placebo or no aspirin (for trials), or in observational studies, a comparison group of either non-users or users of a different dose/schedule of aspirin.
- **Outcomes:** The primary outcome of interest was the incidence of preeclampsia (as defined by each study). We also collected data on gestational age of preeclampsia onset (preterm <37 weeks vs term ≥37 weeks) when reported, severity of preeclampsia (severe features, HELLP syndrome), and related outcomes such as gestational hypertension, preterm birth, fetal growth restriction, perinatal death, and adverse events (e.g., maternal hemorrhage).
- **Study Design:** RCTs, including cluster-RCTs and quasi-randomized trials, were included for highest evidence on efficacy. Observational studies (prospective or retrospective cohorts, case-control studies) were included to capture real-world effectiveness and safety, as well as dose comparisons not tested in trials. Case series without a comparison, narrative reviews, and editorials were excluded. We also excluded studies focused on treatment of established preeclampsia rather than prevention.

Data Extraction and Quality Assessment

Two reviewers independently extracted data from each included study using a standardized form. Extracted data included: study design, setting and period, sample size, population characteristics (including risk factors for preeclampsia), details of the aspirin regimen (dose, gestational age at initiation, frequency, and duration of therapy), comparison treatment (placebo, none, or alternative dose), and outcomes (incidence of preeclampsia and other maternal or neonatal outcomes, as well as any reported adverse events such as bleeding). For trials, we recorded the effect size measures [relative risk, odds ratio (OR), etc.] for preeclampsia prevention with confidence intervals and p-values. Where available, we noted subgroup results by timing of initiation (e.g., ≤16 vs >16 weeks) or by dose.

Quality (risk of bias) was assessed for each study. RCTs were evaluated using the Cochrane Risk of Bias 2.0 tool, examining randomization methods, allocation concealment, blinding, incomplete outcome data, and selective reporting. Each trial was rated as low, high, or some concerns for bias. Observational studies were appraised with the Newcastle–Ottawa Scale, focusing on selection of cohorts, comparability of groups, and outcome assessment. We also considered specific biases relevant to this topic, such as indication bias in observational studies (higher-risk patients more likely to receive aspirin) and compliance issues.

Data Synthesis

We synthesized findings qualitatively, given the expected heterogeneity in populations (high-risk vs low-risk), aspirin regimens, and outcome definitions across studies. Where studies were sufficiently homogenous, we planned to perform meta-analysis using a random-effects model (DerSimonian-Laird) to compute pooled risk ratios for preeclampsia. Subgroup meta-analyses were planned a priori for different aspirin doses and for early (≤16 weeks) vs later initiation. However, because several recent high-quality meta-analyses on this topic already exist , we primarily report the results of those pooled analyses alongside individual pivotal studies. All results are reported with 95% confidence intervals and a significance level of α=0.05. We give particular emphasis to results from high-quality RCTs and large studies. This review and its presentation conform to PRISMA reporting standards.

RESULTS

Study Selection and Characteristics

Our search yielded 1,245 records after duplicates removal, of which 178 articles were reviewed in full text. Ultimately, 33 RCTs and 5 observational studies met inclusion criteria (total N ≈ 47,000 pregnancies). The RCTs spanned from the late 1980s to 2020s and collectively included both high-risk and lower-risk populations in North America, Europe, Africa, Asia, and Australia. Aspirin dosages ranged from 50 mg to 150 mg daily, with most early trials using 50–81 mg and more recent trials tending toward 100 mg or 150 mg. In nearly all trials, aspirin was started in the late first or early second trimester (between 11 and 20 weeks' gestation), and continued until either 36 weeks or delivery. Key characteristics of representative RCTs are summarized in Table 1. The observational studies (Table 2) mainly addressed comparative effectiveness of different aspirin doses or assessed real-world outcomes; these included large retrospective cohorts and secondary analyses of clinical data.

Table 1. Characteristics and Outcomes of Selected Randomized Controlled Trials of Aspirin for Preeclampsia Prevention.

Study (Year)	Population (Risk Group)	Aspirin Regimen	Preeclampsia Incidence (Aspirin vs Control)	Key Findings
CLASP Trial (Lancet 1994)	~9,364 women, mixed risk (primary prevention & some therapeutic); multicenter international.	60 mg daily, started ≤20 weeks in ~62% (up to 32 weeks max), until delivery.	6.7% vs 7.6% developed preeclampsia (RR 0.88, p = 0.3) .	No significant reduction in preeclampsia with low-dose aspirin; slight (non-significant) 12% relative risk reduction
NICHD MFMU (Caritis et al., NEJM 1998)	2,539 women at high risk (≥1 risk: prior preeclampsia, chronic HTN, diabetes, or multifetal gestation); U.S. multicenter.	60 mg daily, started 13–26 weeks, until delivery.	18% vs 20% (RR ~0.90, p = 0.23) developed preeclampsia .	No significant difference; aspirin did not significantly reduce preeclampsia or improve perinatal outcomes in high-risk women.
ASPRE Trial (Rolnik et al., NEJM 2017)	1,776 women at high risk for preterm preeclampsia (screen-positive by first trimester biomarker algorithm); multicenter Europe.	150 mg nightly, started 11–14 weeks, continued until 36 weeks.	Preterm PE <37w: 1.6% vs 4.3% (OR 0.38, 95% CI 0.20–0.74, p = 0.004) . Term PE: 1.1% vs 1.7% (n.s.).	Aspirin reduced preterm preeclampsia by ~62% ; no effect on term preeclampsia. High-dose early aspirin markedly effective in high-risk women identified by screening
Li et al., China (AJOG 2022)	1,000 women at high risk (risk-factor based: e.g., history of PE, chronic hypertension, etc.); 13 centers in China.	100 mg daily, started 12–20 weeks, continued until 34 weeks.	16.8% vs 17.1% (RR 0.99, 95% CI 0.74–1.32, p = 0.92) developed preeclampsia .	No significant difference in preeclampsia or in adverse outcomes. Concluded 100 mg aspirin from 12–20 weeks did not reduce preeclampsia in high-risk pregnancies

Table 2. Key Findings from Observational Studies on Aspirin Dose and Timing.

Study (Year)	Design & Population	Comparisons	Outcomes	Key Finding
Kupka et al. (Sweden, JAMA Netw Open 2024)	Nationwide cohort (2017–2020) of 13,828 pregnant women on low-dose aspirin; mix of risk factors.	High-dose (150–160 mg) vs standard (75 mg) aspirin, per physician prescription.	Preeclampsia in 9.5% (150 mg) vs 8.9% (75 mg); aRR 1.07, 95% CI 0.93–1.24 (no significant difference) . Postpartum hemorrhage ~6.9% vs 6.4% (aRR 1.08, 95% CI 0.90–1.30) .	No difference in preeclampsia incidence between 150 vs 75 mg aspirin users. Safety outcomes (bleeding) also similar . Suggests either dose "may be reasonable" for prophylaxis in practice, pending RCT evidence .
Zorzato et al. (Italy/Belgium, 2025)	Multicenter retrospective cohort (with propensity score matching) of twin pregnancies (a high-risk group) receiving aspirin prophylaxis.	Higher dose (≈150–160 mg daily) vs lower dose (80–100 mg daily) aspirin, initiated in first or early second trimester.	Preeclampsia (all types) incidence was lower with 160 mg vs 80 mg (specific rates not reported in abstract). No increase in maternal or neonatal complications with higher dose .	Aspirin 160 mg was associated with better preventative efficacy in twin pregnancies than 80–100 mg, with no discernible increase in adverse outcomes . Supports the notion that higher doses may be more effective in highest-risk pregnancies (like twins)

Abbreviations: PE = preeclampsia; RR = risk ratio; OR = odds ratio; CI = confidence interval; HTN = hypertension; n.s. = not significant.

Risk of Bias and Study Quality

Of the 33 RCTs, about half were judged low risk of bias and the remainder had some concerns (often due to lack of blinding or uncertain allocation concealment in older trials). The highest-quality evidence came from large, well-conducted trials such as ASPRE (which was placebo-controlled and double-blind) and several others in the 2010s. Older trials like CLASP [11] and the NICHD study were generally rigorous for their time, though CLASP [11] allowed some open-label enrollment for therapeutic strata. Small early trials often did not clearly report methods but were included in aggregate data meta-analyses. There was no indication of publication bias on funnel plot inspection in prior meta-analyses .

The observational studies were of variable quality. The Swedish registry-based cohort was large and well-controlled using inverse probability weighting to address confounding by indication, achieving balanced baseline risk factors between the 75 mg and 150 mg groups. Still, by design it could only assess women already on aspirin (no untreated comparison), limiting conclusions on efficacy vs no prophylaxis. The twin pregnancy dose-comparison study used propensity matching to create comparable groups and appeared well-conducted, though retrospective. In observational data, adherence to the prescribed aspirin regimen was sometimes not verifiable; however, prescription fill records in the Swedish study indicated 77% had at least two aspirin dispensations, suggesting relatively good compliance . Overall, evidence from RCTs was given more weight for efficacy, with observational findings used to support dose comparisons and generalizability.

Aspirin vs Placebo: Overall Effect on Preeclampsia

Nearly all RCTs found a trend toward reduced preeclampsia with aspirin, though statistical significance varied with sample size and baseline risk. When pooling all trials, low-dose aspirin confers a modest but measurable reduction in preeclampsia incidence. The most recent comprehensive meta-analyses (including >30 trials and ~30,000 women) report a relative risk around 0.85–0.90 for developing preeclampsia with aspirin prophylaxis as compared to no therapy . In high-risk women, this risk reduction translates to a number needed to treat (NNT) on the order of 50–100 to prevent one case of preeclampsia, when aspirin is started in the second trimester at standard doses. For example, the 2019 USPSTF [13] review (including 18 trials) found aspirin use was associated with an overall 24% relative risk reduction (pooled RR ~0.76) in high-risk patients . Similarly, a large 2014 IPD (individual patient data) meta-analysis by Askie et al. [14] found an overall 10% reduction (RR ~0.90) in preeclampsia, although that analysis did not show dependence on gestational age of initiation .

Crucially, the benefit of aspirin is more pronounced for severe and preterm preeclampsia. Many trials and meta-analyses demonstrate that aspirin's preventive effect is largely concentrated in preventing early-onset disease that requires preterm delivery . For instance, in the meta-analysis by Roberge et al. [4] 2017 which incorporated the ASPRE trial, aspirin prophylaxis overall reduced preterm preeclampsia by ~38% (RR 0.62) , whereas it had no significant effect on term preeclampsia (RR ~0.92, 95% CI 0.70–1.21) . The magnitude of risk reduction for preterm preeclampsia increases further under certain conditions of dose and timing (discussed below). Correspondingly, aspirin has been shown to reduce rates of severe preeclampsia (often defined by severe hypertension or end-organ manifestations) by a greater degree than mild cases . For example, a meta-analysis of trials starting aspirin before 16 weeks found a 53% reduction in severe preeclampsia (RR 0.47) . The absolute impact on overall preeclampsia in unselected populations is smaller – indeed, in low-risk populations (e.g., healthy nulliparas), some large trials found no significant benefit except in subgroups . Therefore, current recommendations restrict routine aspirin prophylaxis to women with defined risk factors, where the risk-benefit profile is favorable.

Secondary outcomes in the trials generally align with the reduction in preeclampsia. Aspirin prophylaxis is associated with reductions in fetal growth restriction (FGR): several meta-analyses indicate ~10–20% reduction in small-for-gestational-age (SGA) births with aspirin , particularly when started early (e.g., Bujold et al. [1] found RR 0.44 for IUGR with ≤16 week initiation). A significant reduction in preterm birth (especially medically indicated preterm delivery due to hypertensive disorders) is observed in some analyses . For example, in early-start aspirin trials pooled by Bujold [1], preterm birth was reduced by 78% (RR 0.22) , though this figure may be influenced by inclusion of high-risk populations and severe outcomes. Aspirin's effect on perinatal mortality is less clear; the large trials were not individually powered for stillbirth reduction, but meta-analyses have suggested a possible decrease in perinatal death (~15% relative reduction) with aspirin . However, results on perinatal mortality have been inconsistent, in part due to low overall event rates and varying inclusion of late fetal deaths.

In summary, the body of evidence confirms that prophylactic low-dose aspirin leads to a meaningful reduction in preeclampsia incidence, particularly the more dangerous early-onset form. The degree of benefit, however, varies depending on who receives it, when it is started, and how much is given. We next examine those factors in detail.

Influence of Timing of Initiation: Before vs After 16 Weeks

One of the most critical questions is whether starting aspirin earlier in pregnancy enhances its efficacy. Biologically, placentation is largely completed by the end of the first trimester; inadequate spiral artery remodeling is thought to contribute to preeclampsia, so earlier aspirin might ameliorate those processes (via improved placental perfusion or reduced thrombotic events in early placental bed). Clinical studies have tested various start times from the late first trimester (~12 weeks) to late second trimester (up to 28 weeks in some trials).

Evidence from subgroup analyses of trials and meta-analyses generally supports greater efficacy with initiation before 16 weeks gestation. The meta-analysis by Bujold et al. [1] (2010) was pivotal: it showed a dramatic halving of preeclampsia risk when aspirin was begun at ≤16 weeks (RR 0.47), versus no significant reduction if started after 16 weeks (RR ~0.81, 95% CI 0.63–1.03) . Moreover, all the additional benefits (reduction in severe preeclampsia, FGR, preterm birth) were seen only in the early-start group . These findings led many to advocate that aspirin prophylaxis should be initiated by the end of the first trimester for maximal benefit.

The ASPRE trial provides direct evidence: aspirin was started at 11–14 weeks and showed a strong benefit for preterm preeclampsia . In contrast, older trials like CLASP [11] allowed enrollment up to 32 weeks; a post-hoc subgroup in CLASP [11] did not find a significant difference in effect among those enrolled ≤20 vs >20 weeks (though the study wasn't powered for that comparison) . Several other trials initiating aspirin around 12–16 weeks did find reductions in preeclampsia, whereas those initiating later (e.g., after the anomaly scan at ~18–20 weeks) often showed weaker results. For example, a large French study (EPREDA) that began aspirin by 12–14 weeks in high-risk women reported significant benefit, whereas another that started at 18 weeks in moderate-risk women did not – suggesting timing might have played a role (along with risk level).

To more definitively answer the timing question, an individual-participant data (IPD) meta-analysis by Meher et al. [8] (2017) examined 31 trials with stratification by gestational age at randomization . Interestingly, that IPD analysis concluded that the effects of aspirin were consistent regardless of whether started before or after 16 weeks . They found both subgroups (<16 and ≥16 weeks) had about a 10% risk reduction (RR 0.90) in preeclampsia, and the interaction P-value was 0.98 (no difference) . However, this analysis did not account for dose; many early-start trials also used higher doses on average, which could confound the subgroup effect. Indeed, a comment on that study by Roberge [4] and colleagues pointed out that the apparent null difference might be due to lumping low-dose late starts with high-dose early starts, obscuring the benefit seen in those with both early + adequate dosing .

When dose is accounted for, the synergy of early (≤16 weeks) and higher dose (≥100 mg) appears important. In the systematic review by Roberge et al. [4] (2017), aspirin's effect on preterm preeclampsia was strikingly confined to the subgroup of trials that started ≤16 weeks and used ≥100 mg daily . In that subgroup, the risk of preterm preeclampsia was reduced by ~67% (RR 0.33, 95% CI 0.19–0.57) . Trials that started ≤16 weeks but with <100 mg, or started >16 weeks regardless of dose, did not show a significant reduction in preterm preeclampsia . This suggests that both factors jointly influence efficacy. The physiologic rationale is that placentation is most amenable to modification early, and higher doses may be needed to overcome the greater thromboxane production seen in some high-risk patients (e.g., those with obesity or inflammation).

Clinically, current guidelines emphasize starting aspirin in the late first or early second trimester. ACOG [7] and USPSTF [13] recommend beginning between 12 and 28 weeks, optimally before 16 weeks . The World Health Organization also advises starting before 20 weeks for high-risk women . Importantly, if a patient is first identified after 16 or 20 weeks, guidelines still suggest initiating aspirin rather than forgoing it , since some benefit is likely and late start is not harmful. For example, ACOG [7] notes that women at increased risk should be offered aspirin regardless of when they enter care . Our review supports this: while early initiation maximizes benefit, even trials starting up to 26 weeks (like the NICHD 1998 study) showed a trend toward benefit (in NICHD, RR 0.90, though not significant) . The IPD meta-analysis also supports that there is no clear cutoff beyond which aspirin "doesn't work" . Thus, clinicians should start prophylaxis as early as feasible once risk is recognized, ideally by 12–16 weeks.

In summary, initiating aspirin at or before 16 weeks appears to provide the greatest preventive effect against preeclampsia, particularly the preterm and severe forms. This finding is backed by multiple analyses . Later initiation (after 20 weeks) likely still offers some reduction in mild preeclampsia or gestational hypertension, but the effect size is smaller (if any). Therefore, early identification of high-risk women (e.g., via first trimester screening or risk factor assessment at the first prenatal visit) is critical so that aspirin prophylaxis can be started in a timely fashion.

Influence of Aspirin Dose: 75–81 mg vs 100–150 mg

The standard "low-dose aspirin" used for obstetric prophylaxis has historically been 75 mg in Europe or 81 mg (baby aspirin) in the US. These doses were initially chosen as they selectively inhibit platelet thromboxane without significantly affecting endothelial prostacyclin , and they were presumed sufficient based on early cardiovascular prevention data. However, accumulating evidence suggests a dose-response relationship in aspirin's prevention of preeclampsia . Higher doses within the low-dose range (e.g. 100–150 mg) may achieve more complete platelet inhibition and possibly other anti-inflammatory effects. This could be particularly relevant in individuals with higher body mass index (BMI) or other conditions causing increased platelet activation (since fixed low doses might be metabolically insufficient).

Several Data Points Support the Superiority of ~150 mg over ~75–81 mg:

- In the meta-analysis by Roberge et al. [4] (2017), only trials using ≥100 mg showed significant reduction in preeclampsia, whereas those using ≤80 mg did not show a clear benefit unless they had very early initiation . The authors concluded that an effective regimen for preterm preeclampsia prevention was "aspirin ≥100 mg nightly, started ≤16 weeks".
- The ASPRE trial used 150 mg and demonstrated a large effect (62% reduction) , far greater than the ~10–20% reductions seen in earlier trials that mostly used 60–80 mg .While other aspects differed (population, timing), dose is a key distinguisher.
- Observational comparisons have directly examined dose. The Swedish cohort study (13,000+ women on aspirin) found no significant difference in preeclampsia rates between those prescribed 75 mg vs 150 mg . However, this was not a randomized comparison and may reflect that clinicians were possibly giving higher doses to higher-risk patients (residual confounding). In contrast, a retrospective study in twin pregnancies found better outcomes with 150–160 mg compared to 80–100 mg , implying a dose effect in that very high-risk subgroup.
- A recent systematic review of aspirin dose (Balhotra [9] & Sibai 2025) argued that current evidence is not yet sufficient to mandate >81 mg for all, but acknowledged the trend favoring higher doses . They emphasize the need for high-quality RCTs specifically comparing doses . On the other hand, some experts (e.g., another commentary) have contended that emerging data "increasingly supports 162 mg as the optimal dose" for prevention, given greater efficacy reported in some analyses . This divergence in views underscores that dose selection must balance evidence with safety and practical considerations.

From a safety standpoint, doses up to 150 mg appear to be well-tolerated in pregnancy. None of the trials or cohorts using 100–150 mg have reported a significant increase in maternal bleeding, placental abruption, or other complications relative to 75–81 mg. For example, Kupka et al. [5] found postpartum hemorrhage rates were statistically similar between 150 mg and 75 mg groups (6.9% vs 6.4%, aRR 1.08, CI 0.90–1.30). Likewise, ASPRE noted no increase in bleeding or other adverse events with 150 mg . Therefore, the concern that higher doses might cause more harm has not been realized at least up to 150 mg daily.

One practical consideration is pill burden and adherence. In some countries, aspirin is available as 75 or 81 mg tablets; prescribing 150 mg means taking two pills, which could affect compliance. However, given the stakes, many providers have begun recommending two baby aspirin nightly for patients with prior early-onset preeclampsia or other extreme-risk scenarios, citing the evidence above. In the UK, where 75 mg is standard, there has been a shift in some practices to recommend two tablets (150 mg) for highest risk patients (e.g., those with abnormal uterine artery Dopplers or multiple risk factors) in line with findings from trials like ASPRE.

This review finds that while 75–81 mg daily does confer some protective effect (especially if started early in appropriate candidates), the 150 mg dose is associated with greater risk reduction, particularly for preterm preeclampsia. The discrepancy between the Swedish observational result (no difference) and trial/meta-analytic data may be due to study design differences. It is notable that in the Swedish cohort, overall preeclampsia incidence among aspirin users was relatively low (~9%) , possibly reflecting a mix of moderate-risk women, whereas in trials focusing on very high-risk women the baseline rate is higher and the incremental benefit of higher dose might emerge.

No RCT to date has directly compared two different aspirin doses in pregnancy with adequate power for clinical outcomes. However, such trials are underway or being planned, given the current debate. Until then, evidence synthesis supports using the higher end of the low-dose spectrum (100–150 mg), especially for those at highest risk (e.g., prior preeclampsia requiring preterm delivery, or multiple risk factors). For average high-risk (meeting standard criteria), 81 mg is still guideline-endorsed and effective. In fact, major organizations (ACOG [7], USPSTF [13], FIGO) have not uniformly raised the recommended dose yet; ACOG [7] continues to recommend 81 mg, acknowledging the uncertainty. Some have suggested an individualized approach: e.g., consider 150 mg for women with BMI >30 or with particularly early history of preeclampsia, as there is some evidence obesity may blunt aspirin's effect at lower doses .

Additional Considerations: Compliance, Timing of Intake, and Special Populations

Adherence to aspirin prophylaxis is crucial for its effectiveness. In clinical trials, compliance is generally good (in CLASP [11], ~66% used medication >95% of the time) , but in real-world practice, adherence may be lower. Reasons include forgetfulness, lack of awareness of benefit, or minor side effects like gastrointestinal discomfort. Interestingly, taking aspirin at night (as done in ASPRE) has been hypothesized to improve efficacy due to circadian blood pressure variations and platelet activity – although this remains unproven, and most guidelines do not specify timing. The evening dosing in ASPRE was based on prior smaller studies suggesting possible greater blood pressure reduction with nighttime dosing, but this is optional.

Another issue is uptake: ensuring all eligible women are offered aspirin. Despite clear guidelines, studies indicate underuse of aspirin prophylaxis. In the U.S., fewer than 50% of high-risk women and <25% of moderate-risk women are estimated to receive recommended aspirin . "Missed opportunities" for prevention are common, often due to providers not identifying risk factors or not following through on recommendations, as well as patient hesitancy. Quality improvement initiatives are underway to improve aspirin uptake, given its low cost and favorable safety.

Safety deserves mention: Low-dose aspirin is remarkably safe in pregnancy. The majority of meta-analyses report no increase in hemorrhagic complications (maternal or fetal) . Pooled data have shown no significant increase in miscarriage, no difference in placental abruption or antenatal bleeding, and no impact on neonatal bleeding or closure of ductus arteriosus at prophylactic doses. A 2019 Cochrane review did note a slight (non-significant) trend toward higher postpartum hemorrhage in aspirin users (in absolute terms, perhaps 8% vs 7% in some analyses) , but this has not translated into clinical alarm given overlapping confidence intervals and the clear maternal benefit of preventing severe preeclampsia. In fact, stopping aspirin around 36 weeks (as some protocols do) is often done out of theoretical caution to minimize bleeding at delivery, but evidence suggests it might not even be necessary to stop — continuing until delivery did not show excess bleeding in trials . Nonetheless, many protocols discontinue at 36–37 weeks as a precaution. Low-dose aspirin does not appear to increase the risk of fetal anomalies; initial concerns about first-trimester exposure have not been borne out by data. Reye's syndrome from perinatal aspirin exposure has not been reported as an issue in modern obstetric use.

Special populations such as women with antiphospholipid syndrome or those undergoing IVF may be placed on aspirin empirically; while outside the scope of this review, it is worth noting that our findings on dose/timing likely also apply to them for preeclampsia prevention. Multiple gestations (twins, triplets) are an important high-risk group – as seen, they might benefit from the higher dose . For women with prior early-onset preeclampsia (e.g., requiring delivery <34 weeks), consensus is strong to use aspirin in subsequent pregnancies, and our review suggests starting as early as feasible (after confirmation of viable pregnancy) with at least 81 mg, if not 162 mg (two tablets) given the very high recurrence risk.

Lastly, emerging research is exploring biomarkers to better identify who will benefit most from aspirin (for example, uterine artery Doppler indices, placental growth factor levels, etc.). The combination of precision screening and effective prophylaxis (as exemplified by ASPRE) represents a future model of personalized prevention in obstetrics.

DISCUSSION

In this comprehensive review, we examined the evidence on low-dose aspirin for preeclampsia prevention, with a focus on how dose and timing modify its effectiveness. The findings reinforce and extend the guidance that has evolved in the past decade. We found that:

- Aspirin prophylaxis provides a real preventive benefit in pregnant women at elevated risk of preeclampsia. This benefit is most clearly observed in reductions of preterm and severe preeclampsia, outcomes which are most impactful for maternal-fetal health. The prevention of term preeclampsia, while less evident, is of secondary importance since term preeclampsia, though still dangerous, generally has better outcomes than early-onset disease.
- Starting aspirin in early pregnancy (ideally by 12–16 weeks) is associated with greater efficacy than starting later. The biological plausibility and the preponderance of data support early initiation. This doesn't mean starting after 20 weeks has no effect – some late-start trials still show modest reductions – but early start appears to be a key factor in maximizing the effect size. Therefore, risk identification at the first prenatal visit is critical. Our review aligns with PRISMA-guided meta-analyses that found significant risk reductions only in early-start subgroups . Clinically, this underscores the need for obstetric care providers to initiate discussions about aspirin in the late first trimester for those with high-risk profiles (and to consider referrals or screening algorithms that can catch high-risk cases as early as possible).
- A higher aspirin dose (≈150 mg) is likely more effective than 75–81 mg, particularly for preventing preterm preeclampsia in high-risk women. While 81 mg is beneficial and remains the standard recommendation in many places (due to extensive evidence of at least some benefit and long safety track record), the newer evidence showing a two-fold greater risk reduction with 150 mg cannot be ignored. Our review noted that no head-to-head RCT has yet proven 150 mg superior, which is why guidelines have been cautious. Nonetheless, many experts have already embraced higher dosing for those at highest risk (e.g., recommending two baby aspirins nightly). The cohort data from Sweden suggest that in a general population of aspirin users, upping the dose might not drastically change outcomes – but that study also indicates no safety penalty for the higher dose. On the other hand, in twins (a setting of extreme angiogenic stress) the higher dose clearly seemed advantageous . This dichotomy suggests a nuanced approach: an 81 mg dose may suffice for moderate-risk scenarios (e.g., one prior preeclampsia at term, or mild chronic hypertension), whereas 150 mg might be justified for very high-risk scenarios (e.g., prior preeclampsia at <32 weeks, or multiple gestation with additional risks). Notably, in populations with prevalent obesity, some advocate 162 mg to overcome potential aspirin resistance . Ongoing and future trials (such as those by networks in the U.S. and Europe) are expected to directly compare 81 vs 162 mg; their results will hopefully settle this question. Until then, our findings support that more is better up to 150 mg, with the caveat of individualizing treatment.
- Safety of aspirin prophylaxis is reaffirmed. Across RCTs and observational studies, low-dose aspirin – even at 150 mg – did not significantly increase the risk of hemorrhagic complications, and no other consistent harms were seen. This is crucial for risk–benefit considerations. Preeclampsia itself carries substantial risks; thus, even a small benefit of aspirin is valuable if the intervention is essentially harmless. We found that concerns like gastrointestinal irritation or allergy are rare at these doses. Some pregnant patients worry about taking any medication; providing reassurance with data on safety (for both mother and baby) can improve adherence. For instance, explaining that in trials over 30,000 women, aspirin did not lead to more miscarriages or birth defects, and did not cause excessive bleeding at delivery , can be comforting. Our review also highlights that stopping aspirin at 36 weeks (a common practice) is not firmly evidence-based – many clinicians follow it to err on side of caution, but some continue aspirin until labor in very high-risk cases (like those with hypertension in pregnancy) and generally do not encounter problems with neuraxial anesthesia or bleeding .
- Implications for practice: Clinicians (obstetricians, midwives, maternal-fetal medicine specialists) should ensure that all women who meet criteria for aspirin prophylaxis are offered it. Given underutilization rates <50% in high-risk women , there is room for improvement

in implementation. This may involve instituting checklists in early pregnancy, patient education about the benefits of aspirin, and system-level interventions (such as default risk assessment tools in electronic prenatal records). The evidence supports starting by 12 weeks if possible; many providers now initiate at the end of the first trimester visit. If a patient presents later (say at 20 or 24 weeks) and is clearly high-risk, aspirin should still be started – our findings show it can still be beneficial and is certainly better than doing nothing .

- Research gaps: Despite the wealth of data, there remain questions. The optimal dose needs clarification via direct comparison trials – especially to see if 150 mg vs 81 mg yields incremental benefit in a contemporary high-risk cohort. Additionally, identifying which subgroups benefit the most continues to be important. Could low-risk nulliparas with certain biomarkers benefit? (One large trial, ASPIRIN trial in nulliparous women by WHO [12], is ongoing to address broader use.) The role of aspirin in preventing not just preeclampsia but related outcomes like preterm birth and fetal growth restriction in various risk groups could be teased out further. Some have posed whether extending aspirin use postpartum (for those who developed preeclampsia) could improve outcomes like preventing long-term hypertension – but that's beyond prevention in pregnancy per se.
- An interesting point is raised by the discrepancy between aggregate meta-analyses and the IPD meta-analysis on timing . It highlights that how data are analyzed can affect conclusions. Clinicians reading the literature should be aware that one analysis said "before 16 weeks is key" while another said "doesn't matter" – in our discussion, we reconcile this by noting the IPD meta included many lower-dose trials and thus showed a diluted effect, whereas the more selective analyses demonstrated the combined effect of early & adequate dose. Our review's stance, in line with many experts, is that earlier is better, especially if using the standard dose; if one can only start later, consider a higher dose to compensate (though this strategy is not formally proven, it's a logical extrapolation).

In the context of clinical care, these findings support a strong push for aspirin prophylaxis as a standard of care for preeclampsia prevention. It is rare in medicine to have a cheap, simple intervention capable of preventing a life-threatening condition with minimal side effects. Low-dose aspirin in pregnancy is one such intervention. The discussion on dose and timing is essentially about how to maximize this intervention's benefits. Based on current evidence, a reasonable approach is:

- Identify women at high risk (using criteria such as those from USPSTF [13]/ACOG [7]: e.g., prior preeclampsia, multifetal gestation, chronic hypertension, diabetes, kidney disease, autoimmune disease; or multiple moderate risk factors like first pregnancy, obesity, family history, etc.).
- Initiate low-dose aspirin by 12 weeks (or as soon as possible thereafter).
- Use at least 81 mg daily; consider 162 mg (two 81 mg pills) especially if the patient has factors that might attenuate aspirin effect (e.g., BMI >30, or the risk profile is very high).
- Emphasize adherence, perhaps dosing in the evening which might coincide with bedtime routine for better compliance (and potential physiologic benefits).
- Continue aspirin through 36 weeks or until delivery (ensuring it's held at least on the day of delivery or epidural placement to minimize any theoretical bleeding risk, although evidence doesn't mandate stopping early).
- Monitor for preeclampsia signs as usual; aspirin is preventive but not absolutely so – some women will still develop the disease, though hopefully later and milder.

Our review also underscores that observational real-world data support the trial findings, and importantly show that higher-dose aspirin is not causing unexpected harms. This real-world evidence helps in reassuring both clinicians and patients about safety and may guide practice in areas that trials haven't covered (e.g., there likely will never be large trials in twins due to ethical considerations of giving placebo to such a high-risk group, so observational data fill that gap and suggest using higher doses for twins is beneficial).

A limitation of our review is that we relied on published data; we did not conduct a new meta-analysis but synthesized existing ones and key studies. However, by structuring according to PRISMA and including both trial and non-trial evidence, we believe this provides a thorough and up-to-date picture as of 2025. New studies (like the completed but not yet published Chronic Hypertension and Aspirin trial, or various international cohorts) could further refine these conclusions.

CONCLUSION

In conclusion, aspirin prophylaxis is an effective, evidence-based strategy to reduce the incidence of preeclampsia, particularly its most severe manifestations. The dose and timing of aspirin administration are crucial determinants of its prophylactic success. Starting aspirin early in pregnancy (preferably by 16 weeks' gestation) and using doses in the range of 100–150 mg daily are associated with the greatest reductions in preeclampsia risk . Standard low-dose aspirin (75–81 mg) still confers benefit, especially if begun early, and remains the currently recommended regimen in many guidelines for high-risk women . However, emerging data suggest that a regimen of 150 mg (for example, two 81 mg tablets at bedtime) may further improve outcomes, a strategy already adopted in certain high-risk scenarios after the ASPRE trial's success . Crucially, the safety profile of low-dose aspirin in pregnancy is excellent, with no significant increase in bleeding or other adverse effects observed .

For clinicians, these findings support the practice of initiating prophylactic aspirin as early as possible in women at risk for preeclampsia, with attention to ensuring compliance and considering a higher dose for those at highest risk. This approach has the potential to substantially reduce the burden of preeclampsia – translating into fewer preterm births, fewer severe maternal complications, and improved neonatal outcomes. As research continues, we anticipate even more refined recommendations, but current evidence is sufficiently robust to affirm that low-dose aspirin (whether 81 or 150 mg) started in early pregnancy saves lives and should be a cornerstone of antenatal care for preventing preeclampsia and its complications.

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