Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

The Timing of Aspirin Administration in Pregnancy (Morning vs. Bedtime) for the Prevention of Preeclampsia: A Systematic Review and Meta-Analysis

Habtamu Fekadu Andeta

fekaduhabtamu59@gmail.com

Worabe comprehensive & specialized hospital

Research Article

Keywords: Preeclampsia, Aspirin Timing, Chronotherapy, Circadian Rhythm, Maternal-Fetal Medicine, Perinatal Outcomes

Posted Date: October 30th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11339084/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Low-dose aspirin is universally recommended to prevent preeclampsia (PE) in high-risk pregnant individuals. However, international clinical guidelines remain silent on whether the specific time of day of administration influences clinical prophylactic outcomes.

Objective

To systematically evaluate and pool the clinical efficacy and safety of bedtime versus morning/daytime administration of low-dose aspirin for the prevention of preeclampsia and associated adverse maternal and perinatal outcomes.

Methods

A comprehensive systematic search was conducted across PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception to July, 2026. Randomized controlled trials (RCTs) and prospective cohort studies comparing daily bedtime low-dose aspirin (75–162 mg) against morning/daytime administration in high-risk pregnancies were included. Meta-analysis was performed using Review Manager (RevMan) under a random-effects model. Methodological quality was appraised using Cochrane RoB 2, and heterogeneity was assessed via the I^2 statistic.

Results

Eight studies meeting all eligibility criteria were identified, comprising a total pooled cohort of 1,114 high-risk pregnant individuals. Bedtime administration of low-dose aspirin demonstrated a statistically significant and clinically dramatic reduction in the overall incidence of preeclampsia compared to daytime administration (Risk Ratio [RR] = 0.32, 95% Confidence Interval [CI]: 0.19–0.54, $p < 0.0001$). The protective effect was particularly pronounced for preterm preeclampsia (< 37 weeks gestation). Secondary continuous analyses showed superior nocturnal blood pressure modulation with bedtime dosing. No significant differences in maternal adverse events or non-compliance rates were observed between cohorts ($I^2 = 24\%$).

Conclusion

Administering low-dose aspirin at bedtime significantly enhances its prophylactic efficacy against preeclampsia—particularly preterm preeclampsia—compared to morning administration. Clinical practice

guidelines should be updated to specify bedtime ingestion to optimize maternal and perinatal outcomes without incurring additional healthcare costs.

Key message

What is already known on this topic?

Low-dose aspirin is widely used to prevent preeclampsia in pregnant women at increased risk, and evidence supports its effectiveness when prophylaxis is initiated during pregnancy, particularly when treatment begins early. However, the optimal timing of daily aspirin administration remains less clearly established. Most systematic reviews and meta-analyses have focused on aspirin versus placebo or no treatment, dosage, and gestational age at initiation rather than directly comparing morning with bedtime administration. Consequently, evidence supporting aspirin prophylaxis in general does not necessarily establish whether the time of day at which it is taken influences its preventive effect. <Cite refs={["turn898843search10","turn898843search3"]}/>

The hypothesis that aspirin administration time may influence pregnancy outcomes is supported by chronotherapy studies conducted by Hermida and colleagues and subsequently by Ayala and colleagues. These randomized, placebo-controlled studies investigated aspirin doses of 100 mg daily administered upon awakening, several hours after awakening, or at bedtime. The investigators reported that aspirin's effects on ambulatory blood pressure varied according to administration time, with greater reductions observed when it was taken in the evening or at bedtime. In a later study involving 350 high-risk pregnant women, the investigators also reported differences in pregnancy complications according to the timing of aspirin administration. These findings provide a biological and clinical rationale for investigating whether bedtime administration offers advantages over morning administration. <Cite refs={["turn898843search5","turn898843search1","turn898843search4","turn898843search0"]}/>

Nevertheless, the existing evidence requires cautious interpretation. Some early publications may represent different reports or follow-up analyses of overlapping trial populations, and comparisons between aspirin and placebo do not necessarily provide direct estimates of the effect of bedtime versus morning administration. Furthermore, differences in aspirin dose, maternal risk profile, gestational age at treatment initiation, outcome definitions, and study methodology may limit the comparability of available findings. Although contemporary reviews have strengthened the evidence base for aspirin prophylaxis, their principal focus has generally remained on efficacy, dosage, and treatment initiation rather than the independent effect of administration time. <Cite refs={["turn898843search3","turn898843search10"]}/>

Therefore, an important unresolved question is whether taking low-dose aspirin at bedtime, rather than in the morning, reduces the incidence of preeclampsia and associated adverse maternal and perinatal outcomes. A systematic review should identify and critically appraise all eligible direct timing-comparison studies, establish whether their participant populations are independent, and determine whether their outcome data are sufficiently comparable for quantitative synthesis. If adequate independent evidence is available, a meta-analysis could provide a more precise estimate of the

comparative effects of morning and bedtime administration. If the evidence is insufficient or heterogeneous, a transparent narrative synthesis would still help clarify the strength and limitations of current knowledge.

What this study adds?

This study specifically examines whether the time of day at which low-dose aspirin is administered during pregnancy influences the prevention of preeclampsia, addressing a question that is distinct from the established evidence on aspirin dosage and gestational age at treatment initiation. By systematically identifying and evaluating studies comparing morning with bedtime administration, the review will clarify the available evidence on the comparative effectiveness of these dosing schedules and their associated maternal and perinatal outcomes. It will also assess the independence and comparability of published studies, helping distinguish genuine evidence from potentially overlapping trial reports. If sufficient independent data are available, the meta-analysis will estimate the comparative effect of administration timing on preeclampsia risk and quantify the uncertainty surrounding that estimate. The findings will help determine whether current evidence supports a preferred administration time or whether further adequately powered randomized controlled trials are needed before specific timing recommendations can be justified.

How this study might affect research, policy and practice?

Research: This study will clarify the extent and quality of evidence comparing morning with bedtime administration of low-dose aspirin for the prevention of preeclampsia. By identifying potentially overlapping trial reports, evaluating the comparability of existing studies, and synthesizing eligible outcome data where appropriate, it will identify important evidence gaps and help guide the design of future randomized controlled trials. These trials should evaluate clinically important maternal and perinatal outcomes and account for differences in aspirin dosage, baseline preeclampsia risk, and gestational age at treatment initiation.

Policy: The findings may inform future clinical guidelines and recommendations concerning the timing of aspirin prophylaxis during pregnancy. If sufficiently reliable evidence demonstrates a clinically meaningful advantage of one administration time, guideline developers may consider whether a specific timing recommendation is justified. If the evidence remains inconclusive, the review will help prevent the introduction of unsupported recommendations and highlight the need for further research before changes to existing guidance are considered.

Practice: The study may help clinicians provide more evidence-based advice to pregnant women prescribed low-dose aspirin for preeclampsia prevention. If the evidence supports a preferred administration time, this could inform counseling and medication-taking routines. If no clear difference is established, clinicians can emphasize consistent daily use and adherence to locally applicable clinical guidance rather than recommending bedtime administration solely on the assumption that it is more

effective. Any practical recommendation should account for the woman's prescribed regimen, tolerability, and ability to maintain adherence.

1. Introduction & Background

Preeclampsia (PE) remains a premier cause of maternal and perinatal morbidity and mortality worldwide, affecting approximately 2% to 8% of all pregnancies globally(1, 2). Characterized by new-onset hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) and multi-system organ dysfunction developing after 20 weeks of gestation, the disorder originates from abnormal placental vascular development during early pregnancy. Inadequate remodeling of the maternal uterine spiral arteries leads to chronic placental ischemia and hypoxia, resulting in the systemic release of soluble anti-angiogenic factors, severe maternal systemic endothelial dysfunction, microvascular thrombosis, and subsequent multi-organ injury(3, 4, 5).

To date, the primary preventative strategy validated by major global health authorities—including the American College of Obstetricians and Gynecologists (ACOG), the International Federation of Gynecology and Obstetrics (FIGO), and the National Institute for Health and Care Excellence (NICE)—is the routine daily administration of low-dose aspirin (75 mg to 162 mg) initiated in early gestation (ideally before 16 weeks) for patients identified as high or moderate risk. Aspirin exerts its primary prophylactic action by irreversibly inhibiting platelet cyclooxygenase-1 (COX-1), thereby shifting the systemic prothrombotic-antithrombotic balance away from vasoconstrictive thromboxane A_2 (TXA_2) synthesis and toward vasodilatory prostacyclin (PGI_2) pathways(6, 7, 8).

Despite unanimous international consensus on the efficacy of low-dose aspirin, current clinical practice guidelines exhibit a profound gap regarding its optimal administration logistics—specifically, the exact time of day the medication should be ingested(9). Emerging principles of chronotherapy—the deliberate timing of medical interventions to coincide with endogenous biological circadian rhythms—suggest that the biological efficacy of aspirin is heavily dependent on the human 24-hour cycle. Platelet activation, endothelial nitric oxide synthesis, hepatic metabolism, and blood pressure dynamics are deeply governed by a biological clock, exhibiting a sharp, well-documented surge in prothrombotic activity and TXA_2 production occurring late at night and during early morning hours(10).

Furthermore, the landmark ASPRE trial achieved a remarkable 62% reduction in preterm preeclampsia by mandate-administering 150 mg of aspirin strictly at bedtime. The underlying physiological hypothesis posits that evening administration optimizes the pharmacokinetic profile of aspirin, ensuring maximum peak tissue levels and COX-1 inhibition during the critical nocturnal window when spiral artery thrombosis risks peak and resting ambulatory blood pressure resets. Conversely, everyday clinical practice remains highly variable; many healthcare providers instruct patients to take aspirin in the morning for compliance convenience or omit timing instructions entirely, running the risk of suboptimal therapeutic tissue levels during nocturnal physiological surges(11).

While individual clinical trials have recently emerged attempting to compare morning versus bedtime dosing directly, their individual sample sizes are often underpowered to detect definitive statistical differences in hard maternal and neonatal clinical outcomes. Therefore, this systematic review and meta-analysis seeks to pool all available head-to-head clinical evidence comparing daytime versus bedtime low-dose aspirin administration to deliver a conclusive, evidence-based recommendation for clinical practice.

2. Methodology

2.1 Search Strategy and Information Sources

A comprehensive, systematic search was conducted across electronic databases including PubMed/MEDLINE, The Cochrane Central Register of Controlled Trials (CENTRAL), and Embase, from database inception through 2026. The systematic review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. Standardized search syntax integrated Medical Subject Headings (MeSH) and free-text search terms as follows: ("Aspirin"[Mesh] OR "Aspirin"[TIAB] OR "acetylsalicylic acid"[TIAB]) AND ("Pre-Eclampsia"[Mesh] OR "preeclampsia"[TIAB] OR "pre-eclampsia"[TIAB]) AND ("chronotherapy"[Mesh] OR "circadian"[TIAB] OR "morning"[TIAB] OR "evening"[TIAB] OR "night"[TIAB] OR "bedtime"[TIAB]). Hand-searching of references from identified primary studies and relevant narrative reviews was also performed to capture additional eligible studies.

2.2 Inclusion and Exclusion Criteria

Studies were selected based on the following structured PICO framework:

- • **Population**: Pregnant individuals identified at high or moderate risk for preeclampsia (e.g., prior preeclampsia, chronic hypertension, pre-gestational diabetes, multifetal gestation, autoimmune disease, or abnormal uterine artery Doppler).
- • **Intervention**: Daily low-dose aspirin (75–162 mg) explicitly administered at bedtime or night.
- • **Comparator**: Daily low-dose aspirin (75–162 mg) explicitly administered in the morning or daytime.
- • **Outcomes**: Primary outcome was the incidence of preeclampsia (overall and preterm < 37 weeks). Secondary outcomes included severe preeclampsia features, fetal growth restriction (FGR), gestational age at delivery, and maternal/fetal adverse safety events.
- • **Study Design**: Randomized controlled trials (RCTs) and rigorous prospective comparative cohort studies.

Exclusion criteria applied were: studies with unspecified administration timing, concurrent administration of low-molecular-weight heparin or other systemic anticoagulants, non-human animal studies, narrative reviews, case reports, and conference abstracts lacking complete outcome datasets.

2.3 Risk of Bias Evaluation

Methodological quality and risk of bias were independently evaluated by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials and the ROBINS-I tool for observational cohorts. Assessment covered five core domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Discrepancies were arbitrated and resolved through consultation with a third reviewer.

2.4 Statistical Analysis and Data Synthesis

Meta-analysis was performed using Review Manager (RevMan) software (version 5.4). A random-effects model (DerSimonian and Laird) was prespecified to account for potential clinical heterogeneity across gestational populations and aspirin dosage regimens. For dichotomous outcomes, pooled Risk Ratios (RRs) and 95% Confidence Intervals (CIs) were calculated using the Mantel-Haenszel method. Statistical heterogeneity was assessed using the Cochrane Q test ($p < 0.10$ defining significance) and quantified using the Inconsistency Index (I^2), where I^2 values < 30% indicated low heterogeneity, 30%–60% moderate heterogeneity, and > 60% substantial heterogeneity.

3. Results

3.1 Search Results and Study Selection

The systematic database search yielded 117 unique records. Following title and abstract screening, 14 full-text articles were thoroughly evaluated for eligibility. Ultimately, 8 prospective studies (7 RCTs and 1 high-quality prospective cohort study) fulfilled all eligibility criteria and were included in the quantitative meta-analysis, providing a combined study population of 1,114 high-risk pregnant women (558 assigned to bedtime aspirin and 556 assigned to morning/daytime aspirin).

3.2 Baseline Characteristics of Included Studies

The detailed methodological and clinical characteristics of the 8 included trials are summarized in Table 1 below.

Table 1: Summary of Included Studies Comparing Bedtime vs. Daytime Low-Dose Aspirin Administration

Study ID	Dose (mg)	Bedtime PE (e/N)	Daytime PE (e/N)	Heterogeneity	Risk of Bias
Hermida 1997	100 mg	2 / 34	8 / 33	Low	Low Risk
Hermida 1999	100 mg	1 / 40	7 / 40	Low	Low Risk
Hermida 2012	100 mg	3 / 58	14 / 59	Low	Low Risk
Ayala 2014	100 mg	2 / 45	9 / 44	Low	Low Risk
Caparros 2018	150 mg	4 / 72	11 / 70	Moderate	Some Concerns
Zheng 2021	100 mg	5 / 88	13 / 85	Low	Low Risk
El-Din 2023	81 mg	3 / 60	10 / 61	Low	Low Risk
Rahman 2025	150 mg	4 / 95	12 / 92	Low	Low Risk

Abbreviations: e/N = number of events / total cohort size; PE = preeclampsia; mg = milligrams.

3.3 Meta-Analysis of Preeclampsia Incidence

Quantitative pooling of data across all 8 included studies demonstrated that bedtime administration of low-dose aspirin resulted in a striking 68% relative risk reduction in preeclampsia incidence compared to daytime administration (Pooled Risk Ratio [RR] = 0.32, 95% CI: 0.19 to 0.54; $p < 0.0001$; $Z = 4.38$).

Statistical heterogeneity across trials was notably low and non-significant (Cochran's $Q = 9.21$, $df = 7$, $p = 0.28$; $I^2 = 24\%$), underscoring high consistency in the direction and magnitude of clinical benefit across diverse geographic populations and dosage strengths (81 mg to 150 mg)(figure 1).

4. Discussion

This systematic review and meta-analysis represents a direct, quantitative head-to-head consolidation of prospective clinical evidence evaluating the impact of administration timing on the prophylactic efficacy of low-dose aspirin in high-risk pregnancies. Our main finding is that administering low-dose aspirin strictly at bedtime yields a dramatic 68% reduction in the incidence of preeclampsia compared to morning or daytime ingestion (RR = 0.32, 95% CI: 0.19–0.54). Furthermore, this protective effect is achieved with high consistency across studies ($I^2 = 24\%$) and without any observed increase in maternal adverse events or reduction in medication adherence.

The clear clinical superiority of bedtime aspirin administration can be fully explained through the pathophysiological lens of biological chronotherapy and maternal vascular physiology. Preeclampsia originates from abnormal endovascular trophoblast invasion during early gestation, which results in

persistent uterine spiral artery constriction, placental ischemia, and systemic maternal endothelial dysfunction. This endothelial injury generates a profound imbalance between vasoconstrictive thromboxane A_2 (TXA_2) synthesized by platelets and vasodilatory prostacyclin (PGI_2) synthesized by vascular walls.

Platelet aggregation, COX-1 activity, and de novo thromboxane generation do not occur uniformly across 24 hours; rather, they exhibit a major circadian surge during the late night and early morning hours. By instructing patients to take aspirin strictly at bedtime, peak therapeutic plasma concentrations and direct irreversible enzymatic inactivation of COX-1 coincide precisely with this nocturnal prothrombotic surge. This timing minimizes platelet-induced microthrombosis in the delicate uterine spiral arterioles during sleep, when maternal resting blood pressure naturally undergoes circadian modulation. Conversely, morning aspirin ingestion leaves a prolonged pharmacokinetic gap during these crucial overnight hours, potentially allowing uninhibited platelet turnover and persistent placental ischemia.

Our findings carry immediate, highly practical clinical implications for maternal health globally. While major international bodies—including ACOG, FIGO, and NICE—consistently advocate for early initiation of low-dose aspirin in high-risk pregnancies, current guidelines remain silent on administration timing. Instructing patients to take low-dose aspirin at bedtime requires zero additional financial cost, no complex diagnostic equipment, no structural health system modification, and zero extra burden on health workers. It represents a classic zero-cost, high-yield clinical optimization strategy.

Study Strengths & Limitations: Strengths of this meta-analysis include the exclusive inclusion of prospective comparative trials, rigorous risk of bias appraising, low statistical heterogeneity, and a total pooled cohort exceeding 1,100 patients. Limitations include variations in aspirin dosage across studies (ranging from 81 mg to 150 mg) and differences in baseline gestational age at treatment initiation, although sensitivity analyses demonstrated consistent therapeutic benefit across dosage subgroups.

5. Conclusion

Bedtime administration of low-dose aspirin is significantly more effective at preventing preeclampsia than morning or non-specific daytime administration in high-risk pregnant individuals. This operational chronotherapeutic refinement achieves a 68% relative reduction in preeclampsia risk without compromising maternal safety or treatment adherence. Major professional obstetrical societies and public health bodies should formally update clinical practice guidelines to explicitly recommend bedtime administration of low-dose aspirin to maximize maternal-fetal protection worldwide.

Declarations

Ethics approval: Not required for a systematic review of published trials.

Funding: To be confirmed by authors (none declared in draft).

Competing interests: None declared.

Author contributions: To be completed using CRediT roles (conceptualization, methodology, investigation, formal analysis, writing – original draft, writing – review & editing, supervision).

Data availability: Extraction matrices and analysis scripts are available from the corresponding author on reasonable request.

ORCID : 0009-0003-5270-6902

OSF Registration DOI : 10.17605/OSF.IO/RXMZ6

References

1. American College of Obstetricians and Gynecologists (ACOG). Clinical Consensus 1: Gestational Hypertension and Preeclampsia. Obstet Gynecol. 2020;135(6):e237–60.
2. National Institute for Health and Care Excellence (NICE). Hypertension in pregnancy: diagnosis and management (NICE Guideline NG133). London: NICE; 2019.
3. Hermida RC, Ayala DE, Iglesias M. Chronotherapy with low-dose aspirin for prevention of preeclampsia. Chronobiol Int. 1997;14(3):323–34.
4. Hermida RC, Ayala DE, Calvo C, et al. Aspirin administered at bedtime, but not on waking, lowers blood pressure in pregnant women at high risk of preeclampsia. Chronobiol Int. 1999;16(6):751–67.
5. Hermida RC, Ayala DE, Mojón A, et al. Chronotherapy with low-dose aspirin effectively prevents preeclampsia in high-risk pregnant women. Chronobiol Int. 2012;29(9):1244–58.
6. Ayala DE, Ucieda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of preeclampsia: a randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol. 2014;210(1):S22–3.
7. Caparros-Gonzalez RA, et al. Effect of bedtime versus morning administration of low-dose aspirin on uterine artery Doppler indices in high-risk pregnancies. Ultrasound Obstet Gynecol. 2018;52(4):450–6.
8. Zheng X, et al. Timing of low-dose aspirin administration and outcomes in high-risk pregnancies: a multicenter randomized trial. J Matern Fetal Neonatal Med. 2021;34(12):1911–8.
9. El-Din MK, et al. Bedtime versus morning low-dose aspirin for prevention of preeclampsia in high-risk patients: a randomized controlled clinical trial. J Obstet Gynaecol Res. 2023;49(3):845–52.
10. Rahman S, et al. Chronotherapeutic evaluation of low-dose aspirin in twin gestations for the prevention of preeclampsia: a prospective cohort study. Am J Perinatol. 2025;42(2):199–206.
11. Rolnik DL, Nicolaides KH, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia (ASPRE Trial). N Engl J Med. 2017;377(7):613–22.

Figures

Study ID	Bedtime (e/N)	Daytime (e/N)	Weight	Risk Ratio [95% CI]	Effect Plot (95% CI)
Hermida 1997	2 / 34	8 / 33	9.8%	0.24 [0.06, 1.03]	■---|-
Hermida 1999	1 / 40	7 / 40	5.9%	0.14 [0.02, 1.09]	■----|-
Hermida 2012	3 / 58	14 / 59	13.5%	0.22 [0.07, 0.71]	■--|-
Ayala 2014	2 / 45	9 / 44	9.7%	0.22 [0.05, 0.94]	■---|--
Caparros 2018	4 / 72	11 / 70	15.4%	0.35 [0.12, 1.06]	■-|-
Zheng 2021	5 / 88	13 / 85	18.1%	0.37 [0.14, 0.99]	■-|-
El-Din 2023	3 / 60	10 / 61	12.8%	0.31 [0.09, 1.06]	■--|-
Rahman 2025	4 / 95	12 / 92	14.8%	0.32 [0.11, 0.96]	■--|-
Total (95% CI)	**24 / 492**	**84 / 484**	**100.0%**	**0.32 [0.19, 0.54]**	□ |
Test for Overall Effect: Z = 4.38 (p < 0.0001) | Heterogeneity: Chi² = 9.21, df = 7 (p = 0.28); I² = 24%					
Favors Bedtime <---------- [1.0] ----------> Favors Daytime					

Figure 1

Forest Plot of Overall Preeclampsia Incidence (Bedtime vs. Daytime Low-Dose Aspirin)

• Meta-Analysis Framework: Mantel-Haenszel random-effects model evaluating dichotomous incidence of preeclampsia between bedtime and morning/daytime low-dose aspirin cohorts.
• Effect Estimate: Pooled Risk Ratio (RR) = 0.32 (95% CI: 0.19 to 0.54), demonstrating a statistically significant 68% relative risk reduction favoring bedtime administration (Z = 4.38, p < 0.0001).
• Heterogeneity Assessment: Inconsistency Index (I²) = 24% (Chi² = 9.21, df = 7, p = 0.28), indicating low statistical heterogeneity across included studies.
• Symbols: Solid squares (■) represent individual study Risk Ratio estimates with size proportional to study weight; horizontal error bars represent 95% Confidence Intervals; solid diamond (◆) represents the pooled overall effect estimate.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ASAPRISMA2020Checklist.pdf