From Risk Identification to Real-World Prevention of Preeclampsia: A Scoping Review of Aspirin Prophylaxis, Screening Strategies, Treatment Optimization, and Implementation Gaps

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Abstract

Preeclampsia remains a major cause of maternal and perinatal morbidity, and low-dose aspirin is the most established pharmacological preventive strategy for pregnancies at increased risk. However, preventive benefit depends on more than drug prescription. This scoping review mapped the evidence from risk identification through aspirin optimization and real-world implementation. Scopus was searched using a predefined TITLE-ABS-KEY strategy combining low-dose aspirin, preeclampsia, pregnancy, and prevention terms. Of 494 records identified, 35 studies were included in the core evidence map after temporal, document-type, language, and topical screening. Evidence was charted across four domains: risk identification and screening; aspirin dose, timing, adherence, and biological responsiveness; maternal, fetal, neonatal, and safety outcomes; and implementation barriers and facilitators. Clinical risk-factor approaches were accessible but variably sensitive, whereas multimodal strategies incorporating mean arterial pressure, uterine artery Doppler, placental growth factor, pregnancy-associated plasma protein-A, and individualized competing-risks models generally improved risk stratification. Aspirin regimens ranged from approximately 60–81 mg to 150–162 mg, with emerging evidence that earlier initiation, adherence, obesity, baseline vascular risk, and pharmacodynamic response may modify benefit. Reported outcomes extended beyond preeclampsia to preterm birth, fetal growth, postpartum hypertension, and bleeding, with substantial heterogeneity across populations and study designs. Real-world studies repeatedly documented missed eligibility, under-prescription, delayed initiation, nonadherence, and health-system constraints, although structured screening, counseling, checklists, and integrated screen-and-prevent pathways improved uptake in several settings. The evidence therefore supports conceptualizing aspirin prophylaxis as a multistage prevention pathway rather than an isolated medication intervention. Future work should integrate phenotype-specific risk stratification, comparative dosing, standardized adherence measurement, biological response, cost, equity, and pragmatic implementation to translate established efficacy into reliable population-level prevention.

Keywords: preeclampsia; low-dose aspirin; risk stratification; pregnancy screening; implementation science

1. Introduction

Preeclampsia is a multisystem hypertensive disorder of pregnancy whose clinical consequences extend from maternal end-organ injury to fetal growth impairment, indicated preterm birth, neonatal morbidity, and death. Contemporary classifications emphasize that the syndrome is heterogeneous in onset, severity, and organ involvement, and that its causes are not reducible to a single pathway. This heterogeneity is clinically important because the burden of disease is concentrated among women with recognizable maternal, obstetric,

cardiovascular, metabolic, autoimmune, and placental risk profiles, yet severe disease may also arise in pregnancies without obvious antecedent risk. International guidance consequently places prevention and early recognition alongside diagnosis and acute management. (Brown et al., 2018; Magee et al., 2022; Steegers et al., 2010; Mol et al., 2016; Akbar et al., 2026) Low-dose aspirin has become the most established pharmacological prevention strategy for women at increased risk, supported by randomized trials, meta-analyses, and professional recommendations. However, the practical question has evolved beyond whether aspirin can reduce preeclampsia: contemporary care must determine who should receive prophylaxis, how early risk should be identified, what aspirin exposure is sufficient, how residual risk should be monitored, and how prevention can be implemented consistently in routine antenatal systems. (Rolnik et al., 2017; Henderson et al., 2021; US Preventive Services Task Force, 2021; Atallah et al., 2017)

Risk identification remains the entry point to this prevention pathway. Traditional approaches classify women using maternal history and clinical factors such as previous preeclampsia, chronic hypertension, diabetes, renal or autoimmune disease, multifetal pregnancy, nulliparity, obesity, advanced maternal age, and family history. These strategies are simple and scalable, but their sensitivity and concordance with empirical risk vary. In the supplied evidence, guideline-defined “major” and “moderate” risk factors were not uniformly aligned with the strength of association in the underlying evidence, and clinical risk lists performed particularly poorly in some nulliparous populations. (Elawad et al., 2024; Al-Rubaie et al., 2018; Al-Rubaie et al., 2020) At the same time, obesity, pregestational diabetes, assisted reproduction, multifetal gestation, chronic hypertension, and autoimmune disease create distinctive risk contexts that may not be interchangeable biologically or operationally. (Creanga et al., 2023; Irani et al., 2023; Ghidini et al., 2022; Duffy, 2021; Maxwell et al., 2019) The implication is that eligibility for aspirin is not merely a checklist exercise; it is a risk-classification problem in which the choice of threshold changes both the number treated and the proportion of future cases captured.

This limitation has driven the development of individualized and multimodal prediction. First-trimester strategies increasingly combine maternal factors with mean arterial pressure, uterine artery Doppler pulsatility, placental growth factor, pregnancy-associated plasma protein-A, and related biomarkers, while later-gestation models can incorporate fetal size and updated hemodynamic measurements. (Poon et al., 2019; Lourenço et al., 2020; Loussert et al., 2025; Adjahou et al., 2025; Aviram et al., 2025) In the evidence mapped here, the Fetal Medicine Foundation competing-risks approach frequently outperformed or complemented clinical-risk models, and biomarker-enriched screening could materially reduce the screen-positive rate required to detect severe early disease. (Cristofor et al., 2026; Gupta and Gupta, 2026; Duong et al., 2025) Yet higher predictive performance is not synonymous with universal feasibility. Screening models that depend on PlGF assays, standardized blood-pressure measurement, uterine artery Doppler expertise, quality assurance, and integrated risk calculators impose resource and workflow requirements that may be difficult to sustain outside specialized settings. The central issue is therefore not simply whether multimodal screening is more accurate, but whether its additional information translates into timely prophylaxis and improved outcomes across different health systems.

Aspirin itself is also a heterogeneous intervention. “Low dose” spans regimens from approximately 60–81 mg to 100–150 mg and, increasingly, 162 mg in some settings. Major guidelines differ in dose, initiation window, and eligibility criteria, while trial evidence suggests that the timing of initiation and baseline risk may modify benefit. (Horgan et al., 2023; ACOG Committee Opinion No. 743, 2018; Roberge et al., 2017; Roberge et al., 2018a; Van Doorn et al., 2021) The ASPRE trial established a clinically influential screen-and-

prevent paradigm using 150 mg initiated at 11–14 weeks among women at high risk for preterm preeclampsia, whereas newer comparative studies test whether 162 mg provides additional benefit over 81 mg, particularly in obesity. (Rolnik et al., 2017; Amro et al., 2025; Ayyash et al., 2024) Pharmacodynamic evidence strengthens the rationale for moving beyond a one-size-fits-all exposure: class III obesity has been associated with incomplete thromboxane suppression under lower-dose regimens, while newer work continues to investigate whether dose adjustment can overcome obesity-related pharmacokinetic and pharmacodynamic disadvantages. (Finneran et al., 2019; Karaduman et al., 2026) These findings make dose, gestational age at initiation, treatment duration, administration timing, adherence, and biological responsiveness separate dimensions of "aspirin prophylaxis" that should not be collapsed into a single binary exposure.

The clinical outcome literature is similarly multidimensional. Preeclampsia at any gestational age is only one relevant endpoint; preterm and early-onset disease, severe features, fetal growth restriction, small-for-gestational-age birth, spontaneous and indicated preterm birth, postpartum hypertension, maternal bleeding, placental abruption, and neonatal outcomes all contribute to the benefit–harm profile. (Henderson et al., 2021; Roberge et al., 2018b; Berger et al., 2021; Christenson et al., 2023) Studies in women with diabetes, obesity, chronic hypertension, autoimmune disease, inflammatory bowel disease, thrombophilia, and previous placental complications illustrate that the same aspirin regimen may be embedded in very different baseline-risk and co-treatment environments. (Do et al., 2021; Bruno et al., 2023; Asiimwe et al., 2025; Memel et al., 2025; Akinshina et al., 2018; Borella et al., 2023; Mecacci et al., 2019) This diversity is important for a scoping review because apparently conflicting results may reflect differences in phenotype, risk selection, exposure, adherence, concomitant therapy, outcome definition, or study design rather than a simple contradiction about whether aspirin "works."

A further problem emerges after eligibility is established: recommended prophylaxis is frequently not delivered. Studies from urban US systems, Israel, Ethiopia, Brazil, Nigeria, and other settings document under-prescription, delayed initiation, imperfect patient adherence, gaps in provider knowledge, and variable understanding of prevention. (Ayyash et al., 2023; Ganem et al., 2025; Bekele et al., 2024; Jardine et al., 2025; Mahmoud et al., 2025; Martinez-King et al., 2024) Patient-facing information itself may omit or inconsistently communicate aspirin prevention, while digital tools and structured counseling pathways have been explored to improve awareness and uptake. (Geissler et al., 2023; Krishnamurti et al., 2021) In resource-constrained settings, these individual-level barriers are compounded by late antenatal attendance, limited diagnostic capacity, medicine availability, workforce constraints, and the difficulty of implementing technology-intensive screening. (Kupka et al., 2024; Minckas et al., 2025; Ekawati et al., 2021; Escobar et al., 2024) Thus, pharmacological efficacy can be attenuated at multiple stages before a patient ever receives an adequate preventive exposure.

Real-world implementation studies underscore this distinction between efficacy and effectiveness. Programs that combine early screening, risk communication, aspirin prescribing, and follow-up can achieve high uptake and favorable clinical outcomes, yet population-wide implementation has not always reproduced the magnitude of benefit seen in selected high-risk trial populations. (Badr et al., 2026; Minopoli et al., 2026; Mans-Gallart et al., 2026; Nguyen-Hoang, 2024; Okun et al., 2024) Such findings suggest a cascade in which attrition can occur during risk assessment, eligibility determination, prescription, initiation, persistence, adherence, biological response, and follow-up. They also caution against interpreting a negative implementation study as proof that aspirin lacks efficacy, or interpreting an effective drug trial as proof that a health system can deliver the same benefit without addressing workflow and adherence.

Accordingly, this scoping review maps aspirin-based prevention of preeclampsia as an integrated risk-to-prevention pathway rather than as a single intervention comparison. The review asks six linked questions: how women at increased risk are identified; which clinical, biomarker, Doppler, and algorithmic screening strategies guide prophylaxis; which doses, initiation periods, durations, adherence measures, and biological-response determinants have been studied; which maternal, fetal, neonatal, and safety outcomes are reported; which provider-, patient-, institutional-, and health-system factors shape real-world implementation; and where the principal evidence gaps remain. The scientific contribution is therefore an evidence map connecting risk identification to treatment optimization and implementation feedback. This framing is intended to explain why strong evidence for aspirin benefit can coexist with persistent preeclampsia burden, residual risk in treated women, and large missed opportunities in routine care. (Copel et al., 2020; Lee et al., 2024; Del Pozzo et al., 2026; Chung et al., 2019)

This pathway perspective also creates a more disciplined interpretation of novelty. The present review does not attempt to replace systematic review or meta-analysis of a narrowly specified aspirin effect; rather, it charts the interacting evidence objects that determine whether prophylaxis becomes prevention in practice. That distinction matters in a field where randomized efficacy, guideline eligibility, predictive performance, pharmacological responsiveness, and implementation outcomes are often reported in separate literatures. By bringing these strands together, the review can identify where evidence is mature enough for focused synthesis and where further mapping, validation, pragmatic trials, or implementation research is still required. (Munn et al., 2018; Peters et al., 2024; Henderson, 2017)

2. Methods

2.1 Search Strategy

This review was designed as a scoping review because the objective was to map the breadth, characteristics, and interconnections of evidence on preeclampsia risk identification, aspirin prophylaxis, treatment optimization, clinical outcomes, and implementation rather than to estimate a single pooled treatment effect. The methodological approach was informed by the staged scoping-study framework of Arksey and O'Malley, subsequent refinements by Levac and colleagues, JBI guidance for scoping reviews, and the PRISMA extension for scoping reviews (PRISMA-ScR). (Arksey and O'Malley, 2005; Levac et al., 2010; Munn et al., 2018; Peters et al., 2024; Tricco et al., 2018) The Population–Concept–Context logic was used to maintain alignment between the review question, eligibility criteria, data charting, and thematic synthesis.

Scopus was the primary bibliographic database. The final search was conducted using the TITLE-ABS-KEY fields and the following Boolean string: ("low-dose aspirin" OR aspirin prophylaxis) AND ("preeclampsia" OR "pre-eclampsia") AND (pregnancy OR pregnant women OR obstetric*) AND (prevention OR prophylaxis). The search intentionally combined the pharmacological exposure, target disorder, obstetric population, and preventive function. The compiled screening record indicates that 494 records were identified. Records older than 2017 were excluded at the first filtering stage (n=169), leaving 325 reports for subsequent eligibility processing. Article-type and English-language filtering yielded 211 candidate reports, of which 176 were excluded as out of scope; 35 studies were retained for the core evidence map and Tables 1–4. The review therefore emphasizes contemporary evidence while retaining older methodological and seminal supporting literature when needed to interpret the field.

2.2 Eligibility Criteria

Eligible sources involved pregnant women or obstetric populations and examined aspirin used, recommended, or considered for prevention of preeclampsia. Studies were included when they addressed at least one part of the risk-to-prevention pathway: maternal risk factors or eligibility criteria; prediction models; biochemical or biophysical markers; Doppler screening; aspirin dose, initiation, duration, administration schedule, adherence, or biological responsiveness; maternal, fetal, neonatal, or safety outcomes; prescribing practices; implementation strategies; or barriers and facilitators. The intentionally broad design accommodated randomized trials, observational cohorts, prediction studies, implementation studies, qualitative studies, guideline-related analyses, and evidence syntheses. This heterogeneity reflects the review question itself and is consistent with the use of scoping methodology for fields in which research conduct and evidence objects differ substantially. (Collee et al., 2024; Mone et al., 2018; Meiri et al., 2026; McLaughlin et al., 2022; Krishnamurti et al., 2021)

Sources were excluded when aspirin use was unrelated to preeclampsia prevention, the population was nonpregnant, aspirin was used solely for another indication without relevant prevention information, or the publication lacked sufficient Population–Concept–Context relevance. Non-scientific sources and duplicates were excluded. Animal or laboratory studies were not treated as core clinical evidence in Tables 1–4, although selected mechanistic studies were retained as supporting literature for the theoretical background when they directly informed aspirin pharmacology or disease biology. This distinction prevented mechanistic evidence from being conflated with clinical effectiveness.

2.3 Screening, Selection, and Critical-Appraisal Considerations

Records were screened sequentially at title/abstract and full-text levels against the predefined criteria. The compiled PRISMA record shows no duplicate removal, automation exclusion, or retrieval failure. Following the year filter, 325 reports were assessed through document-type, language, and topical eligibility steps, resulting in 35 included studies. Reasons for full-text exclusion were recorded as out of scope in the compiled review file. The screening process is summarized in Figure 1. Consistent with scoping-review methodology, no formal risk-of-bias score was used to exclude otherwise eligible evidence because the purpose was to characterize the landscape rather than adjudicate a pooled causal effect. Nevertheless, study design, sample size, comparator structure, exposure measurement, and major interpretive limitations were charted and considered during synthesis. This was particularly important because the evidence includes randomized dose comparisons, retrospective cohorts, prospective implementation studies, qualitative studies, and mixed-methods research, each of which supports different forms of inference. (Amro et al., 2025; Mahmoud et al., 2025; Asiimwe et al., 2026; Ekawati et al., 2021)

2.4 Data Charting and Evidence Synthesis

A standardized charting framework captured author and year, country and healthcare setting, design, sample size, population and risk profile, risk-identification strategy, biomarkers or biophysical markers, aspirin eligibility criteria, dose, gestational age at initiation, duration and administration, adherence or compliance assessment, biological-response indicators, maternal outcomes, fetal and neonatal outcomes, bleeding or other adverse events, provider-level factors, patient-level factors, health-system barriers and facilitators, and principal findings. Exposure measurement was interpreted cautiously because over-the-

counter aspirin use can be incompletely captured in administrative data, making documented prescription an imperfect proxy for actual medication exposure. (Tailor et al., 2024)

Evidence was synthesized descriptively and thematically into four domains aligned with the review's core argument: (1) risk identification and screening; (2) aspirin treatment optimization; (3) maternal, fetal, neonatal, and safety outcomes; and (4) real-world implementation and evidence-to-practice gaps. Studies could contribute to more than one domain when substantively relevant. Across the four result tables there were 40 study entries representing 35 unique references. Quantitative results were reported as presented in the source studies without meta-analysis, and conflicting results were retained rather than statistically reconciled. This approach preserves the epistemic function of a scoping review: to show the distribution, heterogeneity, and gaps of the evidence base and to identify questions that may warrant subsequent focused systematic review or pragmatic evaluation.

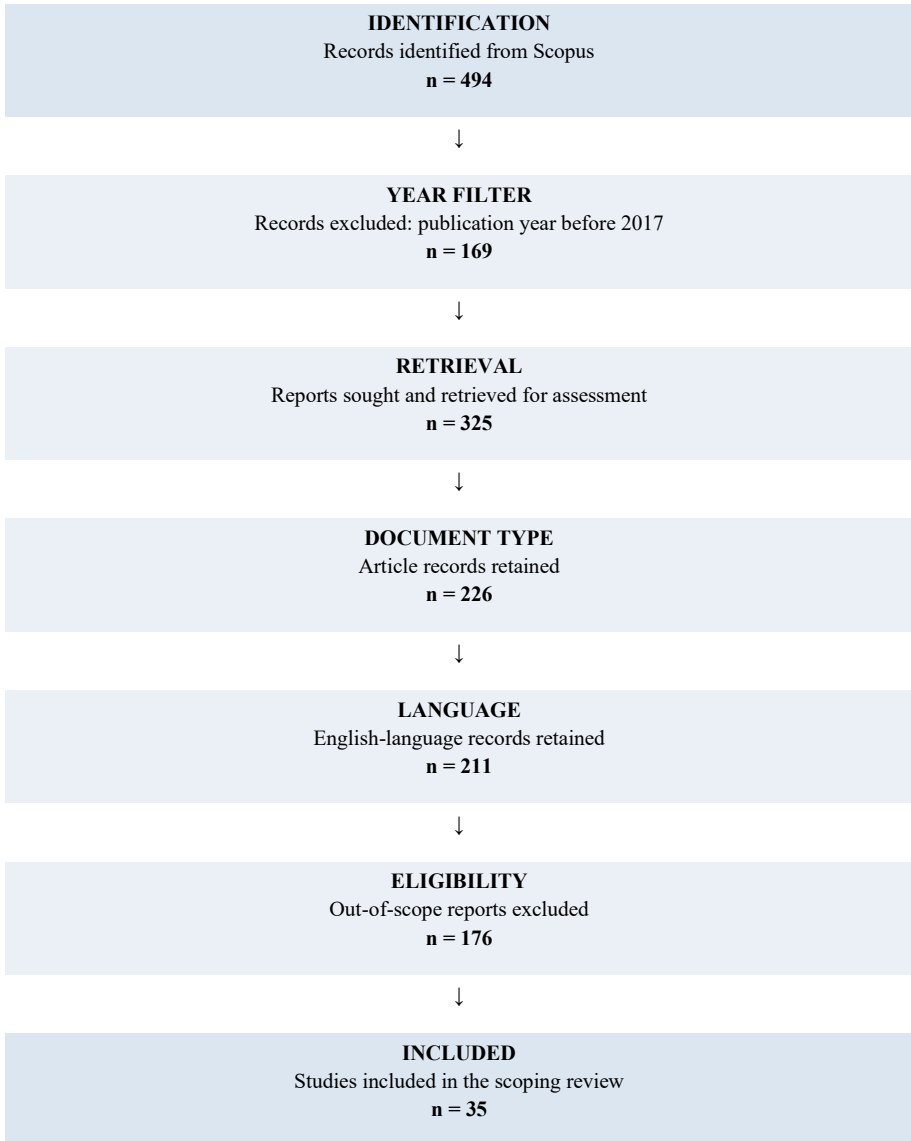

Figure 1. PRISMA-ScR flow of study identification and selection

No duplicates, automation exclusions, or retrieval failures were recorded. Search: TITLE-ABS-KEY ("low-dose aspirin" OR aspirin prophylaxis) AND ("preeclampsia" OR "pre-eclampsia") AND (pregnancy OR pregnant women OR obstetric) AND (prevention OR prophylaxis).*

3. Theoretical Background

3.1 Biological and Clinical Foundations of Risk-Stratified Aspirin Prevention

Preeclampsia is best understood as a heterogeneous syndrome arising from interactions among placental development, maternal vascular adaptation, endothelial function, inflammation, coagulation, and pre-existing cardiometabolic or immune susceptibility. Classical models emphasize abnormal trophoblast invasion and

impaired remodeling of the spiral arteries, leading to reduced uteroplacental perfusion and placental stress, followed by systemic endothelial dysfunction and the clinical maternal syndrome. (Steegers et al., 2010; Mol et al., 2016; Moncrieff, 2018; Mayrink et al., 2018) This framework helps explain why early-onset and preterm disease often display a strong placental phenotype, whereas later disease may reflect a larger contribution from maternal cardiovascular reserve and metabolic vulnerability. Obesity, chronic hypertension, diabetes, lupus, antiphospholipid-related disease, and multifetal pregnancy therefore represent more than administrative risk categories; they can mark biologically distinct pathways converging on a common clinical diagnosis. (Creanga et al., 2023; Mecacci et al., 2019; Irani et al., 2023; Duffy, 2021)

Aspirin is theoretically attractive because low doses preferentially inhibit platelet cyclooxygenase-1 and thromboxane A2 production, shifting the thromboxane–prostacyclin balance away from vasoconstriction and platelet aggregation. This mechanism is compatible with a disease characterized by placental malperfusion, platelet activation, and endothelial disturbance. (Atallah et al., 2017; Roberge et al., 2017; Duley et al., 2019) Experimental work further suggests that aspirin can affect vascular tone through endothelial-derived hyperpolarizing mechanisms, while clinical platelet studies show that hypertensive disorders are associated with altered platelet size and immaturity. (Helgadóttir et al., 2021; Griffin et al., 2025) These findings do not establish a single causal mechanism, but they support a broader model in which aspirin may influence platelet, vascular, and placental pathways simultaneously.

The timing hypothesis follows directly from placental biology. If aspirin modifies processes involved in implantation, trophoblast invasion, spiral-artery remodeling, or early placental vascular adaptation, initiation during the first trimester should plausibly produce a different effect from initiation after placentation is more advanced. The influential ASPRE strategy operationalized this logic by identifying high-risk women at 11–14 weeks and providing 150 mg nightly until 36 weeks. (Rolnik et al., 2017; Poon et al., 2019) Meta-analyses have repeatedly examined whether earlier initiation and higher dose are associated with larger reductions in preterm preeclampsia and fetal growth restriction, although the magnitude and consistency of timing effects vary with study selection and analytic approach. (Roberge et al., 2017; Roberge et al., 2018a; Meher et al., 2017; Van Doorn et al., 2021) The relevant theoretical point is not that a single threshold such as 16 weeks is mechanistically absolute, but that gestational timing is part of effective exposure.

Biological responsiveness also varies. Incomplete thromboxane suppression among women with class III obesity suggests that a fixed dose may not yield equivalent platelet inhibition across body size and metabolic states. (Finneran et al., 2019; Karaduman et al., 2026) Pregnancy itself changes volume of distribution, renal clearance, platelet turnover, and drug handling, and the dose required to achieve a consistent pharmacodynamic response may therefore differ from that in nonpregnant adults. The emerging precision-prophylaxis question is whether dose should be calibrated to phenotype, weight, baseline risk, pharmacodynamic response, or a combination of these factors. Higher-dose comparative trials and dose meta-analyses provide suggestive evidence but not yet a universal dosing rule. (Amro et al., 2025; Ayyash et al., 2024; Seidler et al., 2018; Kupka et al., 2025)

3.2 Evolution from Clinical Risk Factors to Multimodal Screen-and-Prevent Strategies

The earliest prevention architecture was essentially categorical: identify one or more recognized maternal or obstetric risk factors and prescribe aspirin. This remains attractive because it requires no specialized laboratory or imaging infrastructure. Yet risk-list approaches treat heterogeneous factors as if their predictive contributions were easily additive, and their sensitivity depends heavily on the chosen definitions and

thresholds. (ACOG Committee Opinion No. 743, 2018; Al-Rubaie et al., 2018; Elawad et al., 2024) A woman with chronic hypertension, a woman with prior preeclampsia, and a nulliparous woman with obesity may all qualify for aspirin, but their absolute risks and pathophysiological routes to disease can differ markedly.

Multimodal screening attempts to resolve this limitation by integrating maternal factors with continuous biophysical and biochemical variables. Mean arterial pressure reflects maternal vascular state; uterine artery pulsatility captures impedance in the uteroplacental circulation; PlGF and PAPP-A provide information about placental function; and competing-risks models combine these domains into an individualized probability of preeclampsia requiring delivery before a specified gestational age. (Poon et al., 2019; Lourenço et al., 2020; Loussert et al., 2025; Gupta and Gupta, 2026) Machine-learning models have also been tested, but conventional competing-risks approaches remain highly competitive when they incorporate clinically meaningful biomarkers. (Cristofor et al., 2026; Meiri et al., 2026) Importantly, multimodal screening is not only a prediction exercise: its clinical value depends on whether risk classification triggers an effective preventive action early enough to alter the disease trajectory.

The screen-and-prevent model therefore links three stages: early measurement, risk estimation, and prophylactic action. Prospective and implementation studies have shown that such pathways can achieve high screening acceptance and high aspirin initiation among screen-positive women. (Nguyen-Hoang, 2024; Okun et al., 2024; Minopoli et al., 2026) Yet population effectiveness depends on more than model discrimination. PlGF assays, standardized Doppler acquisition, blood-pressure calibration, algorithm access, counseling, prescribing authority, and follow-up must all be available. In lower-resource environments, a simpler maternal-factor plus blood-pressure strategy may produce greater practical benefit than a technically superior model that cannot be delivered reliably. (Kupka et al., 2024; Minckas et al., 2025)

3.3 The Aspirin Prevention Paradox: Heterogeneous Response and Unresolved Clinical Debates

The central paradox is that aspirin can be both evidence-based and incompletely effective. Some women remain at high risk despite early treatment, while population implementation may fail to reproduce trial-level benefit. Residual disease can reflect irreversible or aspirin-insensitive biology, insufficient drug exposure, imperfect adherence, late initiation, misclassification of risk, or competing pathways such as chronic vascular disease, inflammation, or autoimmune activity. (Baschat et al., 2018; Lee et al., 2024; Mans-Gallart et al., 2026) Studies of chronic hypertension, lupus, thrombophilia, and previous placenta-mediated complications illustrate why antiplatelet therapy may be only one component of management. (Monari et al., 2021; Llurba et al., 2020; Lecarpentier et al., 2018; Akinshina et al., 2018; Borella et al., 2023; Garufi et al., 2026)

This paradox also explains current debates over 81 mg versus 150–162 mg, universal versus targeted prophylaxis, and clinical-risk versus biomarker-based screening. Higher dose may improve platelet inhibition in some patients, but dose escalation does not address missed eligibility, late booking, nonadherence, or aspirin-insensitive disease. (Horgan et al., 2023; Asiimwe et al., 2025; Bij de Weg et al., 2025) Conversely, universal prescribing may simplify eligibility but exposes more low-risk women to medication and may dilute attention to risk-specific surveillance. Decision analyses and guideline frameworks therefore treat prevention as a balance among absolute disease risk, expected benefit, medication burden, safety, and feasibility. (Wright et al., 2022; US Preventive Services Task Force, 2021) The theoretical framework adopted in this review consequently spans biological, clinical, behavioral, and health-system levels: aspirin efficacy is necessary, but real-world prevention emerges only when the entire pathway functions coherently.

This multilevel perspective is also useful for interpreting apparently discordant endpoints. Reduction in preterm disease, for example, can coexist with persistent term disease, altered fetal-growth distributions, or unchanged outcomes in a specific comorbidity. Such patterns should be treated as evidence of heterogeneity to be explained, not automatically as evidence that one study invalidates another. (Do et al., 2021; Chen et al., 2025; Henderson et al., 2021)

4. Results

4.1 Identifying Who Should Receive Aspirin: Risk Factors, Prediction Models, and Multimodal Screening

The included evidence demonstrates a clear transition from categorical risk-factor screening toward individualized multimodal prediction (Table 1). The ACOG framework operationalizes eligibility through recognized high-risk and moderate-risk factors and recommends 81 mg/day between 12 and 28 weeks, optimally before 16 weeks. (ACOG Committee Opinion No. 743, 2018) However, when NICE and USPSTF risk lists were evaluated against individual-participant data from 4,524 women, sensitivity was limited, especially among nulliparous women; the NICE approach identified only 8.9% of nulliparous preeclampsia cases while maintaining 97.2% specificity. (Al-Rubaie et al., 2018) A Western Sydney model converted routinely available maternal characteristics into individualized absolute risk, but its discrimination remained modest (c-statistic 0.70) and it did not clearly outperform the NICE approach. (Al-Rubaie et al., 2020)

The more recent literature increasingly adds continuous biophysical and biochemical variables. In 134,443 pregnancies assessed at 19–24 weeks, adding uterine artery pulsatility index to maternal factors, estimated fetal weight, and mean arterial pressure markedly reduced the screen-positive rate required to achieve high detection of early disease. (Adjahou et al., 2025) A technical update similarly concluded that isolated serum markers are inadequate as stand-alone screening tests and favored multimodal strategies incorporating maternal characteristics, blood pressure, uterine artery Doppler, and PlGF and/or PAPP-A. (Aviram et al., 2025) In a real-world first-trimester screen-and-prevent program, PlGF-integrated FMF screening followed by 160 mg aspirin was associated with lower preterm preeclampsia than the preimplementation phase, and the apparent protective effect was strongest among women identified as high risk using PlGF. (Badr et al., 2026)

Comparative modeling reinforced the value of established competing-risks approaches: in a Romanian cohort, the FMF posterior model achieved an AUC of 0.929 compared with 0.844 for the best machine-learning model. (Cristofor et al., 2026) Longitudinal application of FMF screening in 1,650 women classified 9.9% as high risk, although 22.6% of those women still developed preeclampsia, illustrating substantial residual risk despite targeted prevention. (Duong et al., 2025) Implementation of an FMF-based care package in London was associated with a 45.1% relative reduction in term SGA below the 10th percentile, suggesting that screening can influence downstream surveillance as well as aspirin allocation. (Guy et al., 2022) Finally, a biomarker–Doppler strategy combining sFlt-1/PlGF and uterine artery indices achieved an AUC of 0.95 in a high-risk cohort. (Gupta and Gupta, 2026) Collectively, Table 1 shows that higher-dimensional screening can improve risk discrimination, but clinical utility depends on resource requirements, thresholds, and the capacity to translate a risk score into timely prophylaxis and follow-up.

Table 1. Essential summary of evidence on risk-identification and screening strategies used to guide aspirin prophylaxis for preeclampsia

References	Population/Setting	Risk-Assessment Strategy	Predictors/Biomarkers	Eligibility/Risk Threshold	Screening Performance	Implication for Aspirin Prophylaxis
ACOG Committee Opinion No. 743 (2018)	Pregnant women receiving routine antenatal care; guideline population	Clinical risk-factor classification supported by ACOG/SMFM and USPSTF criteria	Previous preeclampsia; multifetal pregnancy; renal disease; autoimmune disease; type 1/2 diabetes; chronic hypertension; nulliparity; age ≥35 years; BMI >30; family/personal history and sociodemographic factors	≥1 high-risk factor or >1 moderate-risk factor	No predictive-performance statistic reported; clinical eligibility framework	Recommends 81 mg/day at 12–28 weeks, optimally before 16 weeks, for high-risk women; prophylaxis considered with multiple moderate-risk factors
Al-Rubaie et al. (2018)	Individual-participant data from 3 RCTs; 4,524 women, 221 PE cases	NICE and USPSTF clinical risk-factor algorithms	Guideline-defined high- and moderate-risk clinical characteristics	≥1 high-risk or ≥2 moderate-risk factors	NICE: parous sensitivity 26.4%, specificity 91.5%, PPV 14.6%, NPV 95.8%; nulliparous sensitivity 8.9%, specificity 97.2%, PPV 14.2%, NPV 95.5%; USPSTF similar	Simple and specific for deciding aspirin eligibility where advanced screening is unavailable, but low sensitivity—especially in nulliparous women—creates substantial missed-risk potential
Al-Rubaie et al. (2020)	12,395 nulliparous births in three public hospitals, Western Sydney, Australia	Western Sydney multivariable prediction model vs NICE risk-factor approach	Maternal age, BMI, ethnicity, multifetal pregnancy, family history of PE, autoimmune disease, chronic hypertension, chronic renal disease	WS model: predicted PE risk ≥8% for aspirin consideration; alternative ≥4% assessed	Validation c-statistic 0.70; at ≥8%: sensitivity 18%, specificity 97%; NICE sensitivity 37%, specificity 91%	Individualized absolute-risk prediction may support counseling and prophylaxis decisions, although the model did not clearly outperform NICE
Adjahou et al. (2025)	134,443 singleton pregnancies at 19–24 weeks in two UK maternity hospitals	Competing-risks mid-gestation screening	Maternal risk factors, estimated fetal weight, MAP, UtA-PI	Risk cut-offs designed to detect ~80%, 85%, or 90% of PE requiring delivery <28, <32, or <36 weeks	For ~90% detection using maternal factors+EFW+MAP: SPR 11.0%, 18.3%, 38.8%; with UtA-PI: 2.6%, 3.8%, 23.6%. Good calibration	Supports sequential risk assessment: first trimester for aspirin allocation and mid-gestation for subsequent surveillance; UtA-PI markedly reduces screen-positive burden
Aviram et al. (2025)	Pregnant individuals undergoing first- or second-trimester serum screening; technical update	Multimodal risk assessment rather than isolated serum-marker screening	Maternal characteristics, BP, UtA Doppler, PlGF, PAPP-A; abnormal hCG, AFP, inhibin-A, uE3	Aspirin considered with combinations of abnormal markers or positive multimodal first-trimester screen	Individual serum-marker predictive performance judged insufficient; multimodal approach described as most accurate for preterm PE	Serum markers should not generally determine aspirin prophylaxis alone; positive multimodal screening provides stronger basis for prophylaxis
Badr et al. (2026)	11,061 singleton pregnancies screened at 11+0–13+6 weeks in a tertiary maternal-fetal medicine center	FMF competing-risks screening with versus without PlGF	Maternal factors, FMF variables, PlGF	Screen-positive high-risk women received aspirin 160 mg/day to 36 weeks	Postimplementation preterm PE 0.6% vs 1.1% preimplementation; effect strongest when high risk identified using PlGF; no significant effect in algorithm without PlGF	Supports biomarker-integrated screen-and-prevent strategy; PlGF may improve identification of women who derive preventive benefit
Cristofor et al. (2026)	1,583 singleton pregnancies screened at 11–14 weeks, Romania	FMF competing-risks algorithm compared with logistic regression, random forest and XGBoost	Maternal factors; MAP; UtA-PI; PAPP-A	Individualized FMF risk; aspirin-treated pregnancies excluded from primary analyses	Maternal-only: FMF AUC 0.841 vs best ML 0.796; augmented: FMF AUC 0.929 vs best ML 0.844; sensitivity at 10% FPR 71.4% vs 57.1%	FMF remained at least as good as commonly used ML approaches for identifying high-risk pregnancies for preventive intervention

References	Population/Setting	Risk-Assessment Strategy	Predictors/Biomarkers	Eligibility/Risk Threshold	Screening Performance	Implication for Aspirin Prophylaxis
Duong et al. (2025)	1,650 first-trimester pregnancies; longitudinal study	FMF first-trimester screening	Medical history, BP, uterine artery Doppler, PAPP-A, PlGF	163/1,650 (9.9%) categorized as high risk and offered aspirin	22.6% of high-risk women developed PE; 14.3% of PE cases had severe evolution	FMF-based early screening permits risk-directed aspirin initiation, although substantial residual PE occurred among high-risk women
Guy et al. (2022)	7,720 pregnancies screened by NICE vs 4,841 screened using FMF approach in a London tertiary hospital	NICE clinical-risk screening vs FMF multimodal screening and care package	Maternal factors, BP, PAPP-A, UtA Doppler	FMF-defined high-risk women received 150 mg aspirin plus enhanced growth surveillance	Implementation associated with 45.1% relative reduction in term SGA <10th percentile at 21 months; no significant reduction for <5th or <3rd percentile	Risk-screening strategy may influence not only PE prevention but downstream placental-growth surveillance and outcomes
Gupta and Gupta (2026)	274 high-risk singleton pregnancies at 10–14 weeks in a tertiary hospital in Uttar Pradesh, India	First-trimester biomarker plus uterine artery Doppler assessment	sFlt-1, PlGF, sFlt-1/PlGF ratio, uterine artery PI, bilateral notching	sFlt-1/PlGF >20; UtA-PI ≥1.5 and/or bilateral notching	Combined biomarker+Doppler model AUC 0.95; abnormalities associated with early/severe PE, FGR, stillbirth and NICU admission	Integrated biomarker and Doppler risk assessment may enable earlier prophylactic aspirin and intensified surveillance in high-risk women

4.2 Optimizing Aspirin Prophylaxis: Dose, Timing, Duration, Adherence, and Biological Responsiveness

Table 2 shows that aspirin prophylaxis is not a uniform exposure. Conventional US guidance favors 81 mg/day initiated between 12 and 28 weeks, optimally before 16 weeks, and continued until delivery. (ACOG Committee Opinion No. 743, 2018) Higher-dose strategies are increasingly studied. In ASPREO, 162 mg versus 81 mg among high-risk obese participants produced severe-feature preeclampsia rates of 35% and 40%, respectively, corresponding to a posterior relative risk of 0.88 and a 78% probability of benefit, but with uncertainty that supports a larger trial rather than a definitive dose conclusion. (Amro et al., 2025) A retrospective high-risk cohort likewise reported preeclampsia in 10.1% of women managed under a 162-mg protocol versus 14.2% under an 81-mg protocol. (Ayyash et al., 2024)

Biological response provides a plausible explanation for dose heterogeneity. Among 1,002 high-risk pregnancies, women with class III obesity had substantially lower odds of complete thromboxane B2 suppression under a 60-mg regimen, with adjusted odds ratios of 0.33 in the second trimester and 0.30 in the third trimester. (Finneran et al., 2019) Conversely, a secondary analysis of ASPRE showed strong reductions in any, preterm, and early preeclampsia among women with high compliance to 150 mg/day, but the residual pattern differed according to baseline FMF risk. (Bujold et al., 2026) The international evidence review by Horgan and colleagues similarly emphasized continuing disagreement over both dose and initiation timing and argued that regimens above 100 mg begun before 16 weeks may merit greater consideration. (Horgan et al., 2023)

The table also shows why optimization cannot be reduced to dose alone. In women already receiving first-trimester 81-mg prophylaxis, those who later developed preeclampsia had persistently higher blood pressure, suggesting an underlying vascular phenotype incompletely mitigated by aspirin. (Baschat et al., 2018) A retrospective study initiating aspirin before 16 weeks did not find significant reductions in IUGR or early/late preeclampsia across its risk strata. (Ali et al., 2025) An integrative review focused on chronic hypertension proposed that dose, initiation before 12 weeks, bedtime administration, and >90% adherence may jointly determine response, but the evidence remained heterogeneous. (Asiimwe et al., 2025) Finally, implementation of near-universal early aspirin prescription among women with preexisting diabetes increased exposure from 25% to 88% yet did not reduce preeclampsia prevalence. (Do et al., 2021) Table 2 therefore supports a multidimensional concept of treatment optimization in which dose, timing, adherence, phenotype, and biological responsiveness interact.

Table 2. Essential summary of aspirin regimen characteristics and determinants of prophylactic responsiveness

References	Population/Risk Group	Aspirin Dose	Gestational Age at Initiation	Duration/Administration	Adherence/Compliance	Biological/Clinical Response	Main Findings
ACOG Committee Opinion No. 743 (2018)	Women with ≥1 high-risk factor or multiple moderate-risk factors	81 mg/day	12–28 weeks; optimally <16 weeks	Daily until delivery	NR	Prevention/delay of PE	Establishes conventional US regimen and highlights early initiation as preferred
Amro et al. (2025), ASPREO	High-risk pregnant individuals with BMI ≥30 kg/m² plus prior PE, hypertension or diabetes	162 vs 81 mg/day	12–20 weeks; median ~15.6–15.9 weeks	Daily to delivery	NR in supplied abstract	PE with severe features: 35% vs 40%; posterior RR 0.88; 78% probability of benefit with 162 mg	Suggests possible benefit of 162 mg in high-risk obese women, but credible interval included no effect; larger trial required
Ayyash et al. (2024)	3,597 high-risk pregnancies; no aspirin, 81 mg, or 162 mg protocols	81 or 162 mg/day	NR	Protocol-based prophylaxis	NR	PE 10.1% with 162 mg vs 14.2% with 81 mg; OR 0.68	Higher dose associated with lower PE in this retrospective cohort without increased measured bleeding complications
Finneran et al. (2019)	1,002 high-risk pregnant women; analysis stratified by BMI	60 mg/day	Randomization at 13–26 weeks	Through later pregnancy; TXB_2 measured serially	Biological response measured by TXB_2 suppression	Class III obesity associated with lower odds of complete TXB_2 inhibition: aOR 0.33 second trimester, 0.30 third trimester, 0.09 at both	Obesity may produce incomplete pharmacodynamic response to standard low-dose aspirin and supports study of dose/frequency adjustment
Bujold et al. (2026)	ASPRE high-risk women identified with FMF first-trimester risk ≥1%	150 mg/day vs placebo	11–14 weeks	Daily to 36 weeks	High compliance defined as ≥90% of tablets	Among high-compliance women, RR 0.64 for any PE, 0.24 for preterm PE, estimated RR 0.06 for early PE	Strong response was observed with high adherence, but residual risk varied by baseline FMF risk
Horgan et al. (2023)	Review of international aspirin recommendations and evidence	75–162 mg/day across guidelines	Generally 11–20 weeks; strongest rationale <16 weeks	Daily; guideline dependent	Identified as important but not uniformly measured	Evidence review suggested >100 mg started before 16 weeks may be more effective	Highlights major international disagreement over dose and timing and calls for direct 81 vs 162 mg trials
Baschat et al. (2018)	237 women at high risk based on maternal history and bilateral uterine artery notching	81 mg/day	Before 16 weeks	Daily	NR	12.2% developed PE despite prophylaxis; women developing PE had persistently higher BP	Mildly elevated early BP may identify residual risk incompletely mitigated by aspirin
Ali et al. (2025)	1,148 pregnancies; high- and low-risk women receiving early aspirin	Low-dose; exact dose not stated in supplied abstract	Before 16 weeks	NR	NR	No significant reduction in IUGR or early/late PE between studied groups	Demonstrates heterogeneity of prophylactic response and supports individualized interpretation rather than assuming universal benefit
Asiimwe et al. (2025)	Integrative review focused on women with chronic hypertension	Various; evidence favored ≥150 mg	Evidence synthesis favored initiation before 12 weeks	Review suggested >90% adherence and bedtime use	Adherence explicitly considered a major efficacy determinant	Higher doses, earlier initiation, bedtime administration and strong adherence showed an optimistic trend	Proposes that dose, timing, administration time and adherence jointly influence effectiveness in chronic hypertension

References	Population/Risk Group	Aspirin Dose	Gestational Age at Initiation	Duration/Administration	Adherence/Compliance	Biological/Clinical Response	Main Findings
Do et al. (2021)	410 pregnancies with preexisting diabetes; universal vs previous selective prophylaxis	Low-dose aspirin; exact dose NR in supplied abstract	~10 weeks in 88% after universal implementation	NR	Prescription coverage 88% vs 25%	PE 12% vs 11%; preterm PE 7% vs 7%	Increasing prophylaxis coverage and earlier exposure did not reduce PE prevalence in this diabetic cohort, illustrating population-specific residual risk

4.3 Maternal, Fetal, Neonatal, and Safety Outcomes Reported with Aspirin Prophylaxis

Clinical outcomes extended well beyond overall preeclampsia incidence (Table 3). The higher-dose observational cohort by Ayyash and colleagues found lower preeclampsia with 162 mg than 81 mg and no significant differences in postpartum hemorrhage, postpartum hematoma, or neonatal intraventricular hemorrhage between the two aspirin-dose groups. (Ayyash et al., 2024) In contrast, a Swedish population study of 313,624 births associated aspirin use with higher intrapartum bleeding, postpartum hemorrhage, postpartum hematoma, and neonatal intracranial hemorrhage, while antepartum bleeding was not significantly increased. (Hastie et al., 2021) A more recent propensity-matched analysis of 162 mg/day did not find a statistically significant increase in postpartum hemorrhage or composite maternal bleeding, illustrating the inconsistency of observational safety signals across populations and designs. (Ali et al., 2026)

Fetal-growth outcomes were also heterogeneous. In a large Asian screen-and-prevent trial, aspirin was associated with lower rates of very early SGA before 32 weeks but a simultaneous tendency toward more late SGA, indicating that gestational timing of the outcome matters. (Chen et al., 2025) Among women with pregestational diabetes, aspirin did not reduce SGA, while birthweight Z-score increased and large-for-gestational-age birth was more frequent in the nonvascular-diabetes subgroup. (Adkins et al., 2017) Prenatal aspirin was also associated with lower postpartum hypertension and lower sFlt-1 and sFlt-1/PlGF values in a small observational subgroup of women with preeclampsia, suggesting possible maternal vascular effects beyond prevention of the index diagnosis. (Christenson et al., 2023)

Other studies expanded the outcome map to preterm birth and timing of disease. In women with previous preterm birth, low-dose aspirin was associated with lower recurrent and spontaneous preterm birth, whereas medically indicated preterm birth was not significantly reduced. (Kupka et al., 2023) In the PlGF-based screen-and-prevent implementation study, preterm preeclampsia fell from 1.1% to 0.6%, overall preeclampsia from 2.5% to 1.4%, and preterm birth from 5.9% to 4.7%. (Badr et al., 2026) By contrast, universal prophylaxis in preexisting diabetes produced similar rates of preeclampsia, preterm preeclampsia, preterm birth, SGA, and LGA compared with the previous selective strategy. (Do et al., 2021) Earlier randomized evidence using 60 mg also found no significant shift in time of preeclampsia diagnosis, delivery, or preeclampsia-indicated delivery within seven days. (Dixon et al., 2017) Overall, Table 3 indicates that benefits and harms differ by endpoint, population, dose, gestational timing, and study design; no single outcome adequately represents the full preventive profile.

Table 3. Essential summary of maternal, fetal, neonatal, and safety outcomes reported with aspirin prophylaxis

References	Aspirin Exposure/Comparison	Preeclampsia Outcome	Preterm Birth	Fetal Growth/SGA	Maternal Outcomes	Neonatal Outcomes	Bleeding/Safety Findings
Ayyash et al. (2024)	162 mg vs 81 mg vs no aspirin	PE 10.1% with 162 mg vs 14.2% with 81 mg	NR	NR	No reported increase in major maternal aspirin-related complications	Intraventricular hemorrhage assessed	PPH, postpartum hematoma and neonatal intraventricular hemorrhage not significantly different between 162 and 81 mg
Hastie et al. (2021)	Aspirin users (n=4,088) vs nonusers among 313,624 Swedish births	Not primary endpoint	NR	NR	Increased intrapartum bleeding (2.9% vs 1.5%; aOR 1.63), PPH (10.2% vs 7.8%; aOR 1.23), postpartum hematoma (0.4% vs 0.1%; aOR 2.21)	Neonatal intracranial hemorrhage 0.07% vs 0.01%; aOR 9.66, wide CI	No significant antepartum bleeding increase; observational signals for intrapartum/postpartum and neonatal bleeding
Ali et al. (2026)	162 mg/day vs matched low-risk controls without aspirin	NR	NR	NR	Composite maternal hemorrhage similar; PPH 12.1% vs 7.0%, P=0.12	Other neonatal bleeding assessed	No statistically significant increase in PPH or other bleeding events at 162 mg/day
Chen et al. (2025)	Aspirin 100–160 mg/day among women identified as high risk for preterm PE	PE prevention program context	Focus on early delivery-associated SGA	Early SGA <3rd, <5th and <10th percentiles reduced before 32 weeks; trend toward increased late SGA	NR	SGA pattern differed according to gestational timing	Highlights heterogeneous fetal-growth effects: benefit for early SGA but heightened attention needed for late SGA
Adkins et al. (2017)	Aspirin vs placebo in 444 women with pregestational diabetes	Original trial did not show PE reduction in diabetic women	NR	Overall SGA 8% in both groups; increased birthweight Z-score with aspirin; LGA 40.2% vs 26.6% in nonvascular diabetes	NR	Increased frequency of LGA may increase neonatal/maternal morbidity	No specific bleeding signal reported
Christenson et al. (2023)	Prenatal low-dose aspirin vs no aspirin among women who developed PE	Study population already had PE	NR	NR	Postpartum hypertension 0% vs 22% among aspirin vs nonaspirin subgroup; lower sFlt-1 and sFlt-1/PlGF ratio; lower rehospitalization	NR	NR
Kupka et al. (2023)	Low-dose aspirin vs no aspirin in 22,127 women with previous preterm birth	Not primary outcome	Any recurrent PTB RR 0.87; spontaneous PTB RR 0.70; no significant reduction in medically indicated PTB	NR	NR	Reduced recurrence of spontaneous preterm birth may translate into neonatal benefit	NR

References	Aspirin Exposure/Comparison	Preeclampsia Outcome	Preterm Birth	Fetal Growth/SGA	Maternal Outcomes	Neonatal Outcomes	Bleeding/Safety Findings
Badr et al. (2026)	PlGF-based screening plus 160 mg aspirin vs preimplementation phase	Preterm PE decreased 1.1%→0.6%; overall PE 2.5%→1.4%	Preterm birth 5.9%→4.7%	NR	Reduced PE burden	Economic model incorporated neonatal consequences of prematurity/cerebral palsy	No major bleeding outcome reported in supplied abstract
Do et al. (2021)	Universal prophylaxis vs previous selective aspirin strategy in diabetes	PE 12% vs 11%; preterm PE 7% vs 7%	<37 weeks: 23% vs 27%	LGA 40% vs 32%; SGA 7% vs 6%; differences not significant	No clear improvement after universal strategy	Birth-size outcomes similar	NR
Dixon et al. (2017)	60 mg aspirin vs placebo in 2,479 high-risk women	Aspirin did not significantly change timing of PE diagnosis	No significant change in gestational age at delivery or PE-indicated delivery within 7 days	NR	No significant delay in PE clinical course after diagnosis	Earlier delivery remained characteristic of multifetal pregnancies	NR

4.4 Translating Evidence into Practice: Prescribing, Adherence, Implementation, and Health-System Gaps

The most consistent real-world finding was attrition between eligibility and actual prophylaxis (Table 4). At Henry Ford Health, only 17.6% of women meeting high-risk criteria and 15.2% meeting expanded high/moderate-risk criteria received low-dose aspirin during the relevant periods. (Ayyash et al., 2023) In Ethiopia, only 23.8% of surveyed prenatal-care providers demonstrated good knowledge and 36.3% good practice, with lack of a national guideline frequently identified as a barrier. (Bekele et al., 2024) In Israel, 44.1% of women eligible under national criteria and 27.9% eligible under broader ACOG criteria received prophylaxis; women qualifying through moderate-risk factors were particularly likely to be missed. (Ganem et al., 2025) These findings suggest that the complexity of risk classification can itself become an implementation barrier.

Patient-level implementation added another layer. A phenomenological study in southwestern Uganda identified delayed initiation, suboptimal provider guidance, side-effect-related nonadherence, and late antenatal attendance, with aspirin commonly started around 20 weeks rather than during the preferred early window. (Asiimwe et al., 2026) Conversely, a universal low-dose aspirin protocol in a US federally qualified health center increased documented adherence from 8.7% to 75.0% and was associated with a lower frequency of severe preeclampsia without a significant increase in transfusion-requiring postpartum hemorrhage. (Del Pozzo et al., 2026) A biomarker-based tertiary program similarly combined screening, 160-mg prophylaxis, and follow-up and projected substantial health-system savings alongside reduced preterm disease. (Badr et al., 2026)

Implementation success remained context-dependent. In Indonesian primary care, structured hypertensive-disorder pathways were considered acceptable and feasible but were constrained by professional hierarchy, limited clinical resources, and regulatory conditions. (Ekawati et al., 2021) An Australian audit found that aspirin was frequently overlooked even among women with chronic hypertension or recognized early risk factors. (Helou et al., 2017) A standardized checklist was proposed as a low-complexity way to reduce omission of recognized risk factors and improve recommendation consistency. (Combs and Montgomery, 2020) Finally, a scoping review of low- and middle-income countries identified medication access, diagnostic availability, infrastructure, professional development, workforce limitations, community perceptions, and outdated local guidance as recurrent barriers. (Escobar et al., 2024) Table 4 therefore shows that real-world prevention is determined by a chain of behaviors and system capabilities; a clinically effective medicine cannot generate population benefit when screening, prescribing, initiation, adherence, or follow-up fail.

Table 4. Essential summary of evidence on real-world implementation of aspirin prophylaxis for preeclampsia prevention

References	Country/Health care Setting	Eligibility/Implementation Strategy	Prescribing/Uptake	Adherence	Barriers	Facilitators/Intervention	Clinical/Implementation Outcome
Ayyash et al. (2023)	USA; Henry Ford Health urban healthcare system	Institutional high-risk criteria expanded in 2019 to high- or moderate-risk criteria	Only 17.6% of high-risk eligible women received LDA in 2015–2019; 15.2% of high/moderate-risk women in 2019–2020	Prescription adherence by providers was low	Failure to consistently translate guideline eligibility into prescribing; diverse high-risk population	Provider education; authors suggest considering universal prophylaxis in highly affected populations	Demonstrated major guideline-to-prescription gap despite clear eligibility criteria
Bekele et al. (2024)	Ethiopia; national tertiary referral hospital and catchment institutions	Survey of prenatal-care providers regarding aspirin prevention practice	Practice score mean 45.8%; only 36.3% demonstrated good practice	Patient adherence NR	Poor provider knowledge; lack of national guideline cited by 61.3%	National practical guideline and in-service training proposed	Only 23.8% had good knowledge, demonstrating major provider-level implementation deficit
Ganem et al. (2025)	Northern Israel; tertiary medical center	Israeli major-risk criteria compared with broader ACOG high/moderate-risk criteria	Israeli criteria: 44.1% of 1,160 eligible women prescribed aspirin; ACOG criteria: 27.9% of 2,559 eligible	NR	Moderate-risk status more likely to be overlooked; risk-specific and population disparities	Standardized risk assessment and provider education	Revealed persistent missed prophylaxis opportunities even among women meeting formal criteria
Asiimwe et al. (2026)	Southwestern Uganda; tertiary hospital antenatal/postnatal services	Ministry of Health policy recommending LDA; phenomenological study of treated women	Aspirin 75 or 150 mg; initiation mean ~20 weeks	Side-effect-related nonadherence emerged as a theme	Delayed initiation, suboptimal provider guidance, limited knowledge, side effects, late antenatal attendance	Provider capacity building, community sensitization, screening tool incorporated into antenatal card, active follow-up	Five implementation themes identified; 81% of aspirin users reportedly progressed to PE in this small qualitative sample
Del Pozzo et al. (2026)	USA; Federally Qualified Health Center serving socially vulnerable patients	Universal LDA protocol for eligible antenatal patients	Adherence increased from 8.7% preintervention to 75.0% after implementation; high-risk subgroup 8.9%→70.9%	Defined by documented patient use at follow-up and delivery	Inconsistent risk assessment and communication before protocol	Universal prescribing protocol	Severe PE decreased (OR 0.14 overall; OR 0.16 high-risk subgroup) without significant increase in transfusion-requiring PPH
Badr et al. (2026)	Tertiary maternal-fetal medicine center	FMF first-trimester screen-and-prevent implementation with PlGF and aspirin 160 mg	High-risk screen-positive women offered aspirin	NR	Biomarker/resource requirements may influence scalability	Integrated PlGF screening, prophylaxis and follow-up	PE and preterm birth decreased; economic model estimated prevention of 403 preterm-PE cases/year and €27.7 million savings nationally
Ekawati et al. (2021)	Indonesia; three public primary-care clinics in Yogyakarta	Implementation of structured HDP management pathways including PE risk-factor screening	Providers attempted pathway recommendations to varying degrees	NR	Professional boundaries, hierarchical barriers, limited resources, regulatory constraints	Champion obstetricians, patient-education toolkits and structured pathways	Pathways considered acceptable and feasible, supporting further scale-up

References	Country/Health care Setting	Eligibility/Implementation Strategy	Prescribing/Uptake	Adherence	Barriers	Facilitators/Intervention	Clinical/Implementation Outcome
Helou et al. (2017)	Australia; tertiary obstetric center	Compliance evaluation against SOMANZ recommendations	Only 12.2% of women with chronic hypertension received aspirin before 16 weeks; among women later developing PE with recognized early risk factors, only 24.3% had received aspirin	NR	Aspirin prophylaxis frequently overlooked despite known risk	Better guideline implementation	Authors estimated that poor uptake may have contributed to excess preventable PE cases
Combs and Montgomery (2020)	USA; maternal-fetal medicine practice	Standardized checklist covering 15 recognized PE risk factors	Not an outcome study	NR	Risk factors may be inadvertently overlooked during routine care	Checklist explicitly designed to improve identification and recommendation of aspirin to eligible patients	Provides low-complexity implementation strategy to reduce risk-assessment omissions
Escobar et al. (2024)	Low- and middle-income countries; scoping review of 27 studies	Mapping prevention, treatment and follow-up strategies for HDP	Variable across settings	Variable/NR	Limited access to medicines and diagnostics, inadequate infrastructure, outdated guidelines, insufficient training and personnel, community perceptions	Standardized protocols, guides and intervention packages	Demonstrated that guideline concordance alone is insufficient when infrastructure and implementation capacity are weak

5. Discussion

The evidence mapped in this review supports a shift from thinking about aspirin as a stand-alone preventive drug to understanding preeclampsia prevention as a sequence of linked decisions and behaviors. The first decision concerns risk recognition: simple clinical criteria are inexpensive and scalable but may miss a meaningful proportion of future cases, whereas multimodal algorithms can improve discrimination at the cost of additional infrastructure and technical complexity. (Al-Rubaie et al., 2018; Poon et al., 2019; Copel et al., 2020; Elawad et al., 2024; Askie et al., 2007) The second decision concerns exposure: the same prescription may translate into different biological effects according to dose, gestational timing, body size, adherence, and baseline vascular phenotype. The third concerns implementation: even a well-chosen regimen cannot reduce population burden if women are not identified, prescriptions are not issued, treatment starts late, or medication is not taken consistently. This pathway model explains why evidence of efficacy can coexist with persistent preventable disease.

The dose question illustrates this interaction particularly well. Observational data favoring 162 mg and the ASPREO signal of possible benefit over 81 mg are biologically consistent with evidence of incomplete thromboxane inhibition in obesity and with dose-response findings from meta-analysis. (Ayyash et al., 2024; Amro et al., 2025; Finneran et al., 2019; Roberge et al., 2017; Van Doorn et al., 2021) Yet the evidence remains insufficient to infer that higher dose should replace lower dose universally. Stage-1 hypertension may identify women who benefit disproportionately from aspirin, while other phenotypes retain substantial residual risk despite treatment. (Hauspurg et al., 2018; Baschat et al., 2018; Do et al., 2021) A small high-risk cohort also reported lower preeclampsia with aspirin than without prophylaxis, but such real-world comparisons remain susceptible to confounding and selection. (Feng et al., 2025) Precision prophylaxis therefore requires direct comparative trials in well-characterized phenotypes rather than extrapolation from pooled populations.

Timing and adherence are equally important components of exposure. Earlier initiation is biologically plausible because placental vascular remodeling begins long before clinical preeclampsia, and several reviews and trials support initiation during the first trimester or before 16 weeks. (Rolnik et al., 2017; Meher et al., 2017; Horgan et al., 2023) However, “early prescription” is not equivalent to sustained adherence. In chronic hypertension, knowledge of preeclampsia did not prevent high rates of nonadherence, and prospective assessment of preventive medication during the COVID-19 period similarly showed gaps in understanding despite substantial reported aspirin use. (Jardine et al., 2025; de Sousa et al., 2023) A contemporary high-risk surveillance study defined adherence across initiation, dose, and continuation, highlighting the value of treating medication exposure as a multidimensional variable rather than a yes/no characteristic. (Khan and Ejaz, 2026) Systematic evidence on aspirin adherence reinforces the need for standardized definitions and measurement methods. (Bij de Weg et al., 2025)

The fetal and maternal outcome map also argues against reducing prophylaxis to a single endpoint. Aspirin can affect the probability of preterm preeclampsia, fetal growth, spontaneous preterm birth, and possibly postpartum vascular outcomes, but these benefits are not uniform across gestation or population. (Chen et al., 2025; Kupka et al., 2023; Christenson et al., 2023) Safety evidence is likewise mixed. Large observational data raise signals for postpartum bleeding and hematoma, while several higher-dose cohorts have not shown statistically significant increases in hemorrhage. (Hastie et al., 2021; Ali et al., 2026; Ayyash et al., 2024; Roberge et al., 2018b) These differences may reflect confounding by indication, delivery mode,

varying bleeding definitions, dose, and study design. They support continued safety surveillance rather than either dismissing hemorrhage concerns or allowing them to overshadow the established benefit of prophylaxis in appropriately selected high-risk women.

Residual risk deserves particular emphasis because it reveals the limits of a drug-centered model. Chronic hypertension, multifetal pregnancy, autoimmune disease, assisted reproduction, thrombophilia, and previous placenta-mediated complications can represent overlapping but nonidentical pathological pathways. (Asiimwe et al., 2025; Duffy, 2021; Mecacci et al., 2019; Cagino et al., 2021; Borella et al., 2023; Karadağ et al., 2017) Case-based literature further illustrates that severe manifestations such as HELLP syndrome, eclampsia, or other life-threatening maternal complications can occur despite complex preventive or anticoagulant regimens; these reports are not efficacy evidence, but they remind clinicians that prophylaxis does not eliminate the need for surveillance and rapid escalation. (Mikolaiczik et al., 2019; Hirsi et al., 2026) Studies in inflammatory bowel disease and aspirin-sensitive pregnancy likewise show that comorbidity, tolerance, and competing treatment priorities can shape whether standard prophylaxis is feasible. (Gosling et al., 2025; Benito-Garcia et al., 2021)

Implementation findings may be the most actionable part of the evidence map. Under-prescription is recurrent across high-income and lower-resource settings, and moderate-risk women are especially vulnerable to being missed. (Ayyash et al., 2023; Ganem et al., 2025; Bekele et al., 2024; Tolcher et al., 2017) Structured counseling, standardized checklists, ultrasound-based risk assessment, and integrated screen-and-prevent programs can improve identification and uptake. (Combs and Montgomery, 2020; Okun et al., 2024; Nguyen-Hoang, 2024) Nevertheless, implementation is not only a provider-knowledge problem. It is shaped by antenatal access, staffing, laboratory and Doppler capacity, medication supply, workflow, risk communication, and socioeconomic context. (Kupka et al., 2024; Ekawati et al., 2021; Escobar et al., 2024; Minckas et al., 2025) This is particularly important in low- and middle-income settings, where severe hypertensive disease continues to contribute to maternal deaths and where late presentation can narrow or eliminate the opportunity for early prophylaxis. (Khan et al., 2025; Akbar et al., 2026)

The review also highlights a methodological issue: heterogeneous evidence should not be forced into a single hierarchy when different designs answer different questions. Randomized trials estimate efficacy under controlled exposure; retrospective cohorts explore effectiveness but may be confounded; prediction studies evaluate discrimination and calibration; qualitative studies reveal barriers; and implementation trials measure the performance of an entire care pathway. (Amro et al., 2025; Cristofor et al., 2026; Asiimwe et al., 2026; Nguyen-Hoang, 2024) Laboratory and animal studies can generate hypotheses about oxidative stress, salicylate biology, or alternative preventive mechanisms, but they should not be interpreted as evidence for clinical substitution or treatment benefit. (Kostadinova-Slavova et al., 2024; Cholik et al., 2026; Fitriana et al., 2025) Similarly, guideline publication does not itself constitute implementation, as shown by population-level studies in which aspirin uptake or outcomes changed less than expected. (Bruno et al., 2023; Mans-Gallart et al., 2026)

Several research priorities follow. First, direct dose-comparison trials should stratify by baseline risk, obesity, chronic hypertension, diabetes, and other phenotypes while measuring adherence and biological response. Second, screening studies should report not only discrimination but also treatment uptake and downstream outcomes. Third, adherence should be measured consistently using transparent definitions and, where feasible, triangulated with pharmacy, biochemical, or electronic data. Fourth, implementation studies should include cost, equity, access, and sustainability rather than reporting prescription rates alone. Finally,

mechanistic work should be linked to clinically interpretable endpoints instead of assuming that biomarker change predicts prevention. The resulting agenda is not simply "more aspirin research," but research on the full sequence from risk recognition to effective exposure and health-system delivery.

This scoping review has limitations. The core search was conducted in Scopus, so studies indexed exclusively elsewhere may have been missed. Restriction to contemporary English-language articles after the initial screening stage may also limit geographic and historical coverage. The 35 included studies are methodologically heterogeneous, and formal risk-of-bias scoring was not used to exclude evidence because the objective was mapping rather than pooled effect estimation. Finally, implementation determinants are often incompletely reported in efficacy-focused studies. These limitations reinforce the principal contribution of the review: evidence for aspirin prophylaxis is mature enough to support prevention, but the route from evidence to population benefit remains contingent on accurate risk identification, optimized exposure, sustained adherence, surveillance for residual risk, and context-sensitive implementation.

6. Conclusion

This scoping review maps aspirin prophylaxis for preeclampsia as a multistage prevention pathway extending from risk identification to real-world implementation. The evidence shows that clinical risk-factor approaches remain practical but may have limited sensitivity, while multimodal strategies integrating maternal characteristics, blood pressure, uterine artery Doppler, and placental biomarkers can improve individualized risk estimation. Aspirin exposure itself is heterogeneous: dose, gestational age at initiation, treatment duration, adherence, body size, baseline vascular phenotype, and biological responsiveness all influence how a prescription translates into preventive effect. Maternal, fetal, neonatal, and safety outcomes likewise vary across populations and study designs.

The principal gap is therefore not simply uncertainty about whether aspirin prevents preeclampsia. It is uncertainty about how best to align screening, eligibility, dose, timing, adherence, surveillance, and health-system delivery for different risk phenotypes and care settings. Residual disease among treated women and recurrent under-prescription among eligible women demonstrate that pharmacological efficacy alone is insufficient. Future research should combine rigorous dose-comparison and phenotype-stratified trials with standardized adherence measurement, biomarker-informed assessment of response, pragmatic implementation studies, cost analysis, and explicit evaluation of equity and access. The theoretical and practical contribution of this review is a unified risk-to-prevention framework: effective prevention depends on identifying the right women early, delivering an appropriate aspirin exposure consistently, monitoring residual risk, and embedding these steps within reliable antenatal systems.

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