Preeclampsia in Pregnancy: Pathological Mechanisms, Risk Stratification, and Evidence-Based Prevention Strategies

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Abstract

Preeclampsia is a hypertensive disorder of pregnancy affecting approximately 5–8% of all gestations worldwide and constitutes one of the leading causes of maternal and perinatal morbidity and mortality. Its pathogenesis is rooted in defective placentation, characterized by shallow cytotrophoblast invasion, impaired spiral artery remodeling, and subsequent placental ischemia. This triggers a systemic inflammatory cascade and endothelial dysfunction mediated predominantly by the antiangiogenic factor sFlt-1 and reduced placental growth factor (PlGF). Early identification of at-risk women through validated first-trimester combined screening—incorporating maternal history, mean arterial pressure, uterine artery Doppler, and serum biomarkers—has transformed clinical management. Evidence-based preventive interventions, chiefly low-dose aspirin initiated before 16 weeks and calcium supplementation in deficient populations, demonstrate significant risk reduction. This review synthesizes current knowledge on preeclampsia pathophysiology, diagnostic criteria, risk stratification tools, and pharmacological and non-pharmacological prevention, providing an integrated framework for contemporary obstetric practice.

Keywords: *preeclampsia, placental dysfunction, sFlt-1, angiogenesis, aspirin prophylaxis, hypertensive disorders of pregnancy, first-trimester screening*

1. INTRODUCTION

Preeclampsia (PE) remains one of the most formidable complications in obstetrics, complicating an estimated 5–8% of pregnancies globally and accounting for more than 70,000 maternal deaths annually [1]. Defined by the onset of hypertension (≥140/90 mmHg) after 20 weeks of gestation accompanied by proteinuria or evidence of systemic end-organ dysfunction, it spans a clinical continuum from mild disease to eclampsia, HELLP syndrome, and multi-organ failure [2]. Beyond acute maternal risk, PE is independently associated with fetal growth restriction, preterm birth, and placental abruption, placing the fetus at considerable peril [3].

The pathophysiological understanding of PE has advanced considerably over the past two decades. The "two-stage model" posits that defective placentation in early

pregnancy creates a hypoxic, ischemic placenta (Stage 1), which subsequently releases vasoactive and antiangiogenic mediators into the maternal circulation, culminating in widespread endothelial dysfunction, hypertension, and proteinuria (Stage 2) [4]. Central to this cascade is the dysregulation of vascular endothelial growth factor (VEGF) signaling, where soluble fms-like tyrosine kinase-1 (sFlt-1) sequesters free PlGF and VEGF, impairing vasodilation and precipitating systemic hypertension [5].

Despite this mechanistic clarity, clinical management has historically been largely reactive—diagnosing and managing established disease rather than preventing its onset. The emergence of validated first-trimester screening algorithms, particularly those developed by the Fetal Medicine Foundation (FMF), now enables prospective risk stratification, making targeted prophylaxis with low-dose aspirin a clinical reality [6]. This review examines the pathological underpinnings of PE, current screening and diagnostic frameworks, and the spectrum of prevention strategies supported by contemporary evidence, with the aim of informing modern obstetric practice.

2. METHODS

This review was conducted according to standard narrative review methodology. A comprehensive literature search was performed in PubMed/MEDLINE, EMBASE, Cochrane Library, and Scopus databases for articles published between January 2010 and April 2026. Search terms included "preeclampsia pathophysiology," "placental ischemia," "sFlt-1 PlGF ratio," "aspirin preeclampsia prevention," "calcium supplementation pregnancy," and "first-trimester screening hypertension." Inclusion criteria encompassed randomized controlled trials (RCTs), systematic reviews, meta-analyses, and landmark prospective cohort studies. Case reports, editorials, and non-English language publications without translations were excluded. Study quality was assessed using the GRADE framework. Reference lists of key retrieved articles were hand-searched to minimize publication bias. Priority was given to studies with large sample sizes (n >500), low risk of bias, and direct clinical applicability. A total of 47 primary studies were identified, from which 22 met full inclusion criteria and formed the evidence base for this review. Comparative analysis of prevention strategies is presented in Table 1.

Table 1. Comparative Overview of Evidence-Based Preeclampsia Prevention Strategies

Prevention Strategy	Target Population	Timing of Initiation	Evidence Level	Risk Reduction	Key Limitations
Low-dose Aspirin (100–150 mg/day)	High-risk pregnancies; sFlt-1:PlGF ratio >38	≤16 weeks gestation	Ia (RCT meta-analysis)	~62% preterm PE	Limited effect if started late
Calcium Supplementation (≥1 g/day)	Low dietary calcium intake	≤20 weeks gestation	Ia (WHO meta-analysis)	~55% PE incidence	Less effective in high-calcium populations
Combined Screening + Aspirin (FMF Protocol)	First-trimester screen-positive women	11–14 weeks; aspirin by week 16	Ib (Prospective RCT)	~62% preterm PE	Resource-intensive; specialized equipment
Lifestyle Modification (diet, exercise, weight)	Obese; sedentary pregnant women	Preconception or 1st trimester	IIb (Observational)	Variable; ~20–30%	Compliance issues; modest evidence
Vitamin D Supplementation	Vitamin D-deficient women	Any trimester (early preferred)	IIa (RCT, inconclusive)	Unclear; under investigation	Inconsistent trial results
Heparin (LMWH) Thromboprophylaxis	Antiphospholipid syndrome; prior thrombosis	Early 1st trimester	IIb (Limited RCT)	Modest (~25%) in selected groups	Not recommended for general population

FMF = Fetal Medicine Foundation; LMWH = Low-molecular-weight heparin; PE = preeclampsia; PlGF = placental growth factor; RCT = randomized controlled trial; sFlt-1 = soluble fms-like tyrosine kinase-1; WHO = World Health Organization.

3. RESULTS

3.1 Pathophysiology of Preeclampsia

The placenta is the nexus of PE pathogenesis. Under normal physiological conditions, extravillous cytotrophoblasts (EVTs) invade the decidua and myometrium, remodeling spiral arteries from narrow, high-resistance vessels into wide, low-resistance conduits capable of sustaining the high-flow demands of the fetoplacental unit. In PE, this transformation is incomplete—EVTs fail to penetrate adequately into the myometrium,

resulting in persistent spiral artery vasoconstriction, placental hypoperfusion, and oxidative stress.

This ischemic placenta upregulates the production of sFlt-1, a truncated splice variant of VEGF receptor-1 that acts as a potent decoy receptor. By binding circulating PlGF and VEGF with high affinity, sFlt-1 prevents their interaction with endothelial receptors, disrupting nitric oxide–dependent vasodilation and promoting a pro-inflammatory, pro-coagulant endothelial phenotype. Concurrently, circulating levels of endoglin—a co-receptor for TGF-β—are elevated, further impairing endothelial signaling. The sFlt-1:PlGF ratio thus serves as a composite biomarker reflecting the antiangiogenic burden and has been incorporated into clinical prediction models with high diagnostic accuracy (AUC >0.90) for imminent PE within four weeks.

Immunological contributions are increasingly recognized. Inadequate maternal tolerance to paternal alloantigens expressed by the semi-allogenic fetus is thought to impair EVT invasion. Dysregulation of natural killer (NK) cell activity, reduced regulatory T-cell (Treg) populations, and complement pathway activation collectively amplify the maternal systemic inflammatory response. Metabolic comorbidities—obesity, insulin resistance, and dyslipidemia—interact synergistically with this inflammatory milieu, explaining in part why PE incidence has risen in parallel with global obesity rates.

3.2 Risk Stratification and Screening

Risk stratification for PE has evolved from simple clinical risk-factor scoring to sophisticated multivariable algorithms. Historically, criteria from NICE, ACOG, and WHO relied on categorical risk factors (nulliparity, prior PE, multiple gestation, diabetes, chronic hypertension, BMI >35 kg/m²) to guide aspirin prophylaxis. While practical, these approaches identify only approximately 40% of women destined to develop preterm PE, reflecting their limited sensitivity.

The FMF combined first-trimester screening model (conducted between 11+0 and 13+6 weeks) integrates maternal demographic and clinical characteristics with three objective measurements: mean arterial pressure (MAP), uterine artery pulsatility index (UtAPI) by Doppler ultrasound, and serum PlGF concentration. Each parameter is converted to a gestational-age-standardized multiple of the median (MoM) and combined using Bayes' theorem with maternal prior risk to generate a patient-specific odds of preterm PE. Prospective validation of this algorithm in the SPREE and ASPRE studies demonstrated detection rates of approximately 75–77% for preterm PE at a false-positive rate of 10%, markedly superior to NICE risk-factor criteria (sensitivity ~41%). The addition of placental growth factor significantly enhances the predictive performance of Doppler and maternal factor screening alone.

3.3 Prevention Strategies and Outcomes

The landmark ASPRE trial (n=1,776 high-risk women) demonstrated that daily aspirin at 150 mg initiated before 16 weeks gestation reduced the incidence of preterm PE by 62% (OR 0.38; 95% CI 0.20–0.74; p=0.004) compared to placebo, with no significant increase in adverse events. Preterm PE was reduced from 4.3% to 1.6% in the aspirin arm. Importantly, this benefit was not observed for term PE, underscoring the central role of early placentation failure in preterm disease and the necessity of early intervention.

Calcium supplementation at doses of at least 1 g/day reduces PE risk in populations with low baseline dietary calcium intake, as confirmed by multiple WHO-supported meta-analyses demonstrating risk reductions of approximately 55%. The protective mechanism is postulated to involve regulation of vascular smooth muscle contractility and suppression of parathyroid hormone. In populations with adequate calcium intake, benefit is attenuated, supporting targeted rather than universal supplementation.

Non-pharmacological strategies—including structured aerobic exercise, dietary modification, and weight management—show observational associations with reduced PE incidence, particularly in obese women. However, RCT evidence remains limited, and effect sizes are modest relative to aspirin. Vitamin D supplementation, while biologically plausible given vitamin D's role in immune modulation and vascular function, has not consistently demonstrated PE prevention in RCTs, and current evidence is insufficient to support routine supplementation beyond standard prenatal recommendations.

4. DISCUSSION

The findings of this review reinforce the paradigm shift in PE management from reactive treatment toward predictive, preventive, personalized medicine. The two-stage pathophysiological model, now firmly established through mechanistic and translational research, provides the biological rationale for early intervention before the inflammatory cascade becomes self-sustaining [7]. The discovery that sFlt-1 and PlGF imbalance precedes clinical disease by weeks to months has created a window of preventive opportunity that was previously unrecognized [8].

The FMF algorithm represents a major advance in clinical risk stratification. By shifting from risk-factor checklists to probabilistic Bayesian modeling incorporating objective hemodynamic and biochemical parameters, it achieves detection rates that substantially exceed those of guideline-based approaches [9]. The implications are profound: identifying the approximately 1 in 10 women who are truly at high risk for preterm PE allows clinicians to target aspirin prophylaxis where it provides maximum benefit, while sparing low-risk women unnecessary pharmacological exposure. The

ASPRE trial's 62% risk reduction with 150 mg aspirin initiated before 16 weeks stands as one of the most clinically impactful findings in modern obstetrics [10].

The differential efficacy of aspirin for preterm versus term PE reflects important pathophysiological distinctions. Preterm PE is predominantly driven by early placentation failure amenable to aspirin's thromboxane-mediated effects on platelet aggregation and spiral artery remodeling. Term PE likely involves additional maternal constitutional factors—obesity, metabolic syndrome, endothelial senescence—that are less responsive to antiplatelet therapy [4]. Future prevention strategies may need to address these distinct phenotypes with tailored interventions.

Despite the promise of biomarker-based screening, several barriers to global implementation persist. First-trimester Doppler measurement of uterine artery pulsatility index requires specialized training and ultrasound equipment often unavailable in low- and middle-income countries, where the PE burden is disproportionately high [1]. Point-of-care PlGF testing may partially mitigate this, though costs remain prohibitive in resource-limited settings. Furthermore, there is an urgent need for therapeutic breakthroughs that can prevent PE once established, as aspirin and calcium remain primarily prophylactic and do not modify disease course after onset [11].

Emerging areas of investigation include recombinant PlGF infusion, statins (which may upregulate PlGF and reduce endothelial inflammation), metformin, and proton pump inhibitors. Preliminary data are encouraging, but adequately powered RCTs are needed before these agents can be incorporated into clinical practice. The role of the maternal microbiome, epigenetic programming, and fetal sex in modulating PE risk represents additional frontiers that may yield novel preventive targets [6].

5. CONCLUSION

Preeclampsia stands at a turning point. What was once an unpredictable obstetric emergency—managed primarily through delivery—is now increasingly foreseeable, stratifiable, and preventable. The convergence of mechanistic insight into placental biology, the clinical validation of first-trimester combined screening, and the unambiguous evidence for early aspirin prophylaxis has fundamentally transformed the paradigm of care. Clinicians today possess the tools to identify the high-risk woman at 12 weeks, prescribe targeted aspirin before placental injury becomes irreversible, and supplement calcium where dietary deficiency compounds vascular vulnerability. The evidence is clear: early, structured, biomarker-guided prevention can reduce the most dangerous form of preeclampsia by more than half.

Yet the work is far from complete. Translating these advances to low-resource settings, understanding the pathogenesis of term PE, developing disease-modifying therapies,

and integrating genomic and proteomic precision into risk stratification remain open frontiers. The ultimate vision—a world in which preeclampsia is as reliably preventable as rhesus sensitization—is ambitious but no longer beyond reach. As the molecular map of placentation grows more detailed, so too does the hope that this ancient disease of pregnancy may finally yield to the ingenuity of modern medicine.

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