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PRE-ECLAMPSIA: ADVANCES IN PREDICTION MODELS AND PREVENTIVE APPROACHES

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Abstract

Preeclampsia remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide, typically manifesting as new-onset hypertension and proteinuria after 20 weeks of gestation. Early prediction and timely prevention are critical in reducing complications such as preterm birth, fetal growth restriction, and long-term cardiovascular risks for both mother and child. Recent advances in predictive modeling have combined clinical risk factors, biochemical markers, and imaging techniques to improve early detection. Machine learning approaches, particularly those integrating maternal demographic data with biomarkers like placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1), have shown promise in enhancing diagnostic accuracy. Moreover, the application of uterine artery Doppler studies has provided valuable insights into placental dysfunction, strengthening risk stratification efforts.

Preventive strategies have also evolved, with low-dose aspirin emerging as the most widely recommended pharmacological intervention for high-risk women, supported by large-scale trials. Nutritional interventions, such as calcium supplementation, have demonstrated benefits in populations with low dietary intake, while lifestyle modifications including weight management and physical activity are gaining recognition as adjunctive strategies. Despite these advances, challenges remain in ensuring model generalizability across diverse populations, cost-effectiveness in clinical practice, and equitable access to preventive care in low-resource settings.

Overall, integrating advanced prediction models with evidence-based preventive measures offers a promising pathway to reduce the global burden of preeclampsia. Continued research should focus on refining predictive algorithms, validating biomarkers in multi-ethnic cohorts, and ensuring that preventive interventions are accessible and scalable within routine antenatal care.

INTRODUCTION

Pre-eclampsia (PE) is a pregnancy-specific hypertensive disorder characterized by new-onset hypertension and proteinuria after 20 weeks of gestation. It remains a leading cause of maternal and perinatal morbidity and mortality worldwide, particularly in low- and middle-income countries (Brown et al., 2018). Despite improvements in obstetric care, the unpredictable nature of PE continues to challenge clinicians, making early detection and effective prevention a global health priority.

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Over the last decade, advances in biomedical research and computational science have contributed to the development of predictive models aimed at identifying women at high risk of developing PE. These models integrate maternal risk factors, biochemical markers, and biophysical parameters to improve risk stratification beyond traditional clinical assessment (Wright et al., 2019). Machine learning and artificial intelligence applications have further enhanced predictive accuracy, offering personalized risk assessment tools that can be adapted across diverse populations (Suff et al., 2021).

Preventive strategies have also evolved, with low-dose aspirin emerging as a widely recommended prophylactic intervention for high-risk women (Rolnik et al., 2017). Nutritional interventions, lifestyle modifications, and the exploration of novel biomarkers have added depth to prevention research. However, disparities in accessibility, implementation, and population-specific effectiveness remain significant barriers.

This paper explores recent progress in predictive modeling and preventive strategies for PE, highlighting their clinical implications, limitations, and potential to transform maternal health outcomes. By synthesizing existing evidence, the discussion aims to provide a comprehensive perspective on how prediction and prevention can be optimized to reduce the global burden of pre-eclampsia.

Pathophysiology of Pre-eclampsia

Pre-eclampsia is characterized by abnormal placental development, impaired maternal vascular adaptation, and systemic endothelial dysfunction. During normal pregnancy, trophoblast invasion remodels maternal spiral arteries, ensuring adequate blood flow to the placenta. In pre-eclampsia, this process is incomplete, leading to shallow trophoblastic invasion and high-resistance uteroplacental circulation. The resulting hypoxia and ischemia cause the release of anti-angiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1), which antagonize vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). This imbalance disrupts endothelial function, contributing to hypertension and proteinuria (Staff et al., 2022).

Endothelial dysfunction also increases vascular permeability and promotes vasoconstriction through reduced nitric oxide bioavailability and elevated endothelin-1 levels. The maternal immune system further plays a role, as maladaptation to paternal antigens may trigger an exaggerated inflammatory response, worsening vascular injury (Burton et al., 2019). Additionally, oxidative stress from hypoxic placental tissue amplifies cellular damage and inflammatory pathways, perpetuating a cycle of maternal vascular dysfunction.

The multi-system involvement of pre-eclampsia reflects its complex pathophysiology. The kidneys show glomerular endotheliosis, resulting in proteinuria, while hepatic involvement leads to elevated liver enzymes and, in severe cases, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count). The brain may also be affected, with vasogenic edema contributing to headaches, visual disturbances, and seizures in eclampsia (Gathiram & Moodley, 2020).

Thus, pre-eclampsia is not merely a disorder of blood pressure but a systemic condition originating in the placenta and manifesting through widespread endothelial dysfunction. Understanding its pathophysiology is critical for developing early diagnostic biomarkers and targeted therapies to reduce maternal and neonatal morbidity.

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Study (Year)	Design & Setting	Focus / Predictors or Intervention	Main Findings	Practice Notes
Poon et al. (2019)	FIGO pragmatic guide	First-trimester combined screening (maternal factors, MAP, UtA-PI, PlGF)	Recommends universal first-trimester screening; basis for aspirin prophylaxis in high-risk women.	Practical algorithm many programs adopt, especially where biomarkers are available. (obgyn.onlinelibrary.wiley.com)
Noël et al. (2021)	Review/perspective	Routine first-trimester combined screening with targeted aspirin	Screening is useful because treating the high-risk group with aspirin reduces preterm PE by ~60%.	Supports "screen-and-treat" pathway in real clinics. (obgyn.onlinelibrary.wiley.com)
Chaemsaithong et al. (2022)	Narrative/state-of-the-art review (AJOG)	FMF triple test (maternal factors, MAP, UtA-PI/PlGF)	Reported detection ≈90% for early-onset and 75% for preterm PE at 10% FPR.	Strong benchmark for performance of integrated models. (ajog.org)
Mohamed et al. (2022)	Health Technology Assessment (Ontario)	FMF-based program vs standard care; cost-effectiveness	Lower risk of PE <37 wks (RR ~0.64–0.70); ICER ≈ $3,446 per case prevented; higher costs but offset by savings from prevented PE.	Useful for policy/implementation planning. (PMC)
Oancea et al. (2020)	Review of clinical evidence	Uterine artery Doppler (first trimester)	UtA Doppler is an effective non-invasive screen for PE in at-risk pregnancies.	Valuable where biomarkers are limited; operator/setting dependent. (PMC)
Velegrakis et al. (2023)	Systematic review	sFlt-1/PlGF ratio (angiogenic markers)	Elevated sFlt-1 and low PlGF associated with PE; ratio aids short-term triage and prediction.	Widely used "rule-out/rule-in" aid, especially in suspected PE. (PMC)
Ahn et al. (2023)	Review	Low-dose aspirin timing and dose	Prevention benefit when started <16 weeks; higher doses (≥100 mg) more	Reinforces early start and adequate dosing in high-risk women. (PMC)

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Study (Year)	Design & Setting	Focus / Predictors or Intervention	Main Findings	Practice Notes
			effective than ≤60 mg.	
Dwarkanath et al. (2024)	Two RCTs (NEJM)	Calcium 500 mg/day vs high-dose calcium	Low-dose (500 mg) noninferior to high-dose for preventing PE-related outcomes.	Supports scalable calcium strategies in low-intake populations. (New England Journal of Medicine)
Gomes et al. (2022)	Narrative review	Calcium supplementation in pregnancy	Calcium reduces hypertensive disorders/PE where dietary intake is low; recommended public-health measure.	Particularly relevant for LMICs and low-calcium diets. (PMC)
Zhang et al. (2023) / BMC review (2023)	Systematic review	Machine-learning models for PE prediction	ML models often outperform traditional statistics; heterogeneity and external validation remain gaps.	Promising for precision screening; needs standardized pipelines. (BioMed Central)

Advances in Prediction Models

The prediction of pre-eclampsia (PE) has evolved considerably over the past two decades, shifting from reliance on clinical risk factors alone to the integration of advanced biochemical, biophysical, and computational tools. Early prediction is essential because it allows for timely preventive interventions, including low-dose aspirin, calcium supplementation, and closer monitoring of at-risk women (Rolnik et al., 2017). Traditional methods depended primarily on maternal history, age, parity, and pre-existing conditions such as chronic hypertension or diabetes. However, these models lacked sensitivity and failed to capture the complex pathophysiology of PE (Cetin et al., 2021). More recent advances have introduced diverse categories of prediction models that combine multiple data sources to improve accuracy.

1. Clinical Risk Factor–Based Models

These are the most widely used approaches in routine practice and form the foundation of early screening. They include maternal characteristics such as age, body mass index (BMI), parity, and medical history (Hypertension in Pregnancy Task Force, 2019). While simple and inexpensive, their predictive value is limited, especially in low-risk populations. For instance, nulliparity is a recognized risk factor, yet not all nulliparous women develop PE, highlighting the limited specificity of this approach.

2. Biophysical Marker–Based Models

Biophysical parameters, including uterine artery Doppler ultrasound and mean arterial pressure (MAP), have significantly improved risk stratification. Abnormal uterine artery pulsatility index (PI) in the first or second trimester reflects impaired placental perfusion, a hallmark of early-onset PE (Gallo et al., 2020). When combined with MAP, Doppler

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screening improves the detection rate compared to maternal risk factors alone. These models are particularly effective in identifying women at risk for early-onset disease, which carries higher maternal and neonatal morbidity.

3. Biochemical Marker–Based Models

Biochemical markers offer insights into the underlying molecular processes of PE, including angiogenic imbalance and placental dysfunction. Key biomarkers include placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and pregnancy-associated plasma protein-A (PAPP-A) (Zeisler et al., 2016). Low levels of PlGF or elevated sFlt-1/PlGF ratios have been shown to strongly correlate with disease onset and severity. These tests are now incorporated into several risk prediction algorithms and are increasingly available in clinical settings.

4. Multimodal Integrated Models

Recent advances emphasize combining maternal risk factors, biophysical measurements, and biochemical markers into unified prediction models. The **Fetal Medicine Foundation (FMF) algorithm** is one of the most widely validated multimodal models, achieving detection rates of over 90% for early-onset PE when applied in the first trimester (O'Gorman et al., 2017). Such models allow clinicians to implement preventive strategies early in pregnancy, improving maternal and fetal outcomes.

5. Artificial Intelligence (AI) and Machine Learning–Based Models

Emerging technologies in AI and machine learning (ML) are reshaping PE prediction. These approaches can analyze high-dimensional datasets, including genomics, proteomics, and electronic health records, to uncover complex patterns that traditional statistical models may miss (Alanis-Garza et al., 2021). Machine learning algorithms such as random forests, support vector machines, and deep neural networks have demonstrated promising results in pilot studies, with some outperforming conventional prediction models (Akolekar et al., 2021). Despite their potential, challenges remain, including the need for external validation, data standardization, and ethical considerations related to patient privacy.

Preventive Approaches

Preventive strategies for pre-eclampsia focus on early identification of high-risk women and timely interventions to reduce maternal and fetal complications. Current approaches include low-dose aspirin, which has shown significant effectiveness in lowering the incidence of pre-eclampsia when initiated in early pregnancy (Roberge et al., 2022). Calcium supplementation is another preventive measure, particularly beneficial in populations with low dietary calcium intake, as it reduces the risk of hypertensive disorders in pregnancy (Hofmeyr et al., 2019). Lifestyle modifications, such as maintaining healthy body weight, controlling pre-existing hypertension, and optimizing metabolic health before conception, are also emphasized to minimize risk (Khalil & Granger, 2021). Recent advances highlight the role of predictive biomarkers, machine learning–based risk models, and personalized monitoring as preventive tools for timely detection and intervention (Wagner et al., 2023). Collectively, these preventive measures offer a multi-faceted approach aimed at mitigating the global burden of pre-eclampsia and improving maternal-fetal outcomes.

Comparative analysis of current models and approaches for pre-eclampsia

1) Bedside clinical risk scores for admitted PE (short-term deterioration)

fullPIERS (tertiary settings). Uses maternal demographics and symptoms plus labs (e.g., platelets, creatinine, AST) and vitals to estimate risk of severe maternal complications within 48 h to 7 days after admission for PE. External assessments report good discrimination and clinical utility for triage and timing of delivery. Strengths: transparent, calibrated for short-term outcomes. Limitations: designed for already-diagnosed PE in hospital, not population screening. pre-empt.obgyn.ubc.caPMC+1Lippincott Journals

miniPIERS (low-resource/primary care). Predicts adverse outcomes among pregnant women with hypertensive disorders using readily available signs/symptoms. Strengths: minimal labs, suitable for LMIC contexts. Limitations: lower AUC than fullPIERS; not a first-trimester screening tool. PMCPubMedpre-empt.obgyn.ubc.ca

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2) First-trimester combined screening (11–13+6 weeks)

FMF/Bayesian combined algorithms. Combine maternal factors with mean arterial pressure (MAP), uterine artery Doppler pulsatility index (UtA-PI), and biochemical markers (PlGF ± PAPP-A). In high-quality programs, detection of **preterm PE (<37 wks)** can be high at acceptable false-positive rates, and positive screens guide **aspirin prophylaxis**. Strengths: actionable in first trimester; linked to prevention (ASPRE). Limitations: performance depends on strict measurement protocols, quality control, and population calibration; late-onset PE prediction remains modest. fetalmedicine.org+1PMCAHA Journals

Aspirin linkage (ASPRE). In women screened high-risk by the combined algorithm, **150 mg nightly aspirin** from 11–14 to 36 weeks reduced **preterm PE** by ~60% vs placebo; effect on term PE was not significant. Dose-response meta-analyses support 150–162 mg for greater benefit in preterm PE. New England Journal of MedicinePubMedThe ObG ProjectScienceDirect

Doppler alone? As a single predictor, UtA-PI detects <50% of PE; it's better when combined with MAP and biomarkers. PMC

3) Angiogenic biomarker–based tests (diagnostic adjuncts later in gestation)

sFlt-1/PlGF ratio (and PlGF alone). Widely validated to **rule out** PE short-term when ratio <38 (negative predictive value high over ~1 week). Ratios ≥85 or higher cutoffs are often used to "rule in" impending PE over 4 weeks, though positive predictive values vary with gestational age and setting. Strengths: operational, fast turnaround, clarifies equivocal hypertensive cases. Limitations: limited predictive value **early** in pregnancy; best as a **diagnostic/monitoring** adjunct from mid-gestation onward. New England Journal of MedicinePMC+1Obstetrics & GynecologyNature

4) Machine learning (ML) models using routine EHR + prenatal data

Recent reviews show tree-based ensembles (XGBoost, random forest, gradient boosting) and elastic-net models often top classic regressions, using maternal history, vitals, routine labs, and ultrasound. Reported AUCs are promising, sometimes matching combined screening, but most models face **dataset shift**, **calibration**, and **external validation** gaps, and few are embedded in care pathways (e.g., linking to aspirin). Strengths: scalable on EHR data; can update longitudinally. Limitations: heterogeneous features, small or single-center training, limited prospective impact studies. BioMed CentralPubMedScienceDirectCureus

5) Multi-omics and proteomic signatures

Proteomic panels can predict PE within weeks of onset and may refine timing compared with single markers, but cross-cohort reproducibility is an issue and costs/logistics limit deployment. Evidence suggests angiogenic markers gain predictive power as gestation advances, while early-pregnancy multi-omics remain research-stage. Strengths: potentially earlier signal and subtype resolution (early- vs late-onset). Limitations: assay standardization, external validation, and cost-effectiveness not yet settled. PMCTaylor & Francis OnlineMDPI

Side-by-side: what each approach is best for

- **Who to screen early?** Use **combined first-trimester algorithms** (maternal factors + MAP + UtA-PI + PlGF ± PAPP-A). They are the only approach tightly coupled to an **effective prevention** strategy (150 mg aspirin) and have the best evidence for cutting **preterm PE** at the population level when implemented with quality control. PMCNew England Journal of MedicinePubMed
- **Who needs admission or delivery soon?** Use **fullPIERS/miniPIERS** after diagnosis to gauge **short-term risk** and guide triage in hospital or primary care. PMC+1
- **Who likely won't develop PE in the next week?** Use **sFlt-1/PlGF <38** to safely **rule out** short-term PE in symptomatic patients, reducing unnecessary admissions. New England Journal of Medicine
- **Augmenting routine care with data science?** **ML/EHR models** are promising but should be prospectively validated, calibrated, and tied to interventions; otherwise they risk alert

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fatigue without outcome gains. BioMed Central

Practical considerations for our paper

1. **Define the use-case** before comparing models Early **screening and prevention** vs **diagnosis/triage** are different problems with different winning tools. Mixing them obscures value. Frame comparisons by gestational window and actionability.
2. **Performance vs implementability** Combined algorithms need trained staff, validated devices for MAP and Doppler, and lab access for PlGF/PAPP-A. Angiogenic ratios need assay availability and reimbursement. Clinical risk scores need only routine labs. ML models need EHR integration and governance. Report not just AUC, but calibration, decision thresholds, turnaround time, and costs.
3. **Population calibration matters** Performance shifts across ethnicities, baseline risk, and care pathways. Local recalibration and external validation are mandatory for any model you adopt.
4. **Tie prediction to intervention** The strongest outcome evidence remains: **high-risk by first-trimester combined screening → 150 mg aspirin nightly to 36 weeks → reduced preterm PE**. Without a linked intervention, prediction alone rarely improves outcomes.
5. **What's next**
    - **Longitudinal/temporal ML** that updates risk as new labs, vitals, and biomarkers arrive.
    - **Hybrid models** that fuse EHR features with **angiogenic markers** to improve rule-in performance mid-gestation.
    - **Prospective impact trials** comparing "model-guided care" vs standard care on maternal/neonatal outcomes and costs

Future Directions

Despite major progress in understanding and predicting pre-eclampsia, significant gaps remain that call for targeted research. Future studies should focus on integrating longitudinal risk assessment models that update predictions as pregnancy progresses, rather than relying on a single first-trimester screen. Combining maternal characteristics, hemodynamic measures, angiogenic biomarkers, and routinely collected electronic health record (EHR) data within machine learning frameworks may improve accuracy and allow earlier interventions.

Another promising direction is the application of multi-omics approaches—including genomics, transcriptomics, proteomics, and metabolomics—to identify novel biomarkers that can differentiate early-onset from late-onset disease and capture diverse pathophysiological pathways. Standardization of assays and validation across multiple populations will be essential before such methods can enter routine practice.

On the prevention side, the optimization of aspirin prophylaxis remains a priority. More trials are needed to refine dose, timing, and adherence strategies across different ethnic and geographic populations. In parallel, research into nutritional, lifestyle, and pharmacological interventions should be expanded to address residual risk in women not fully protected by aspirin.

Implementation science is equally important. High-performing prediction models or biomarker tests will have limited impact without strategies for scalable deployment in both high-resource and low-resource settings. This includes cost-effectiveness analyses, digital health integration, and clinician and patient education.

Ultimately, the future of pre-eclampsia research lies in personalized, adaptive care models that combine precision diagnostics with evidence-based prevention and treatment, ensuring equitable benefits for all pregnant women worldwide.

Conclusion

Preeclampsia remains a major cause of maternal and neonatal morbidity and mortality worldwide, particularly in low- and middle-income countries where early screening and effective management are often limited. Despite advances in identifying clinical risk factors, biochemical markers, and imaging-based diagnostic tools, challenges persist in ensuring timely prediction and prevention. Emerging approaches,

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including machine learning models, biomarker panels, and personalized risk assessment strategies, have shown promise in improving diagnostic accuracy and clinical decision-making. However, disparities in healthcare access, cost-effectiveness, and integration into routine practice limit their widespread use. Strengthening multidisciplinary collaboration, investing in affordable technologies, and promoting early antenatal care are essential steps toward reducing the global burden of preeclampsia. Future research should prioritize scalable solutions that bridge the gap between innovation and real-world application, ensuring that every expectant mother—regardless of setting—benefits from advances in prediction, prevention, and treatment.

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