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Review Article

Emerging biomarkers and integrated models for preeclampsia prediction

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Abstract: Preeclampsia (PE) is a heterogeneous maternal-placental syndrome and an important cause of maternal and perinatal morbidity. PE is diagnosed after the development of hypertension with proteinuria and/or other qualifying features, whereas placental and maternal systemic changes may precede clinical presentation. These include abnormal placentation, angiogenic imbalance, endothelial damage, inflammation, metabolic disturbance and molecular changes. Biomarkers of these pathways may enable risk stratification of women before the onset of disease and guide better management. Biomarker clinical utility varies by gestational age, target phenotype and application. Angiogenic markers currently have the strongest evidence base. Placental growth factor (PlGF) is incorporated into first-trimester combined screening models for early and preterm PE. The soluble fms-like tyrosine kinase-1 (sFlt-1)/PlGF ratio is primarily used for acute triage of women with suspected PE. Routine blood-derived composite inflammatory indices such as NLR, SII, SIRI, PIV and NAR are derived from inexpensive, readily available blood tests. They lack specificity to be used alone for diagnosis. Proteomic, metabolomic, cell-free DNA, methylation, cell-free RNA, microRNA, chimeric RNA and epitranscriptomic markers have enriched the field of PE biomarkers. Their translation to clinical use, however, is variable. Given the diversity of PE in terms of underlying mechanisms and clinical features, context-specific and combined models might offer greater value than individual markers. Future applications should align biomarkers to clinical needs and require standardized assays, external validation, calibration, cost-effectiveness analysis and thresholds for action.

Keywords: Preeclampsia, biomarkers, angiogenic imbalance, systemic inflammation, cell-free DNA, multi-omics, prediction model

Introduction

Preeclampsia (PE) is a hypertensive disorder of pregnancy that typically occurs after 20 weeks' gestation. It can manifest with proteinuria, maternal organ dysfunction and/or uteroplacental dysfunction [1-4]. PE complicates 2-8% of pregnancies globally and is a significant cause of maternal and perinatal morbidity. In the clinic, its complications include preterm birth, fetal growth restriction (FGR), placental abruption, eclampsia and hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome. The consequences of PE extend beyond childbirth, as women who develop PE are at increased risk of long-term cardiovascular and renal disease [1, 2]. The various classifications of PE (early- and late-onset disease, preterm and term PE, and PE with or without severe features) reflect the diversity of this condition. For clarity, early-onset and late-onset PE are defined by gestational age at diagnosis (<34+0 and ≥34+0 weeks, respectively), whereas preterm and term PE are defined by gestational age at delivery (<37+0 and ≥37+0 weeks, respectively). Some screening studies instead classify early PE by delivery before 34 weeks. These study-specific endpoints should not be assumed to be identical to diagnosis-based definitions.

The etiology of PE is thought to be due to abnormal placentation and subsequent inappropriate maternal systemic responses. Defective trophoblast invasion and spiral artery transformation may compromise placental blood flow,

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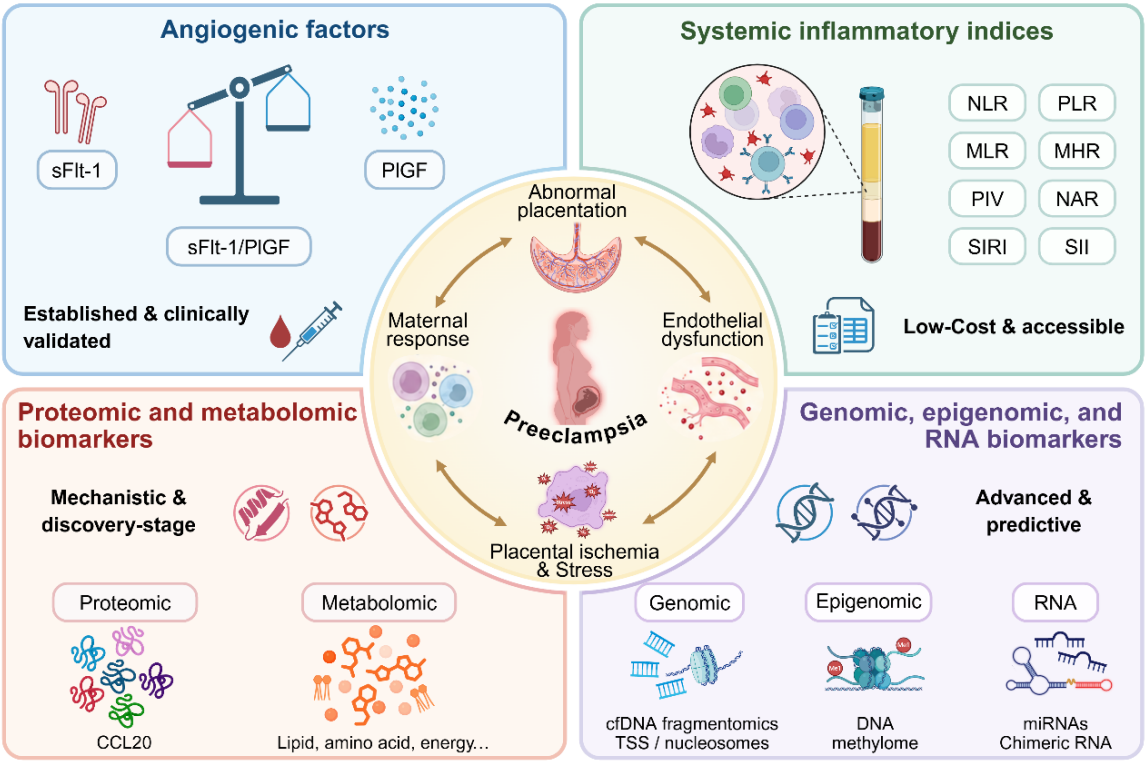


Figure 1. Biomarker landscape and pathophysiological framework of preeclampsia. Major biomarker categories in PE are shown in relation to abnormal placentation, placental ischemia and stress, maternal responses, and endothelial dysfunction. Angiogenic factors represent the most clinically validated biomarker class, whereas inflammatory indices, proteomic/metabolomic biomarkers, and genomic, epigenomic, and RNA-based markers provide complementary information for risk assessment and disease characterization.

resulting in hypoxia, oxidative stress, and ischemia-reperfusion. Placenta-derived extracellular vesicles (EVs) can transmit anti-angiogenic, inflammatory and vascular signals across the maternal-fetal interface and are being investigated as mechanistic and circulating indicators of PE [5]. The stressed placenta can secrete anti-angiogenic proteins, inflammatory cytokines, EVs and nucleic acid fragments into the maternal circulation, thus contributing to angiogenic imbalance, endothelial dysfunction, inflammation, coagulation defects and organ damage [6-8]. Delivery remains the definitive obstetric intervention, but maternal disease can persist or first present postpartum. Management includes blood pressure control, magnesium sulfate when indicated, maternal-fetal monitoring and individualized delivery planning [1-3]. Mechanistic studies continue to generate candidate pathways rather than immediately deployable tests. The LAT1-NRF2 axis has been linked experimentally to sFlt-1/PlGF imbalance and oxidative stress [9].

These characteristics have shifted the research of PE beyond diagnosis at clinical presentation to earlier, mechanism-based risk prediction. The angiogenic biomarkers, systemic inflammatory indices, proteomic and metabolomic signatures, cell-free DNA (cfDNA)-derived features, methylation profiles, and RNA-based markers can all potentially capture different layers of the maternal-placental disease process [10-13]. Their clinical usefulness, however, lies in time and purpose of use. First-trimester markers are most applicable to prevention-oriented screening, mid- and late-pregnancy markers can be used to support triage and short-term risk assessment, and molecular markers can be used to support biological subtyping. This review is a summary of new PE biomarkers and combined prediction models, focusing on clinical context, maturity of evidence, and translatability. The biomarker landscape and pathophysiological framework are summarized in **Figure 1**.

Literature selection approach. This narrative review drew on English-language literature identified in PubMed, Web of Science, and Google Scholar through 30 August 2026. We prioritized human studies and evidence syntheses relevant to PE biomarkers or prediction models, with emphasis on defined sampling windows, target phenotypes, quantitative performance measures, and prospective or external validation when available. Mechanistic studies were included when they clarified biological interpretation, but were not treated as evidence of clinical utility.

Angiogenic factors

Angiogenic markers are the best-validated biomarker group in PE research and clinical practice. PlGF is a marker of placental angiogenic activity, whereas sFlt-1 is a marker of anti-angiogenic activity and maternal endothelial stress. Sampling across the maternal-fetal circulation has confirmed placental release of PlGF and sFlt-1 and demonstrated phenotype-dependent differences in angiogenic and vasoactive proteins [14]. PlGF is more useful in the first trimester when combined with maternal characteristics, mean arterial pressure (MAP) and uterine artery Doppler indices. It has been reported that the Fetal Medicine Foundation (FMF) first-trimester combined model can detect about 90% of early PE and 75% of preterm PE at a 10% false-positive rate [15]. This result has clinical implications since risk assessment in early pregnancy may guide aspirin prophylaxis and tighter maternal-fetal surveillance [15-18].

Transportability is an important qualification to these performance estimates. In the prospective PREDICTION study of nulliparous women, the FMF algorithm detected 63.1% of preterm PE and 77.3% of early-onset PE at a 15.8% false-positive rate [19]. A separate prospective comparison of first-trimester models found no significant difference in sFlt-1 levels between subsequent PE and unaffected pregnancies, underscoring that biomarker value depends on sampling time [20]. An Asian stepped-wedge cluster-randomized implementation trial found no significant overall reduction in preterm PE between intervention and nonintervention phases; aspirin use among high-risk women was associated with lower risk in a secondary analysis [21]. Thus, test performance, treatment uptake and population-level effectiveness must be distinguished.

The performance of angiogenic screening varies across PE phenotypes. Predictive value is generally greater for early and preterm PE than for term PE, consistent with the stronger placental contribution to earlier-onset disease. At the cellular level, defective placentation is closely linked to impaired extravillous trophoblast invasion and abnormal cell-matrix interactions. Evidence from other placental disorders, including recent work on WIPF1/ACTN4-dependent podosome formation, also highlights the importance of trophoblast invasive machinery in placental pathology [22]. Term PE is itself heterogeneous. In a nested case-control study, angiogenic and cytokine profiling distinguished term PE subgroups with different inflammatory burdens and clinical characteristics [23, 24]. Maternal cardiovascular, metabolic, or inflammatory susceptibility may contribute differently across these subgroups. PlGF-based screening alone may therefore underestimate risk in this phenotype, supporting the incorporation of routine laboratory markers, metabolic and inflammatory variables, and longitudinal clinical information into future models.

The sFlt-1/PlGF ratio has a distinct role later in pregnancy, particularly in women with suspected PE. It is best considered a short-term risk-stratification tool rather than a standalone diagnostic test. A low ratio, especially a value of 38 or less in the appropriate clinical setting, has a high negative predictive value (NPV) for ruling out PE within 1 week, whereas higher ratios are associated with disease progression, adverse outcomes, and shorter time to delivery [13, 25-27]. In a recent multicenter study using Roche Elecsys assays, an NPV of 98.4% was reported at a cutoff of 38 for ruling out PE within 1 week; prediction within 4 weeks yielded positive predictive values (PPVs) of 48.2% and 65.0% at cutoffs of 38 and 85, respectively [25]. Angiogenic markers should therefore be interpreted together with blood pressure, symptoms, laboratory findings, fetal growth, and Doppler assessment, rather than as a replacement for clinical judgment [27]. Low-background luminescent lateral-flow technologies may improve analytical sensitivity for pro-

Table 1. Definitions of principal systemic inflammatory indices discussed in this review

Index	Formula	Input units
SII	platelets × neutrophils/lymphocytes	Cell counts, all $\times 10^9$/L
SIRI	neutrophils × monocytes/lymphocytes	Cell counts, all $\times 10^9$/L
PIV	platelets × neutrophils × monocytes/lymphocytes	Cell counts, all $\times 10^9$/L
NLR	neutrophils/lymphocytes	Cell counts, all $\times 10^9$/L
PLR	platelets/lymphocytes	Cell counts, all $\times 10^9$/L
MLR	monocytes/lymphocytes	Cell counts, all $\times 10^9$/L
NAR	neutrophils/albumin	Neutrophils $\times 10^9$/L; albumin g/L
MHR	monocytes/high-density lipoprotein cholesterol	Monocytes $\times 10^9$/L; high-density lipoprotein cholesterol mmol/L
CTGI	ln[CRP × triglycerides × fasting glucose/2]	CRP mg/L; triglycerides mmol/L; fasting glucose mmol/L

NLR, PLR, MLR, SII, SIRI, and PIV are hematologic indices. NAR and MHR combine hematologic variables with nutritional or metabolic measures, whereas CTGI is an inflammation-metabolism composite. All values should be calculated using the units specified above. Reported thresholds are study- and population-specific and should not be interpreted as universal diagnostic cutoffs [34, 38-40].

tein biomarker assays; FKBPL/CD44 detection has been demonstrated for early-onset PE, but prospective clinical validation is still required. These strategies may ultimately support risk stratification [28, 29].

The assay, population and prediction horizon must be specified when discussing cutoffs. In the US PRAECIS study of hospitalized women with hypertensive disorders at 23-35 weeks, an sFlt-1/PlGF ratio of at least 40 stratified progression to PE with severe features within 2 weeks, with a validation NPV of 96% and PPV of 65% [30]. This is a different endpoint from ruling out any PE within 1 week at a threshold of 38. Angiogenic markers may also add prognostic information after PE is already diagnosed [31]. However, better risk classification does not guarantee improved outcomes: PARROT-2 did not show improved perinatal outcomes with routine repeat PlGF-based testing in women with suspected preterm PE [32].

Systemic inflammatory indices

Routine inflammatory indices have attracted interest because they are inexpensive, widely available, and biologically plausible. Placental ischemia, oxidative stress, endothelial activation, and altered maternal-fetal immune communication may promote neutrophil activation, monocyte/macrophage dysregulation, lymphocyte imbalance, platelet activation, and coagulation abnormalities [6]. Circulating EVs and neutrophil extracellular traps have also been implicated in endothelial injury [33]. These observations provide a rationale for evaluating blood-derived indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), monocyte-to-high-density lipoprotein cholesterol ratio (MHR), pan-immune-inflammation value (PIV), neutrophil-to-albumin ratio (NAR), systemic inflammation response index (SIRI), and systemic immune-inflammation index (SII). Definitions and calculation formulas for the principal indices are provided in **Table 1**.

Mechanistic plausibility does not necessarily translate into clinical utility. Composite indices may capture broader immune and hematologic perturbations than individual cell counts, but their predictive performance varies across studies. First-trimester SII, PIV, and SIRI have been associated with subsequent PE, particularly when combined with clinical risk factors [34]. SII has also been evaluated as an adjunctive diagnostic or prognostic marker [35-37]. Recent large-cohort analyses further support the potential value of accessible composite biomarkers: first-trimester PIV showed an independent, dose-dependent linear association with subsequent PE risk [38], whereas the CRP-triglyceride-glucose index (CTGI), an inflammation-metabolism composite index, showed an independent nonlinear association with PE risk and may provide complementary early risk stratification [39]. NAR has likewise attracted interest because it integrates neutrophil-related inflammation with albumin-related nutritional, inflammatory, and endothelial status, and it has demonstrated a threshold-dependent relationship with future PE risk in early pregnancy [40].

The main limitation of these indices is their lack of disease specificity. Leukocyte, platelet, albumin, and lipid-related parameters can be

influenced by infection, obesity, autoimmune disease, metabolic disorders, medication use, gestational age, and laboratory variation. They should therefore not be regarded as independent diagnostic markers. Their most practical role may be low-cost risk enrichment, particularly in settings where angiogenic or omics-based testing is unavailable. Future studies should determine whether these indices provide measurable incremental value beyond models that already include maternal risk factors, MAP, PlGF, uterine artery Doppler, or routine biochemical markers [37, 41].

Proteomic and metabolomic biomarkers

Proteomic and metabolomic analyses can reveal changes that are not reflected in clinical markers. In PE, these may include placental dysfunction, endothelial damage, inflammation, oxidative stress, lipid metabolism, amino acid metabolism and mitochondrial function. These strategies can be used for risk stratification as well as to gain insight into disease processes and improve PE phenotyping. Proteomic analyses have identified proteins involved in immune activation, angiogenesis, extracellular matrix remodeling and placental stress. C-C motif chemokine ligand 20 (CCL20) was found to be a potential inflammatory marker for the prediction and diagnosis of PE in plasma Olink proteomic profiling [42]. A multi-omics discovery study of early-pregnancy chorionic villus biopsies identified molecular alterations associated with subsequent preterm and term PE, supporting molecular phenotyping [11]. The discovery groups were small (6 controls, 4 preterm PE, and 4 term PE pregnancies), and the invasive tissue findings do not establish a maternal blood screening test.

Discovery studies require careful separation by specimen and disease stage. Maternal plasma proteomics identified APOM, LCN2 and QSOX1 as candidate diagnostic proteins in established PE [43], while serum-exosome proteomics identified differential proteins related to angiogenesis and inflammation [44]. Placental proteomics and VEGFR2-associated protein studies provide complementary mechanistic evidence [45, 46]. Because placental tissue is commonly obtained at delivery, such findings do not by themselves establish an early, non-invasive screening test.

Metabolomics provides a complementary view of maternal and placental metabolic adaptation during pregnancy. Untargeted metabolomic studies have linked PE to alterations in lipid metabolism, amino acid metabolism, oxidative stress, energy metabolism, and endothelial function [47]. Serum metabolomic profiles may also help distinguish PE from gestational hypertension in early pregnancy [48]. Genetically informed approaches can further help distinguish association from potential causality. A two-sample Mendelian randomization study of circulating inflammatory cytokines and plasma metabolites provided genetic evidence supporting potential causal cytokine-PE relationships and possible metabolite-mediated pathways [49]. Cross-platform proteome- and transcriptome-wide genetic analyses have additionally prioritized circulating proteins and pathways supported by colocalization, although genetically supported targets are not necessarily useful screening markers [50]. Nevertheless, proteomic and metabolomic biomarkers remain largely at the discovery and validation stages rather than in routine clinical use. Translation is limited by modest sample sizes, variation in gestational sampling windows and fasting status, platform and batch effects, and insufficient external validation. Evidence that these markers improve prediction beyond established models incorporating maternal factors, MAP, PlGF, and uterine artery Doppler remains limited. Until prospective validation and head-to-head model comparisons are available, these approaches are best positioned for candidate discovery, mechanistic investigation, and refinement of PE phenotypes.

Longitudinal multi-omics work has reported an independently validated early-pregnancy urine-metabolite model and additional discrimination from multimodal integration, although the cohorts remained small [51]. In a separate study, combining metabolite biomarkers with PlGF, MAP, and uterine artery pulsatility index improved performance within a model-development dataset [52]. In a different clinical setting, a prospective serum-metabolomics study identified candidate predictors among women already suspected of PE in mid-to-late pregnancy [53]. These studies address distinct populations and decision points and should not be compared as interchangeable first-trimester screening tests.

Genomic, epigenomic, and RNA biomarkers

Genomic and epigenomic biomarkers offer noninvasive approaches for interrogating placental dysfunction and maternal-fetal communication in PE. cfDNA is particularly attractive because it is already widely used for prenatal aneuploidy screening and contains biological information beyond fetal chromosomal dosage, including potential applications in noninvasive screening of fetal monogenic conditions [54]. In addition to fetal fraction, cfDNA carries fragmentomic features such as fragment-size distribution, nucleosome positioning, transcription start site (TSS) coverage, and tissue-of-origin signals. Recent studies have shown that data generated from routine prenatal cfDNA sequencing can be repurposed for PE risk prediction. Low-coverage whole-genome sequencing of placental and endothelial nucleosome signatures has achieved an area under the curve (AUC) of 0.85 in a validation cohort and 0.84 in an external cohort for predicting preterm PE months before clinical diagnosis, while fragmentomic features may capture early changes in placental chromatin structure and gene regulation [55]. A separate fragmentomics study further supports the feasibility of extracting PE-associated signals from prenatal cfDNA data [10].

The incremental value of simple cfDNA measures should not be conflated with that of fragmentomic or methylomic signatures. In the prospective SMART cohort analysis of 17,520 pregnancies, total cfDNA and fetal fraction added little to preterm or term PE prediction, and neural networks performed similarly to logistic regression; the additional contribution was more apparent for early-onset disease [56].

Epigenetic features may provide more placenta-specific signals. DNA methylation is highly tissue specific and can be altered by placental hypoxia and abnormal trophoblast development, both of which are relevant to PE pathogenesis. cfDNA methylome analysis may therefore help detect placental dysfunction before clinical symptoms, and combining fragmentomic and methylomic features is a rationale for further study, rather than an established clinical advantage of the methylation-only studies cited here [57, 58]. Important practical barriers nevertheless remain. Model performance can be influenced by sequencing depth, platform choice, fetal fraction, bioinformatic pipelines, population heterogeneity, and cost. Fetal fraction itself is sensitive to both biological and technical conditions: higher triglyceride and low-density lipoprotein cholesterol levels have been associated with lower fetal fraction and increased noninvasive prenatal testing (NIPT) screen failure [59], while cfDNA concentration, library concentration, and uniquely mapped reads can affect fetal fraction in size-selection workflows [60]. In early-pregnancy-loss samples, size-based fetal-fraction enrichment has been shown to increase fetal fraction, improve test success, and reduce false-negative results [61]. These observations underscore the need to separate technical and pre-analytical variation from disease-related biological signals when adapting NIPT-derived cfDNA features for PE prediction. The cross-platform and cross-population transferability of these models still requires rigorous evaluation.

Inherited susceptibility is a separate information layer from circulating placental DNA. A large multi-ancestry genetic study developed PE and gestational-hypertension polygenic scores that predicted risk in external cohorts [62]. However, adding a systolic-blood-pressure polygenic score did not significantly improve clinical prediction in a separate EHR-based study [63]. Genetic association, biological plausibility and incremental predictive utility therefore require separate evaluation.

RNA-based biomarkers differ substantially in their evidence base; circulating miRNAs, placental chimeric RNAs and multigene plasma cell-free RNA (cfRNA) signatures should be evaluated separately. Several circulating miRNAs, including miR-423-5p, miR-21, and miR-137, have been associated with PE development, disease severity, or early detection [12, 64, 65]. However, miRNA studies are highly sensitive to sample handling, hemolysis, RNA extraction, normalization strategy, and study design, and many have used case-control or relatively small cohorts. Placenta-specific chimeric RNAs, such as PGBD2-SZT2, have also been identified in preeclamptic placentas and may provide complementary information on disease biology [66]. These miRNA and chimeric-RNA findings remain exploratory and require

prospective validation of clinically accessible assays. They should not be used to infer the maturity of all cfRNA prediction approaches.

Plasma cfRNA profiling has attracted interest as a noninvasive approach to PE prediction [67]. In contrast to isolated candidate-RNA studies, plasma cfRNA signatures have undergone independent validation. Moufarrej and colleagues identified an 18-gene signature measured at 5-16 weeks [68], and Rasmussen and colleagues demonstrated presymptomatic PE-associated transcriptomic patterns across prospectively collected cohorts [69]. A subsequent study using samples collected at 12-33 weeks combined RNA signatures with clinical variables and reported validation AUCs of 0.81 for preterm PE and 0.88 for early-onset PE [70]. These results describe presymptomatic prediction across a broad gestational window, rather than exclusively first-trimester screening. These estimates should be interpreted in relation to case sampling, outcome prevalence and gestational window rather than directly compared with unselected population-screening results.

More recent cfRNA studies also emphasize subtype specificity. Trimester-specific models showed better first-trimester prediction of early-onset than late-onset PE, with lower performance for some endpoints in external validation [71]. LEP and PAPPA2 cfRNAs were associated with PE accompanied by FGR; notably, the external dataset with an AUC of approximately 0.95 contained established PE, so that result does not demonstrate equivalent presymptomatic prediction [72]. Transcriptomic subtyping has further distinguished placental-associated and immune-associated hypertensive disorders of pregnancy [73].

Computational cfRNA reanalyses can generate useful hypotheses but need additional scrutiny. A fully convolutional dense-network study used extensive synthetic augmentation and a constructed individual risk score; agreement with that score does not establish calibration for observed PE risk in an independent clinical population [74]. Overall, cfRNA- and cfDNA-based approaches both show promising validation evidence, but neither can yet be considered universally more clinically mature without head-to-head comparisons and implementation studies.

Integrated prediction models and clinical translation

PE arises from interacting biological pathways, making it unlikely that any single marker will perform consistently across all clinical phenotypes. Integrated prediction models seek to address this limitation by combining maternal characteristics, ultrasound findings, blood pressure, angiogenic biomarkers, routine laboratory tests, and molecular features. The optimal predictor set depends on gestational age, target phenotype, and intended clinical use. The FMF first-trimester model is a well-validated example, although its performance varies across populations and phenotypes [15, 19]. Its lower performance for term PE has motivated the evaluation of additional laboratory and phenotype-specific variables. Representative studies are summarized in **Table 2**. The multidomain inputs, integrated prediction models, and their clinical utility are summarized in **Figure 2**.

Recent studies illustrate the potential benefit of such integration. A study of 17,955 pregnancies from two centers combined inflammatory markers, red blood cell indices, and maternal factors, reporting AUCs of 0.82 in the training set and 0.73 in the test set after a random 1:1 split of the pooled cohort [75]. Blood was collected at 8-14+6 weeks (mean, 12.43 weeks). This represents internal split-sample validation rather than independent external validation. The model included gestational diabetes; whether this diagnosis was available at the intended early-pregnancy prediction time requires clarification before clinical application. Another retrospective study of 12,715 pregnancies incorporated routine biochemical markers into the FMF framework and reported an AUC of 0.954 for preterm PE, with detection increasing from 65.0% to 92.5% at a 14% false-positive rate. For term PE, the reported AUC was 0.913 and detection increased from 47.7% to 81.1% [76]. These findings are particularly relevant because term PE remains difficult to predict using many first-trimester screening strategies. However, improvements in discrimination should be interpreted alongside calibration, external validation, and clinical utility. These within-study comparisons should not be interpreted as independently replicated improvements; validation of biological associations in an external transcriptomic dataset

Table 2. Selected representative biomarker and integrated-model studies, organized by clinical use

Biomarker or model	Sampling window	Population and target outcome	Principal performance	Validation setting	Intended application
FMF combined model [15, 19]	11-14 weeks	Screening; early-onset and preterm PE	~90% early and 75% preterm PE at 10% FPR; PREDICTION 77.3% early-onset and 63.1% preterm PE at 15.8% FPR	Prospective external validation	Population screening and prevention planning
sFlt-1/PlGF ratio [25, 30]	18-36+6; PRAECIS 23-34+6 weeks	Suspected PE or hypertensive disorders; short-term PE risk	Elecsys: NPV 98.4% for PE within 1 week at cutoff 38; KRYPTOR/PRAECIS: NPV 96% and PPV 65% for severe features within 2 weeks at ≥40	Prospective multicentre studies	Triage and short-term risk assessment, not population screening
Prenatal cfDNA model [55]	≤16 weeks (median 12.1)	Prenatal screening; preterm PE	AUC 0.85 validation; 0.84 external cohort	External cohort	Early population-level risk assessment under evaluation
Plasma cfRNA plus clinical models [70]	12-33 weeks	Presymptomatic samples; preterm and early-onset PE	Validation AUC 0.81 for preterm PE; external-validation AUC 0.88 for early-onset PE	Independent validation cohorts	Presymptomatic molecular risk assessment; not exclusively first-trimester screening
Inflammatory plus red-cell model [75]	8-14+6 weeks; mean 12.43	Two-centre cohort, n=17,955; PE	Training AUC 0.82; internal test AUC 0.73	Random 1:1 split of pooled two-centre data; internal validation	Investigational early risk assessment; predictor availability needs clarification
Longitudinal EHR model [78]	28-40 weeks; rolling	Routine-care sites; PE onset within 1, 2, or 4 weeks	At 34 weeks: AUC 0.863 development site; 0.808-0.834 validation sites; varies by prediction horizon	Cross-site validation; transfer, fine-tuning, and retraining evaluated separately	Dynamic short-term risk assessment

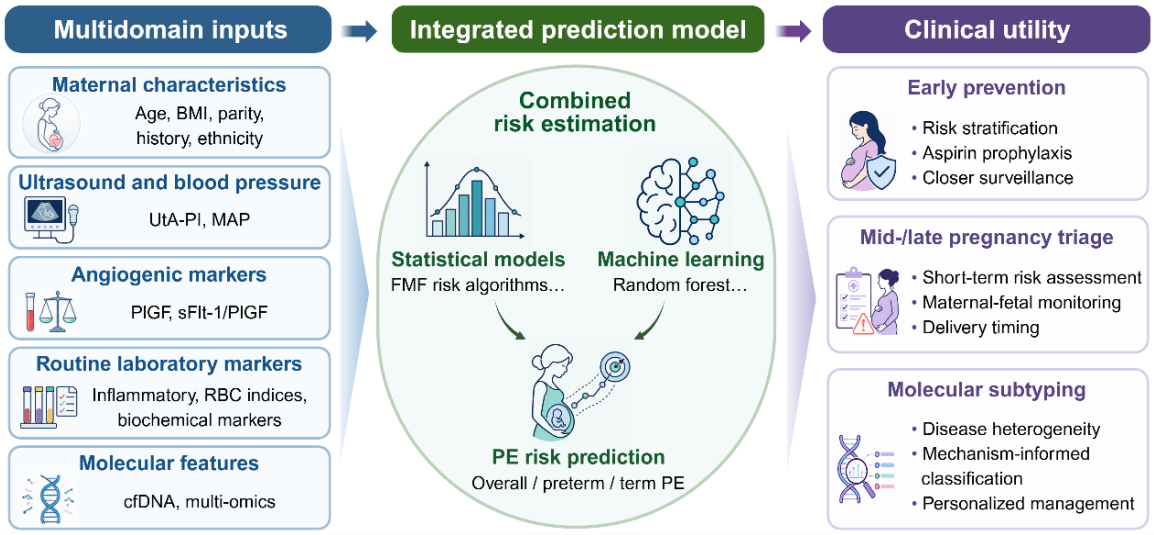


Figure 2. Multidomain inputs, integrated prediction models, and clinical utility in preeclampsia. Integrated PE prediction models combine maternal characteristics, ultrasound and blood pressure measurements, angiogenic biomarkers, routine laboratory indices, and molecular features. Depending on gestational age and clinical purpose, these models may support early prevention, mid- and late-pregnancy triage, short-term risk assessment, delivery planning, and molecular subtyping.

does not establish external validation of the clinical prediction model.

Additional circulating markers may improve specific clinical models without being universal replacements for angiogenic assays. Across four prospective cohorts, high-sensitivity cardiac troponin I added information to maternal factors and the sFlt-1/PlGF ratio, supporting further evaluation of maternal cardiovascular injury alongside placental dysfunction [77].

Dynamic prediction provides another strategy for risk assessment later in pregnancy. Longitudinal electronic health record (EHR) models can update risk as blood pressure, laboratory values, and clinical events evolve. A recent study developed longitudinal models for PE onset within 1, 2, or 4 weeks and reported AUCs at 34 weeks of 0.863 at the development site and 0.808-0.834 at validation sites [78]. Performance varied by observation window, prediction horizon, and transfer strategy; these values should not be generalized to every model configuration. Such models do not replace first-trimester prevention screening; rather, they may be useful for repeated assessment of short-term PE onset risk; adverse-outcome prediction and delivery timing require separately developed endpoints and models. Together with cfDNA-based approaches [55], these strategies support increasingly personalized risk assessment. Prevention-oriented models are most relevant in early pregnancy, dynamic and triage models in mid-to-late pregnancy, and molecular models for mechanistic subtyping. Importantly, a higher AUC alone is insufficient to establish clinical value. Useful models also require adequate calibration, interpretability, robustness, external transportability, decision-curve benefit, and demonstrable incremental value over current care [79].

Related models target outcomes other than PE onset. A machine-learning analysis in women with suspected PE combined angiogenic markers with clinical and ultrasound data to predict adverse outcomes [80]. Prediction of time to delivery also reflects clinical management and should not be interpreted solely as a measure of biological disease progression.

Late-pregnancy assessment may support a different preventive pathway. Systematic reviews indicate that prediction of late-onset PE remains less mature than prediction of preterm PE and requires gestation-specific biomarkers and external validation [81]. In PREVENT-PE, risk-stratified planned early-term birth reduced PE incidence from 5.6% to 3.9% compared with usual care (adjusted risk ratio, 0.70; 95% CI, 0.58-0.86), without increasing emergency

caesarean section or neonatal-unit admission [82]. This randomized evidence concerns a specified screening-and-delivery strategy in two UK hospitals and does not establish the clinical utility of every biomarker model.

Limitations and future perspectives

Several barriers continue to limit the clinical translation of PE biomarkers. A central challenge is disease heterogeneity. Biomarker profiles may differ across early-onset, late-onset, preterm, term, placenta-driven, maternal-factor-dominant, FGR-associated, and non-FGR PE. Future studies should prespecify the target phenotype before model development rather than treating all PE cases as a single outcome. This distinction is particularly important for improving term PE prediction and for differentiating PE from gestational hypertension or isolated fetal growth restriction.

The reliability of reported biomarkers is also affected by methodological heterogeneity. Many candidate markers have been derived from retrospective or single-center cohorts that differ in outcome definitions, sampling windows, assay platforms, and cutoff values. Case-control designs may overestimate discrimination, and the relatively low prevalence of PE can substantially reduce positive predictive value in population screening even when AUC appears acceptable. Before biomarker-based prediction can be considered robust, prospective cohorts, standardized outcome definitions, prespecified gestational windows, and independent validation across diverse clinical settings are required. Model evaluation should distinguish internal validation from testing a fixed model in independent data, and should report calibration, discrimination and decision-curve net benefit in the intended population [83]. External-validation sample size should be chosen to estimate these quantities with adequate precision rather than by a universal events-per-study rule [84].

Technical and implementation requirements also differ across biomarker classes. Angiogenic assays require platform-specific interpretation, gestational-age adjustment, validated cutoffs, and clear clinical pathways. Inflammatory indices are readily affected by infection, obesity, autoimmune disease, metabolic disorders, medication use, and laboratory variation. Proteomic and metabolomic studies require strict standardization of sample processing, fasting conditions, batch effects, platform variability, and analytical reproducibility. cfDNA-based models depend on sequencing depth, fetal fraction, computational pipelines, and cross-platform transferability across NIPT systems. RNA and epitranscriptomic biomarkers require standardized pre-analytical processing, normalization, and functional validation. FTO-mediated N6-methyladenosine (m6A) demethylation has been linked to decidualization and vascular remodeling through the IGF1R/YTHDF2 signaling axis, suggesting a potential but still exploratory role for epitranscriptomic regulation in PE biomarker research [85]. In addition to technical accuracy, models should demonstrate calibration, decision-curve benefit, cost-effectiveness, interpretability, and that biomarker-guided management leads to better maternal or perinatal outcomes [55, 78, 79, 85, 86]. Reporting should follow TRIPOD+AI, and appraisal should use PROBAST+AI to identify bias, applicability and fairness concerns [87, 88]. Early clinical evaluation of decision support should also assess safety, clinician interaction and workflow effects, as emphasized by DECIDE-AI [89]. Recent evidence syntheses reinforce these domain-specific limitations: inflammatory biomarkers show substantial between-study heterogeneity, metabolomic candidates remain sensitive to platform and cohort design, and broad biomarker reviews emphasize the need for prospective validation [90-92]. Assay interpretation also depends on whether total or placenta-specific sFlt-1 is measured [93].

Conclusion

PE is a heterogeneous maternal-placental syndrome, and no single biomarker fully reflects its clinical and biological spectrum. The most clinically validated biomarkers are angiogenic markers, with PlGF incorporated into first-trimester combined screening models for early and preterm PE and the sFlt-1/PlGF ratio used to triage suspected PE over the short term. Inflammatory indices, proteomic and metabolomic signatures, cfDNA-derived features, methylation profiles, miRNAs, chimeric RNAs, and epitranscriptomic markers provide further insight into immune activation, metabolic disturbance, placental stress, and molecular regu-

lation, but their clinical availability differs. Validated multigene plasma cfRNA signatures are promising for early molecular risk stratification, although implementation evidence remains limited. Future models should select predictors according to clinical purpose, incremental value beyond current care, feasibility, and cost, while accounting for gestational age and PE phenotype. Standardized assays, external validation, calibration, actionable thresholds, and evidence that biomarker-guided care improves maternal or perinatal outcomes remain necessary before routine implementation.

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Disclosure of conflict of interest

None.

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