# Strengthening global pre-eclampsia diagnosis: the potential role of biomarkers in low-income and middle-income countries

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**Pre-eclampsia is a leading cause of maternal and perinatal morbidity and mortality, disproportionately affecting low-income and middle-income countries (LMICs). Limited access to diagnostic resources, delayed presentation, and health-system constraints contribute to later detection and higher rates of complications. Tools enabling early diagnosis and risk stratification could improve outcomes. Biomarkers, such as placental growth factor and soluble fms-like tyrosine kinase-1, improve accuracy and speed of pre-eclampsia diagnosis in high-income countries, reducing maternal adverse outcomes. The value of these biomarkers might be even greater in LMICs where women more frequently experience severe complications. Biomarker-based testing could help identify those requiring urgent intervention while allowing others to continue routine care, supporting efficient use of scarce resources. This Review summarises evidence on pre-eclampsia diagnosis in LMICs, including biomarker performance, emerging low-cost and point-of-care approaches, and areas of opportunity in low-resource environments, where the potential for benefit is greatest. Harnessing these diagnostics could enhance pre-eclampsia detection, support timely intervention, and ultimately reduce preventable deaths among women and babies.**

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## Introduction

Pre-eclampsia remains a major contributor to maternal and perinatal morbidity and mortality worldwide, causing an estimated 42 000 maternal and 500 000 perinatal deaths annually.[1] The burden of disease is greatest in low-income and middle-income countries (LMICs), where 92% of maternal deaths occur.[2] Globally, hypertensive disorders of pregnancy account for 16% of maternal deaths.[3] Prevalence of pre-eclampsia is highest in Africa, with 335 cases per 100 000 women of reproductive age compared with 75 per 100 000 in Europe, where the majority of pre-eclampsia research is done.[4] Disease severity is typically greater in LMICs; severe presentations are twice as common in African countries compared with the USA,[5] and eclampsia incidence can be nearly 100-times higher in LMICs than in high-income countries.[6]

Survivors of pre-eclampsia face increased risks of chronic hypertension, cardiovascular disease, and metabolic, renal, and neurological complications.[7–9] Pre-eclampsia is also associated with fetal growth restriction, stillbirth, and iatrogenic preterm birth.[10,11] As elective early delivery is the only definitive management for pre-eclampsia, many babies are delivered preterm, contributing to high perinatal mortality in regions with constrained neonatal care.[12] Infants born following a pregnancy affected by pre-eclampsia have increased risks of cardiovascular, renal, immune, and neurodevelopmental disorders.[13]

Most hypertension-related deaths in pregnancy are preventable with prompt, accurate diagnosis and timely intervention.[14] In many LMICs, systemic barriers, such as inadequate antenatal care provision, workforce shortages, constrained diagnostic capacity, and referral delays, impede early detection and management of pre-eclampsia.[15–17] Consequently, many women are diagnosed with severe disease, when complications have developed and opportunities for intervention with antihypertensives, magnesium sulfate, enhanced surveillance, or timely delivery are reduced.

Tools that enable earlier and more accurate detection could markedly improve outcomes. A recent priority-setting consultation identified early diagnosis as the top research priority for women affected by pre-eclampsia in Ghana.[18] Scaling up basic antenatal care remains essential, but novel diagnostics, such as biomarkers and clinical assessment tools, offer opportunities to refine pre-eclampsia diagnosis and identify women at highest risk of adverse outcomes.[19]

This Review describes the potential for improving pre-eclampsia diagnosis and risk stratification in resource-limited settings by using clinical prediction models and focusing on the potential for biomarker testing after 20 weeks gestation. First-trimester placental growth factor (PlGF) screening or the use of angiogenic markers as therapeutic targets are outside the remit of the Review.

## Current methods of pre-eclampsia diagnosis

Pre-eclampsia diagnosis is inherently complex because symptoms can be absent or non-specific until late-stage disease. Furthermore, the disease course is unpredictable, making it difficult to distinguish those at risk of severe complications from those who remain stable until term.[20,21] The definition of pre-eclampsia has evolved from hypertension with proteinuria to now include hypertension during pregnancy with any evidence of end-organ or placental dysfunction.[22–25] Detecting end-organ disease can be challenging in low-resource settings due to barriers to access validated blood pressure monitors, laboratory testing, and obstetric ultrasound.[26–29] Many LMICs do not have updated, context-specific

guidelines and continue to rely on conventional WHO definitions.[30,31] Blood pressure measurement and dipstick proteinuria have long been the mainstay of pre-eclampsia detection, but both have limitations. Identifying hypertension is essential for diagnosis of pre-eclampsia, and regular blood pressure assessment is a fundamental component of quality antenatal care. Severity of hypertension does not reliably predict the most serious pre-eclampsia complications, such as stillbirth, eclampsia, and maternal death, although it is a useful predictor of other important complications, such as renal damage and critical care admission.[32,33] Blood pressure assessment is inexpensive and non-invasive, but accuracy depends on correct technique, and most blood pressure devices are not validated for pregnancy or pre-eclampsia.[34] Urine dipsticks are cheap (€0·03–0·81)[35] and widely used for proteinuria screening; however, availability can be inconsistent in many low-resource settings and they have low negative predictive value (NPV) and poor sensitivity for pre-eclampsia; a 2022 meta-analysis reported that a diagnosis might be missed in up to 40% women with proteinuria.[35] The protein to creatinine ratio or albumin to creatinine ratio are recommended over a 24-h urine sample collection for accurate diagnostics,[36] but often unaffordable or inaccessible in LMICs. The presence of proteinuria has not been shown to accurately predict adverse outcomes.[32,37] These limitations contribute to delayed diagnosis, preventable morbidity, and inefficient use of scarce resources.

## Clinical risk-stratification tools

To improve risk stratification and identify women at highest risk of adverse outcomes, several prediction models incorporating routine clinical tests, laboratory investigations, and maternal signs and symptoms have been developed. The fullPIERS model has been shown to predict severe adverse maternal outcomes within 48 h in high-income settings with an area under the receiver operating characteristic curve (AUROC) of 0·88 (95% CI 0·84–0·92),[38] although its performance deteriorates over time from testing and the predictions should be interpreted with increasing caution as the pregnancy continues beyond 48 h.[39] In upper-middle-income settings, a similar performance was seen in retrospectively collected, single-site cohort studies from South Africa,[40] Mexico,[41] and Brazil,[42] although when used in a prospectively collected cohort of 757 women from five LMICs, the AUROC was lower at 0·77 (0·72–0·82) for predicting the development of an adverse outcome within 48 h, potentially related to differences in the populations studied and the resources for management available.[43]

The PREP-S model, which uses a different combination of clinical signs, symptoms, and laboratory investigations, shows a C-statistic of 0·75 (95% CI 0·69–0·81) for prediction of adverse maternal outcomes within 48 h.[44] Both fullPIERS and PREP-S can be considered for use to help guide decisions about care in the UK according to the National Institute of Health and Care Excellence (NICE); however, neither model has definitively shown an effect on clinical outcomes.[23] Both models rely on laboratory tests frequently unavailable in LMICs. Consequently, the miniPIERS model was developed specifically for use in LMICs. MiniPIERS uses only demographics, symptoms, blood pressure, and dipstick proteinuria, all of which can be assessed using history taking or widely available and cheap diagnostic tools, making the tool attractive for low-resource settings. The miniPIERS model has shown an AUROC of 0·713 (0·66–0·77) for predicting adverse maternal outcomes.[45] Although a retrospective validation of miniPIERS in Zanzibar found that the model had no discriminative ability to predict adverse outcomes in its main cohort, it showed an AUROC of 0·72 (0·63–0·82) when used in a subgroup of women at less than 34 weeks gestation. The model had poor utility in this setting, where the majority of women with suspected pre-eclampsia presented either already in labour or with an adverse outcome present at admission.[46] When used in LMICs as part of a community-level intervention to improve early detection and guide management or pre-eclampsia, the miniPIERS model was not found to affect adverse pregnancy outcomes.[47] A cross-sectional study[48] from Zimbabwe examined the predictive value of commonly found signs and symptoms of pre-eclampsia for adverse outcomes and determined that they are ineffective at predicting serious complications and should not be used to guide interventions. These findings highlight the need for more effective, scalable diagnostic tools and general health-system strengthening.

## Angiogenic biomarkers

Among the many biomarkers studied in pre-eclampsia, the angiogenic proteins PlGF and soluble fms-like tyrosine kinase-1 (sFlt-1) are the most extensively validated and clinically useful. The development of fully automated assays and the introduction of testing for PlGF and the sFlt-1 to PlGF ratio represent the biggest advancements in pre-eclampsia diagnostics in recent decades.[49,50]

Pre-eclampsia is characterised by dysregulated angiogenesis and an angiogenic imbalance, specifically marked by an excess of antiangiogenic factors, such as sFlt-1 and soluble endoglin (sEng), and reduced maternal concentrations of the proangiogenic factor PlGF, a member of the vascular endothelial growth factor (VEGF) family.[51,52] Abnormal placentation and chronic inflammation is thought to contribute to maternal endothelial dysfunction by stimulating excess placental production of sFlt-1, which acts as circulating antagonist and decoy receptor that sequesters both PlGF and VEGF, thereby acting as potent inhibitor of PlGF.[51,53,54] Both biomarkers directly reflect the underlying disease pathology, unlike conventionally used indicators of pre-eclampsia, such

as blood pressure and proteinuria, which represent inherent organ dysfunction. Biomarker concentration abnormalities are detectable before the presentation of clinical disease; circulating concentrations of sFlt-1 increase sharply approximately 5 weeks before the onset of clinical symptoms and a reduction in maternal PlGF concentrations can be seen in pregnancies that go on to develop pre-eclampsia as early as the first trimester.[55,56]

### PlGF

Normal maternal PlGF concentrations rule out pre-eclampsia requiring delivery with an NPV of up to 98% (95% CI 0·93–0·99)[57] as shown in multicentre prospective studies among women presenting with suspected pre-eclampsia before 35 weeks' gestation.[57,58] PlGF concentrations also correlate strongly with time to delivery in women with suspected disease before 35 weeks' gestation. Women with normal concentrations have a median latency of up to 62 days (IQR 38–90),[57] whereas those with very low PlGF might require delivery within as little as 3 days. Clinical trials show real-world benefits of PlGF testing; PlGF testing halved time to diagnosis and reduced a composite of severe maternal morbidity, without affecting perinatal outcomes or gestational age at delivery in a multicentre trial among women with suspected pre-eclampsia in the UK.[59] Testing for PlGF alone offers cost-efficiencies as compared with testing for two angiogenic proteins.[60]

### sFlt-1 to PlGF ratio

A normal maternal sFlt-1 to PlGF ratio (<38 when measured using the Elecsys platform [Roche, Mannheim, Germany]) has been shown to exclude pre-eclampsia within 1 week with an NPV of up to 99·3% (95% CI 97·9–99·9) and 80·0% sensitivity (51·9–95·7).[61] Similar performance has been reported in other studies[62,63] and test performance remains high for 4 weeks.[64,62] A normal ratio (using a threshold of ≥40 when measured using the BRAHMS KRYPTOR platform [Thermo Fisher Scientific, Henningsdorf, Germany]) outperforms standard clinical tests for ruling out pre-eclampsia in the USA.[63] The sFlt-1 to PlGF ratio achieved 100% sensitivity (95% CI 85·8–100) and NPV (97·1–100) for predicting disease within 1 week, improving diagnostic precision and stratification, without negatively impacting health resource use in a single-centre trial in the UK.[65]

Several commercial assays exist for testing both PlGF and the sFlt-1 to PlGF ratio and perform with similar accuracy, but their thresholds for rule-out and rule-in of disease are not interchangeable because they measure different isoforms and use different detection technologies.[66] Diagnostic performance also varies by PlGF isoform. Some testing assays enhance accuracy by measuring both angiogenic markers and reporting the ratio, whereas others achieve similar accuracy using PlGF alone.[61,66] No assay measuring sFlt-1 alone provides equivalent diagnostic performance for pre-eclampsia.

## Benefits of angiogenic biomarker testing

Angiogenic biomarkers consistently outperform traditional indicators such as blood pressure and proteinuria in detecting preterm pre-eclampsia in women presenting with suspected disease (panel 1).[57,67] Large prospective studies show both PlGF and the sFlt-1 to PlGF ratio have high diagnostic accuracy for identifying either pre-eclampsia or related adverse events, particularly before 35 weeks of gestation.[57,67–69]

Angiogenic biomarker testing enables clinicians to safely defer intervention in women with normal results, for whom adverse outcomes are unlikely, while prioritising closer monitoring and targeted admission for those with abnormal concentrations and higher risk of complications.[67] This enables more efficient use of resources and minimises unnecessary hospital stays, an important priority for pregnant women.[70,71]

PlGF-based testing does not need to be routinely repeated in suspected preterm pre-eclampsia as it does not improve perinatal outcomes, although it shortened time to diagnosis (mean 3·8 days [95% CI –7·1 to –0·5]) in a multicentre trial in the UK.[71] A single test being

***Panel 1:* Strengths and weaknesses of diagnostic and risk-stratification approaches**

**Clinical approaches**

*Strengths*

- Widespread availability: tools such as blood pressure monitors and urine dipsticks are found in many clinical settings
- Require minimal training: risk prediction tools are simple to use
- Low-cost: signs, symptoms, history, blood pressure, and dipstick proteinuria are inexpensive methods of assessment

*Weaknesses*

- Accuracy: traditional clinical signs are non-specific, prone to observer error, and poor predictors of serious adverse outcomes
- Late detection: hypertension and proteinuria are features that often manifest only after end-organ damage has already occurred

**Angiogenic biomarkers**

*Strengths*

- Accuracy: biomarkers outperform traditional clinical markers like blood pressure and proteinuria in identifying preterm pre-eclampsia
- Early detection: abnormal biomarker concentrations can precede clinical signs of disease by more than 10 weeks
- Risk stratification: testing correlates with time to delivery and the risk of severe complications enabling clinicians to target care to high-risk patients
- Long-term cost savings: despite upfront costs, biomarkers lead to reduced overall health-care spending
- Point-of-care tests are available, offering a cheaper and easier alternative to traditional laboratory-based biomarker testing

*Weaknesses*

- High initial costs: validated laboratory platforms can be expensive
- Infrastructure needs: tests require specialised equipment, stable power, and often cold chain storage
- Reduced performance at term: diagnostic accuracy typically declines after 37 weeks' gestation

sufficient reduces costs and logistical demands, increasing the feasibility and affordability of PlGF-based diagnostics for low-resource settings.

Angiogenic biomarker testing consistently shows cost savings through improved risk stratification and reduced monitoring costs for women at low risk of pre-eclampsia-related complications with normal PlGF concentrations.[72] Estimates from the UK, where commercial tests cost £50–79 per test,[60] suggest savings of £229 per patient tested (excluding test cost), equating to £2 891 196 annually.[59] Estimates from other settings range from saving USD$15–1881 per patient tested.[72–74]

The 2021 International Society for the Study of Hypertension in Pregnancy guidelines recognise angiogenic imbalance as evidence of utero-placental dysfunction. Consequently, pregnancy hypertension after 20 weeks with abnormal angiogenic markers meets the criteria for pre-eclampsia, even if no other signs of disease are present. Clinical guidelines in Canada,[75] the UK,[60] and the USA now recommend PlGF-based testing for evaluating suspected pre-eclampsia.[76]

## Population heterogeneity

Racial disparities exist in both the prevalence and outcomes of pre-eclampsia, with higher rates and more severe adverse outcomes seen in Black women when compared with White women.[77,78] It is vital that steps are taken to reduce these inequalities, and that they are not inadvertently worsened by the introduction of new interventions.

There is some evidence that angiogenic biomarker concentrations vary according to race, with higher concentrations of PlGF and a lower sFlt-1 to PlGF ratio reported in Black and south Asian women compared with White women.[79–81] However, it is not yet clear what the clinical significance of this finding is and whether the clinical benefits of using angiogenic biomarker testing are similar across women of different races and ethnicities. Variation in test performance according to race and effect on clinical interpretation has not yet been comprehensively investigated; evaluation and clear clinical guidance is urgently required to ensure that test interpretation does not disadvantage women based on race or ethnicity.

## Evidence for angiogenic biomarker testing in LMICs

Most angiogenic biomarker evidence comes from high-income settings; however, emerging LMIC data show strong diagnostic performance, feasibility, and clinician acceptance, supporting the need for further evaluation. PlGF concentrations have repeatedly been shown to be significantly lower in women with pre-eclampsia compared with women who are normotensive in case–control studies from India,[82] Nepal,[83] Indonesia,[84,85] South Africa,[86] Uganda,[87] and Nigeria.[88] Diagnostic performance of PlGF tests in two cohorts from LMIC settings (Uganda [AUROC of 0·94 (95% CI 0·91–0·97)][87] and India [0·88 (0·81–0·95)]) has been shown to be similar to performance reported in high-income countries. The sFlt1 to PlGF ratio has also been shown to perform well in diagnosing pre-eclampsia in populations from Uganda (AUROC 0·95; 0·93–0·98)[87] and Iran (0·90; 0·83–0·98).[89]

Prospective cohorts across varied LMICs[90,91] consistently show that low PlGF or an elevated sFlt-1 to PlGF ratio identifies women at a high risk of pre-eclampsia and adverse outcomes. In Sierra Leone, a normal maternal PlGF concentration ruled out pre-eclampsia with severe maternal adverse events (maternal death and eclampsia) with up to 95·5% (95% CI 77·2–99·9) and 97·3% (85·8–99·9). Normal PlGF concentration ruled out perinatal death with sensitivity of 97·0% (84·2–99·9) and NPV of 97·3% (85·8–99·9). Very low results identified women at particularly high risk of these very serious adverse outcomes.[90] Half of women with a very abnormal PlGF result experienced a stillbirth or a neonatal death, and 1 in 5 either died or experienced eclampsia, these complications did not occur in any women with a normal PlGF result.[90] Similarly, in Mozambique, low PlGF concentrations were associated with higher rates of pre-eclampsia, perinatal death, and adverse outcomes.[91] In this setting, a third of women with a PlGF less than 50 pg/mL experienced a stillbirth, compared with 5% of women with a PlGF concentration of 100 pg/mL or above (p<0·0001) when measured using the Quidel Triage (QuidelOrtho Corporation, San Diego, CA, USA) PlGF test.[92] Unlike studies from high-income countries where perinatal death is often rare,[93] the cohort study from Mozambique allowed evaluation of biomarkers to predict fetal death; a threshold of 50 pg/mL predicted stillbirth with 76·9% sensitivity (95% CI 60·7–88·9) and 74·1% specificity (68·0–79·5). The findings highlight the potentially transformative ability of biomarker testing to stratify risk, even in the absence of access to other tests or investigations, and monitor fetal or maternal wellbeing. Future studies will need to investigate whether biomarker results can be used to prevent these deaths by informing delivery decisions when ultrasound or fetal monitoring is unavailable.

Strong associations between abnormal angiogenic biomarker concentrations and adverse maternal or perinatal adverse events have been further confirmed in studies in a diverse range of settings, including Haiti,[94] Brazil,[95,96] Mexico,[97,98] India,[99–102] and Indonesia.[103] Biomarkers outperformed routine biochemical and clinical parameters in predicting adverse outcomes in two Indian studies, with AUROCs ranging from 0·80[104] to 0·88 (95% CI 0·80–0·96).[100] Furthermore, evidence from Haiti suggests that angiogenic imbalance is associated with adverse outcomes even at term gestations,[94] which has been challenging to identify in high-income settings where women are delivered promptly upon diagnosis of term pre-eclampsia.

A normal sFlt-1 to PlGF ratio showed 100% NPV for pre-eclampsia with severe features in an Indian outpatient setting, supporting its role in ruling out high-risk disease,[101] and an elevated ratio was associated with early, more severe disease in a Brazilian population.[96] A ratio less than 38 (measured using Elecsys) ruled out severe maternal morbidity or mortality more effectively than the fullPIERS model, with an NPV of 97·3% (95% CI 93·9–99·1) in a randomised trial in Brazil.[105] Although the intervention did not reduce preterm births, probably because most participants already had confirmed disease at enrolment (60·9% with sFlt-1 to PlGF ratio >38), it might have contributed to reductions in eclampsia and other adverse outcomes through improved surveillance and risk awareness among clinicians.[105]

Across multiple LMIC cohorts, biomarker results meaningfully stratify risk. Women with normal biomarker concentrations remain pregnant substantially longer than those with abnormal results, with median differences of more than 30 days in Sierra Leone[90] and Mexico,[98] and 20 days in Mozambique.[91] These findings illustrate the potential of biomarkers to identify pregnancies where intervention can safely be deferred, allowing constrained resources to be focused on women at higher risk. A pilot programme incorporating biomarker-guided referral pathways in Mozambique showed this in practise; integrating PlGF testing in antenatal triage increased detection of pre-eclampsia and referral to higher-level care.[92] Further research should assess how biomarker-guided triage optimises referrals without overwhelming services.

Angiogenic biomarkers can help differentiate pre-eclampsia from other hypertensive disorders, a frequent diagnostic challenge in LMICs. Among 810 women with a clinical diagnosis of pre-eclampsia at enrolment, adverse maternal outcomes only occurred in women with an abnormal sFlt-1 to PlGF ratio (>85, measured using the Elecsys in a prospective study in Mexico.[98] All women with a normal ratio (≤38) were later confirmed to have been misdiagnosed and were largely found to have chronic hypertension rather than pre-eclampsia. When comparing angiogenic biomarker concentrations of women with superimposed pre-eclampsia with those with uncontrolled chronic hypertension in an observational study in Mexico, PlGF was shown to be lower (34·39 *vs* 169 pg/mL, p<0·001), and the sFlt-1 to PlGF ratio to be higher (7564 *vs* 1281 pg/mL, p<0·001) in superimposed pre-eclampsia when measured using the BRAHMS KRYPTOR test.[97] These results indicate that PlGF-based testing might be a valuable triage tool for distinguishing pre-eclampsia and directing appropriate care, helping to avoid unnecessary interventions including preventable preterm delivery in women with normal biomarker levels.

Using only blood pressure measurement and biomarker results, a US study showed that women who develop pre-eclampsia with severe features or associated adverse outcomes could be effectively identified using only blood pressure measurements and biomarker results. These findings suggest that biomarkers could be used at the point of triage and further laboratory investigations could be reserved for those with abnormal biomarker concentrations. In setting with limited resources, this strategy could help direct investigations to those who are most at risk of complications.[106]

Overall, results from diverse LMIC settings show that angiogenic biomarkers provide good diagnostic accuracy, stratify maternal and fetal risk, and could help reduce unnecessary admissions or interventions. However, nearly all the described studies used laboratory-based biomarker testing, which requires centrifugation, limiting the potential for widespread use in LMICs. Key questions remain regarding whether biomarker-guided decisions can reduce maternal and perinatal deaths in settings where ultrasound and fetal monitoring are limited and how to implement cost-effective, whole-blood, point-of-care (POC) assays without overwhelming referral systems.

## Other pre-eclampsia biomarkers

Glycosylated fibronectin (GlyFN), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and sEng have emerged from recent research as promising, clinically relevant, non-angiogenic biomarkers for pre-eclampsia.

### GlyFN

GlyFN, a protein involved in haemostasis, cell adhesion, migration, and tissue repair,[107] is elevated in pre-eclampsia. Unlike angiogenic biomarkers, GlyFN reflects endothelial, metabolic, and inflammatory function.[108] Concentrations rise with systemic inflammation and metabolic stress, and elevated maternal serum GlyFN in pre-eclampsia probably reflects the endothelial dysfunction characteristic of the disease.[109]

Several studies have examined the diagnostic accuracy of GlyFN for identifying pre-eclampsia (table 1).[109–114] A systematic review and meta-analysis of 11 studies found significantly higher GlyFN concentrations in women with pre-eclampsia compared with controls, with pooled sensitivity 0·81 (95% CI 0·77–0·85, p<0·001), specificity 0·80 (0·77–0·82, p<0·001), and AUROC 0·90 for diagnosis of pre-eclampsia.[115] However, most studies were small, heterogeneous, case–control designs from high-income settings that used stored samples, limiting their generalisability, particularly in low-resource settings.

GlyFN was shown to outperform angiogenic biomarkers with an AUROC of 0·99 (95% CI 0·98–0·99) for diagnosis of pre-eclampsia in a prospective case–control study in India among 798 women at more than 20 weeks' gestation.[111] GlyFN performed similarly to sFlt-1 to PlGF ratio-based tests when using a threshold of 263 μg/mL to rule out pre-eclampsia at 7 days (NPV 82·6%, 95% CI 64·1–92·7) and 510 μg/mL to rule

| | Design | Setting | Sample size | Glycosylated fibronectin threshold | Sensitivity | Specificity | PPV | NPV | AUROC (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| Rasanen et al (2015)[109] | Case–control | Finland | 107 | 176·4 µg/mL | NA | NA | NA | NA | ELISA 0·99 (0·98–1·00); POC 0·93 (0·85–1·00) |
| Huhn et al (2020)[110] | Cohort | Switzerland | 151 | 315 µg/mL | 91% | 86% | NA | NA | 0·94 (0·90–0·98) |
| Nagalla et al (2020)[111] | Case–control | India | 798 | ≥263 µg/mL | 98·5% | 92·8% | 5% PE prevalence 99·9%; 7% PE prevalence 99·9% | 5% PE prevalence 41·9%; 7% PE prevalence 50·7% | 0·99 (0·98–0·99) |
| Sokratous et al (2023)[112] | Cohort | UK | 409 | 510 µg/mL | 62·4% | NA | NA | NA | 0·643 (0·581–0·705) |
| Wah et al (2024)[113] | Cohort study | China | 236 | >263 µg/mL; >510 µg/mL | NA | NA | Within 28 days: >263 µg/mL 35·5%; >510 µg/mL 50·0% | Within 7 days: >263 µg/mL 82·6%; >510 µg/mL 70·4% | Within 1 week: 0·94 (0·91–0·97); within 4 weeks: 0·82 (0·75–0·89) |
| Wirawan et al (2025)[114] | Cohort | Indonesia | 54 | 34·31 ng/mL | 83·3% | 66·7% | NA | NA | 0·81 (0·67–0·94) |

NA=not available. NPV=negative predictive value. PE=pre-eclampsia. POC=point of care. PPV=positive predictive value. AUROC=area under the receiver operating curve.

***Table 1:*** **Studies examining the diagnostic accuracy of glycosylated fibronectin**

in pre-eclampsia at 28 days (positive predictive value 50%, 95% CI 12·6–87·5) in a cohort study in China among 236 women with gestational hypertension.[113] Large, prospective studies are required, particularly in LMICs, to confirm these findings and establish standardised test thresholds.

### NT-proBNP

NT-proBNP, the inactive fragment of brain natriuretic peptide (BNP), is released from ventricular myocytes in response to pressure or volume overload.[116] Pre-eclampsia, characterised by impaired cardiovascular adaptation and increased long-term cardiovascular risk,[117] is associated with elevated NT-proBNP concentrations that rise with disease severity.[118] BNP is an established biomarker for heart failure[119] and emerging evidence suggests NT-proBNP might have diagnostic value for pre-eclampsia.[120] A case–control study among 316 women with suspected pre-eclampsia found that NT-proBNP had similar performance to sFlt-1 to PlGF ratio for predicting early-onset pre-eclampsia within 1 week at a threshold of 116 pg/mL with 90·9% (95% CI 70·8–98·9%) sensitivity, 94·3% (91·2–96·5%) specificity, a NPV of 99·9% (99·9–100%), and AUROC of 0·97 (0·94–1·00).[121] A systematic review of five studies linked raised NT-proBNP concentrations to adverse outcomes;[118] however, current evidence is insufficient to support its diagnostic use. If validated, existing POC tests for NT-proBNP could facilitate affordable and accessible testing, particularly in LMICs.

### sEng

sEng is an antiangiogenic protein released from the placenta under hypoxic conditions and contributes to enthothelial dysfunction in pre-eclampsia.[122–124] Studies show sEng concentrations are elevated in preeclamptic pregnancies.[122,124–126] A systematic review and meta-analysis of 20 studies found significantly elevated sEng concentrations in the second and third trimesters in women with pre-eclampsia (mean difference [MD] in the second trimester 5·554, 95% CI 2·671–8·436, p<0·001, $I^2$ 97%, and third trimester MD 31·006, 24·734–37·278, p<0·001, $I^2$ 98%).[127] However, more research is required to establish its accuracy and clinical utility.

Studies in India,[124,125,128] Pakistan,[129] and Indonesia[130] show similar findings, supporting the potential diagnostic value of sEng in low-resource settings, but no studies have been done in sub-Saharan Africa, where the burden of pre-eclampsia is greatest. Most studies were small, single-centre investigations using varied cutoffs (8–47 ng/mL) and reporting AUROC values from 0·795–0·913, limiting generalisability. Large, prospective studies are needed to define reference ranges and evaluate the diagnostic performance of sEng in LMICs.

## POC pre-eclampsia biomarker testing

Laboratory-based biomarker testing is unfeasible in many real-world clinical settings due to the necessary resources and associated costs. However, POC biomarker testing devices could greatly expand access in LMICs by removing the need for laboratory infrastructure, centrifugation, and continuous electricity. These portable, battery-powered devices use whole blood, require minimal training, and provide results within minutes to support timely decision making, making them ideal for use in low-resource settings. Table 2 describes three currently available POC biomarker tests, the Quanti (Lepzi, Sofia, Bulgaria) and RONIA (Revvity, Turku, Finland) PlGF tests, and the Lumella (Diabetomics, Medak, India) GlyFN test, and outlines how they align with the WHO criteria for LMIC-appropriate POC diagnostics.

Evidence from Sierra Leone shows that the Quanti and RONIA POC tests for PlGF are accurate, feasible, and acceptable to both patients and clinicians in an LMIC.[90] A UK evaluation using frozen plasma samples confirmed

For **more on the WHO REASSURED criteria** see https://www.globalaccessdx.com/reassured-a-framework-for-developing-diagnostics-for-resource-limited-settings/

| | RONIA PlGF (Revvity) | Quanti PlGF (LEPZI) | Lumella GlyFN (Diabetomics) |
|---|---|---|---|
| Real-time connectivity | Results displayed on screen of the reader; results can be downloaded via USB-C port | Results displayed on screen of the reader and print out provided; results can be downloaded via USB-A port | Results displayed on screen of the reader; Bluetooth printer available |
| Ease of specimen collection | 20 µL whole blood collected via finger stick | 200 µL whole blood collected via standard venous draw | 5 µL whole blood collected via finger stick |
| Affordable | Cost for commercial use in LMICs not yet available | Cost for commercial use in LMICs not yet available | Cost for commercial use in LMICs not yet available |
| Sensitive | Using rule-out threshold <60 pg/mL at <34 weeks' gestation: maternal adverse outcomes (94·9%) and perinatal adverse outcomes (100%) | Using rule-out threshold <90 pg/mL at <34 weeks' gestation: 100% for maternal and perinatal adverse outcomes | Using rule-out threshold <263 µg/mL at >20 weeks' gestation: 98·5% for diagnosis of pre-eclampsia |
| Specific | Using rule-in threshold <20 pg/mL at <34 weeks' gestation: 23·7% for death or eclampsia and 31·3% for stillbirth or perinatal death | Using rule-in threshold <12 pg/mL at <34 weeks' gestation: 42·6% for death or eclampsia and 51·9% for stillbirth or perinatal death | Using rule-out threshold <263 µg/mL at >20 weeks' gestation: 92·8% specificity for diagnosis of pre-eclampsia |
| User friendly | Easy fingerprick specimen collection; mixing with buffer required; minimal training required | Requires venepuncture skills, then simple two-step test procedure; minimal training required | Easy fingerprick specimen collection; mixing with buffer required; four-step process; minimal training required |
| Rapid and robust | Results available in 1–30 min; cartridges and buffer solution require refrigeration at >2–8°C | Results available in 15 min; cartridges require refrigeration at >2–8°C | Results available in 10 min |
| Equipment free, simple, environmentally friendly | Rechargeable battery via micro-USB (6 tests per charge); single-use test cartridge required; environmental sustainability of consumables unknown | Mains power or disposable batteries (3 × AAA); single-use test cartridge required; environmental sustainability of consumables unknown | Battery powered; single-use test cartridge required; environmental sustainability of consumables unknown |
| Deliverable to end users | Portable; requires cold chain storage of consumables; currently for research purposes only | Portable; requires cold chain storage of consumables; available for commercial use | Handheld; no cold chain requirements; available for commercial use |

The WHO REASSURED framework criteria assess suitability for use at the point of care in LMIC settings. LMIC=low-income and middle-income counties.

***Table 2:*** **Currently available point-of-care pre-eclampsia biomarker tests according to the WHO REASSURED framework criteria**

the accuracy of the Quanti to rule out pre-eclampsia, reporting performance similar to gold-standard validated laboratory analysers (NPV 97% [95% CI 84·2–99·9]; AUROC 0·88 [95% CI 0·79–0·96]).[131] Ongoing whole-blood validation studies of POC-PlGF tests will be crucial for confirming clinical utility and benchmarking against NICE-approved assays. Although the sFlt-1 to PlGF ratio performs similarly to PlGF alone, no POC test for the ratio is yet available; however, testing of a POC single-use, electrochemical enzyme-linked lateral flow immunoassay for determination of the concentration of sFlt-1 and PlGF in 20 µL whole blood from fingerstick is ongoing (ISRCTN31137599).

A company-sponsored study of the Lumella POC GlyFN test showed 98·5% sensitivity (95% CI 0·92–1·00) and 92·8% specificity (0·87–0·98) for diagnosis of pre-eclampsia at a threshold of 263 µg/mL.[111] NICE reports diagnostic accuracy comparable to that of the laboratory-based GlyFN immunoassay.[132]

Urinary PlGF concentrations are also reduced in pre-eclampsia,[133] raising the possibility of a urine-based POC test that would be less invasive, easier to use, and potentially cheaper than current blood-based assays. Such a test could greatly expand access in low-resource settings, but no validated urine PlGF POC device is yet available.

### *Panel 2:* Research gaps and future directions

- Evaluate clinical and cost-effectiveness of biomarker testing in lower-income and middle-income countries (LMICs) to reduce adverse pre-eclampsia outcomes. The PAPAGAIO-Diagnosis Trial (ISRCTN70040289), an international randomised controlled trial in four LMICs, aims to address these uncertainties (ISRCTN70040289).
- Advance point-of-care (POC) biomarker technologies. Priorities include reducing costs, eliminating cold-chain requirements, extending shelf-life, enabling non-invasive sampling, validating performance in real-world LMIC conditions, and developing a POC s-Flt1 to PlGF ratio test. This is an active area of research with several ongoing studies.
- Identify effective implementation strategies for biomarker testing across diverse LMIC health systems, including determining the appropriate level of care for test deployment and optimising logistics, supply chains, and training.
- Explore the potential for angiogenic biomarkers to serve as therapeutic targets, and POC biomarker testing to monitor therapeutic response and determine who will benefit from treatments targeted to underlying pathophysiology.

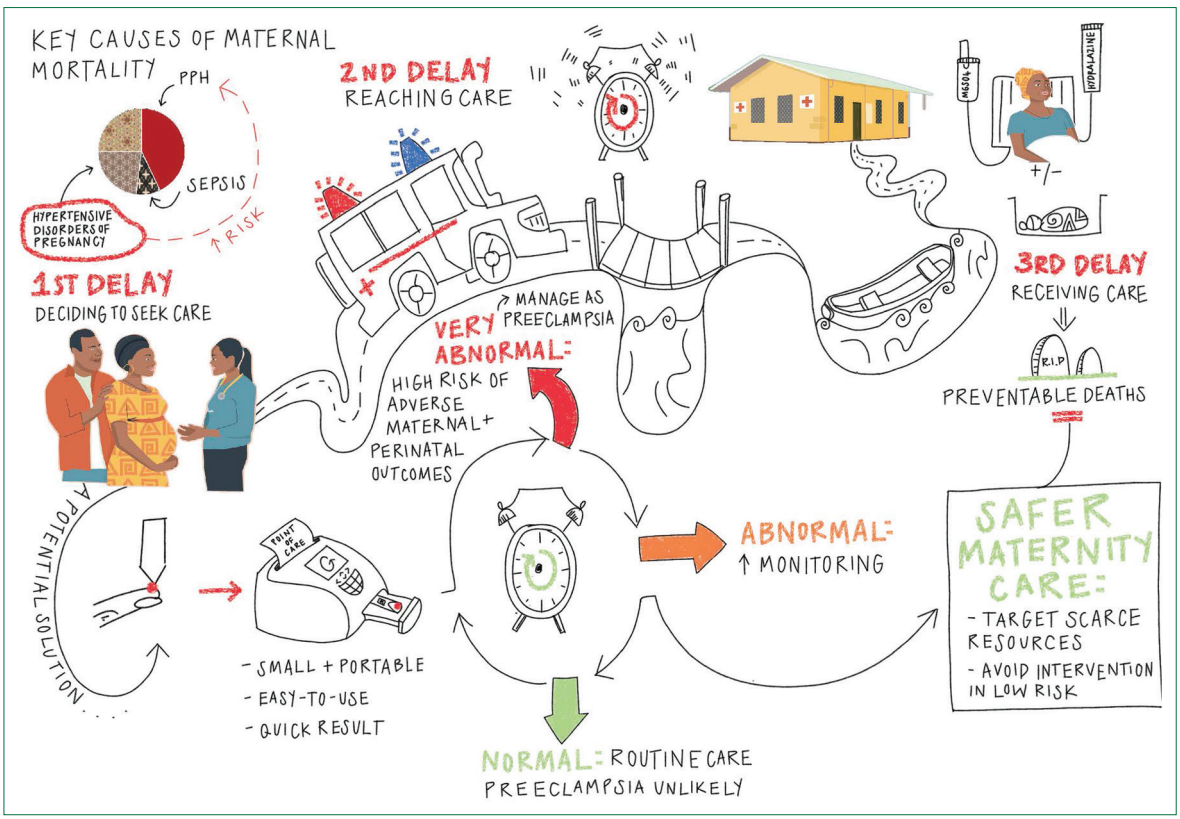


***Figure:*** **Potential for point-of-care biomarker testing to improve pre-eclampsia outcomes in low-income and middle-income settings**
Point-of-care biomarker testing can aid clinicians in making a diagnosis and stratifying risk, potentially resulting in safer maternity care and targeted resource use. Illustration by KK. PPH=postpartum haemorrhage.

***Panel 3:*** **Priorities for policy and implementation**

- Integrate biomarker testing into national and international maternal health guidelines if clinical benefit, feasibility, and affordability are confirmed.
- Develop clear clinical management pathways utilising biomarker results to guide monitoring, referral, and delivery decisions.
- Ensure deployment of testing aligns and integrates with existing referral pathways and available resources.
- Establish reliable procurement and supply-chain systems, favouring tests suited to use in lower-income and middle-income country contexts and conditions.
- Provide adequate training for health-care workers on test administration, interpretation, and associated clinical decision pathways.
- Ensure equitable access to testing, prioritising underserved, rural, and high-burden regions.
- Incorporate sustainability measures from the outset, including long-term financing plans and the development of local manufacturing capacity.

POC pre-eclampsia tests could transform management pathways by enabling diagnostics in facilities without laboratory infrastructure. With appropriate training and referral systems, they could be used in community or remote settings, allowing primary care providers to identify women at high risk of adverse outcomes and make more targeted referrals, improving equity of care in remote areas (panel 2).[90]

## Conclusions

Access to biomarker testing remains scarce across LMICs outside research settings or occasional private sector use. Biomarker testing offers an opportunity to strengthen maternal health services and improve diagnosis of pre-eclampsia in LMICs (figure), but adoption is limited by major financial and operational barriers, including affordability, fragile supply chains, and constrained laboratory infrastructure. POC tests provide a more accessible and scalable alternative, provided they are embedded in antenatal guidelines and supported by clear clinical pathways and practical training for health-care workers; a test result only adds value when it triggers a clear, evidence-based action. Affordable pricing and validation of multiple tests to maintain market competition will be crucial for cost-effectiveness and sustainability. LMIC-specific cost-effectiveness analyses will be needed to support policy adoption. Equitable implementation must prioritise rural and underserved populations to avoid widening existing disparities that

### Search strategy and selection criteria

References for this Review were identified through searches of PubMed, MEDLINE, Embase, the Cochrane Library, WHO Global Index Medicus, and Google Scholar using combinations of controlled vocabulary and free-text terms related to pre-eclampsia, diagnostic biomarkers, and low-income and middle-income country health systems. Search terms included "diagnosis", "preeclampsia", "hypertensive disorders of pregnancy", "low- and middle-income country", "placental growth factor", "PlGF", "sflt-1", "angiogenic markers", "glycosylated fibronectin", and "biomarker". The search was performed on Sept 12, 2025, and included all manuscripts published since database inception. Studies were selected based on originality, relevance, and contribution to the conceptual aims of the article rather than through predefined inclusion criteria. Papers were excluded if they focused on screening for pre-eclampsia risk rather than diagnosis. We prioritised high-quality clinical trials, diagnostic accuracy studies, cohort studies, feasibility studies, implementation research, health-economic analyses, and major global guidelines. Reference lists of key publications were used to identify additional sources. Only papers published in English were reviewed. Literature from 2000 onwards was emphasised, reflecting the development of angiogenic biomarkers, although older seminal work was included where appropriate.

arise from resources concentrated in urban facilities (panel 3). Although biomarkers already support diagnosis and risk stratification in high-income settings, their value could be even greater where other diagnostics are scarce, helping target care and potentially prevent maternal deaths and stillbirths. However, they remain an adjunct to, and not a replacement for, quality universal antenatal care.

#### Contributors

Conceptualisation: AHS, LDO, and AH; writing original draft outline: LS, AH, LCC, and AHS; original draft preparation: LS and MM; review and editing: KK, AH, LDO, LCC, and AHS; image design and creation: KK; supervision: AHS, LCC, and LDO. All authors have given their final approval of the version to be submitted.

#### Declaration of interests

LDO received payment from QuidelOrtho Brazil for delivering two lectures. AHS received expenses as an invited speaker at conferences from Revvity and QuidelOrtho, and acts as a consultant strategy advisor for Roche. All other authors declare no conflicts of interest.

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