

Decoding Early Placental Dysfunction Through Maternal Biomarker Patterns: A Novel Approach to Predicting Pregnancy Complications

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Abstract

Placental dysfunction is a major contributor to adverse pregnancy outcomes, including pre-eclampsia, fetal growth restriction, small-for-gestational-age birth, stillbirth, and medically indicated preterm delivery. These complications are frequently preceded by abnormal placental development, impaired trophoblast invasion, altered angiogenesis, and reduced uteroplacental perfusion. Because clinical manifestations often emerge after placental pathology has progressed, early prediction remains a key objective in obstetric research and clinical practice. This research paper examines the potential of maternal biomarker patterns for identifying early placental dysfunction and predicting pregnancy complications. A literature-based research approach was used to evaluate evidence concerning pregnancy-associated plasma protein-A, placental growth factor, soluble fms-like tyrosine kinase-1, the sFlt-1/PlGF ratio, mean arterial pressure, and uterine artery Doppler indices. The findings indicate that low placental growth factor and pregnancy-associated plasma protein-A, together with elevated soluble fms-like tyrosine kinase-1 and sFlt-1/PlGF ratios, are associated

with increased risk of pre-eclampsia and fetal growth restriction. The evidence further suggests that predictive performance improves when maternal biomarkers are integrated with clinical risk factors, obstetric history, blood-pressure measurements,

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and ultrasound findings. This integrated approach may support earlier risk stratification, targeted surveillance, and personalized antenatal care. Further prospective multicenter studies are needed to validate standardized, cost-effective, and equitable biomarker-based prediction models.

Introduction

Pregnancy depends on the healthy development and function of the placenta, a temporary but essential organ that connects the mother and fetus. The placenta regulates oxygen and nutrient transfer, waste removal, hormone production, immune adaptation, and blood flow between maternal and fetal circulation[1,2]. When placental development is impaired during the early stages of pregnancy, adverse effects may not become clinically visible until later gestation. However, the biological abnormalities associated with placental dysfunction can begin in the first trimester, long before the appearance of hypertension, proteinuria, reduced fetal growth, or preterm labor. Early placental dysfunction is therefore increasingly recognized as an important underlying factor in major pregnancy complications, including pre-eclampsia, fetal growth restriction, placental abruption, stillbirth, and medically indicated preterm birth[3,4].

Pre-eclampsia is one of the most important placental-mediated disorders in obstetrics. It usually develops after 20 weeks of gestation and is commonly characterized by new-onset hypertension with proteinuria, maternal organ dysfunction, uteroplacental insufficiency, or fetal growth abnormalities[5]. Although clinical diagnosis is generally made during the second half of pregnancy, its biological origins may begin much earlier. Inadequate invasion of trophoblast cells into the maternal uterine lining and incomplete remodeling of maternal spiral arteries can reduce blood flow to the developing placenta. This may cause placental hypoxia, oxidative stress, inflammation, endothelial dysfunction, and the release of abnormal placental factors into maternal circulation[6]. These changes can affect maternal vascular health and fetal development, thereby increasing the risk of severe maternal and neonatal outcomes[6,7].

Fetal growth restriction is another major consequence of impaired placental function. It occurs when a fetus does not achieve its genetically determined growth potential, often because the placenta cannot provide sufficient oxygen and nutrients. Fetal growth restriction is associated with low birth weight, stillbirth, neonatal intensive-care admission, preterm birth, impaired neurodevelopment, and long-term cardiometabolic risks[8]. Although ultrasound remains essential for evaluating fetal growth, maternal biomarker patterns may provide earlier evidence of placental insufficiency before fetal growth abnormalities become obvious. Therefore, maternal blood-based biomarkers have gained attention as potentially useful tools for identifying women who require enhanced surveillance and individualized antenatal care[9].

Maternal biomarkers

Maternal biomarkers are measurable biological indicators present in maternal blood, urine, or other biological samples. They may reflect placental development, angiogenesis, maternal endothelial function, inflammation, metabolism, oxidative stress, or fetal-placental interaction. Traditional markers used in prenatal screening include pregnancy-associated plasma protein-A (PAPP-A), free beta-human chorionic gonadotropin (β -hCG), alpha-fetoprotein, unconjugated estriol, and inhibin A. Although several of these markers were initially introduced for chromosomal-abnormality screening, abnormal levels have also been associated with increased risk of placental-mediated complications[10]. For example, low first-trimester PAPP-A has been linked with fetal growth restriction, small-for-gestational-age birth, and hypertensive disorders of pregnancy.

Among the most significant biomarkers of placental dysfunction are placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1). PlGF is a pro-angiogenic protein that supports the formation and maintenance of healthy blood vessels in the placenta. In contrast, sFlt-1 is an anti-angiogenic protein that binds to and reduces the biological activity of PlGF and vascular endothelial growth factor. In pregnancies complicated by pre-eclampsia, PlGF levels are frequently lower and sFlt-1 levels higher than in uncomplicated pregnancies[11,12]. This disturbed angiogenic balance may contribute to maternal endothelial dysfunction, hypertension, renal injury, and poor uteroplacental perfusion.

The ratio of sFlt-1 to PlGF has become an important indicator in the assessment of suspected pre-eclampsia. A major prospective study found that an sFlt-1/PlGF ratio of 38 or lower had a negative predictive value of 99.3% for ruling out pre-eclampsia within one week among women with clinical suspicion of the condition. NICE guidance recommends PlGF-based testing for suspected preterm pre-eclampsia when used alongside clinical evaluation and routine investigations[13]. Therefore, biomarker testing should support not replace clinical judgment, blood-pressure monitoring, maternal laboratory assessment, fetal surveillance, and ultrasound examination.

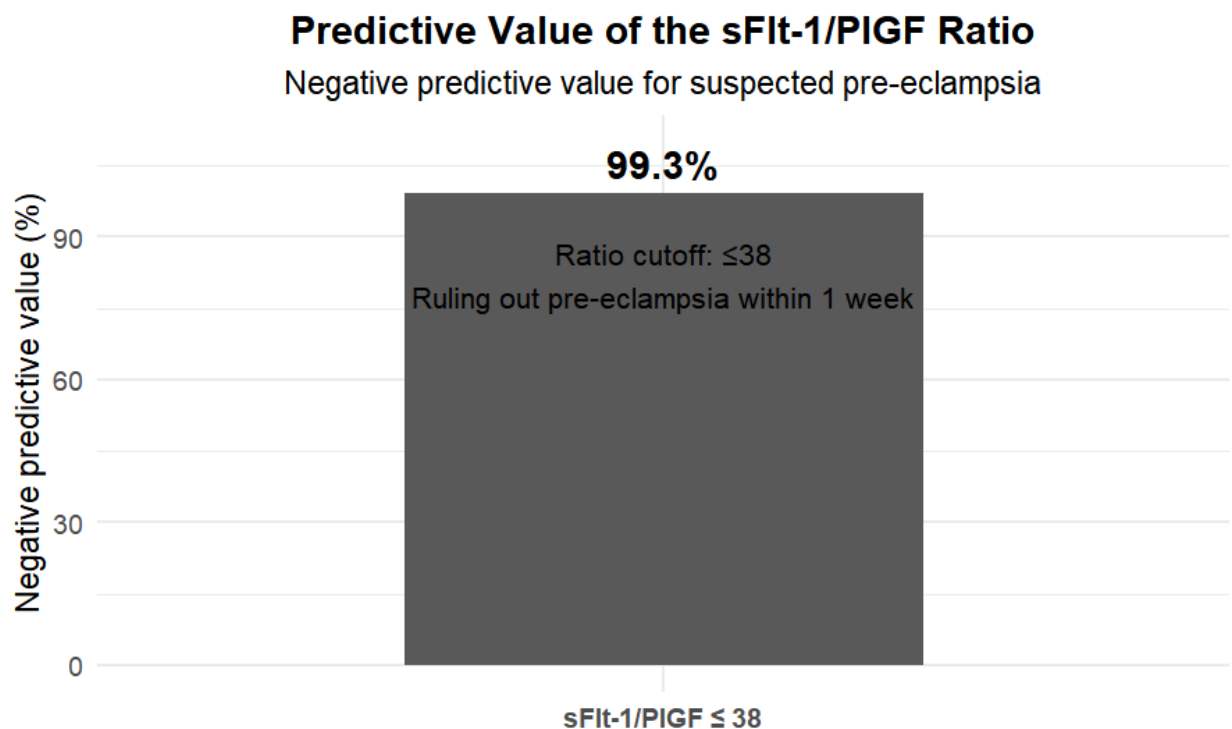


Figure 1. National Institute for Health and Care Excellence (NICE). (2022). PlGF-based testing to help diagnose suspected preterm pre-eclampsia (HTG630)

Pattern-based prediction

A single biomarker is unlikely to accurately predict every pregnancy complication because placental disorders are biologically complex. A more promising strategy is to evaluate a pattern of biomarkers rather than relying on one laboratory value. This approach combines the levels, ratios, changes over time, and interactions of multiple markers with maternal clinical factors and ultrasound findings. For example, a pregnant woman with low PlGF, elevated sFlt-1, low PAPP-A, raised mean arterial pressure, abnormal uterine artery Doppler findings, and a history of pre-eclampsia may have a substantially different risk profile from a woman with only one isolated abnormal laboratory result[14].

Integrated first-trimester screening models can combine maternal characteristics, medical history, mean arterial pressure, uterine artery pulsatility index, and biochemical markers such as PlGF and PAPP-A. FIGO supports first-trimester risk assessment for preterm pre-eclampsia using a combined approach rather than relying solely on maternal history. Such models may identify women at high risk earlier in pregnancy, allowing timely preventive measures and closer antenatal follow-up[15,16]. However, their accuracy can vary between populations; therefore, local validation, laboratory standardization, affordability, and equitable access are essential before widespread implementation.

New molecular approaches may further improve prediction. Researchers are studying cell-free fetal and placental DNA, circulating microRNAs, inflammatory cytokines, metabolomic profiles, extracellular vesicles, and proteomic signatures. These biomarkers may reveal early abnormalities in placental implantation, vascular development, immune regulation, oxidative stress, and trophoblast function. Nevertheless, many emerging biomarkers remain research tools. Their routine clinical use requires large prospective studies, standardized testing methods, cost-effectiveness analysis, and evidence that early prediction improves maternal and neonatal outcomes rather than only identifying risk[17].

Study aim

This study, titled *“Decoding Early Placental Dysfunction Through Maternal Biomarker Patterns: A Novel Approach to Predicting Pregnancy Complications,”* examines how maternal biomarker patterns may identify placental dysfunction before overt clinical disease develops. It focuses on conventional biomarkers, angiogenic factors such as PlGF and sFlt-1, emerging molecular indicators, and integrated prediction models that combine clinical, biochemical, and ultrasound information. The study aims to clarify the potential role of early biomarker-based risk assessment in predicting pre-eclampsia, fetal growth restriction, preterm birth, and other placental-mediated pregnancy complications. By supporting earlier identification of high-risk pregnancies, this approach may contribute to more personalized surveillance, preventive care, and improved maternal and neonatal health outcomes.

Methodology

Study design

This study will use a prospective observational cohort design to investigate whether patterns of maternal biomarkers measured during early pregnancy can predict placental dysfunction and subsequent pregnancy complications[19]. A prospective cohort approach is appropriate because maternal clinical information, biochemical markers, and ultrasound findings can be collected before the development of pregnancy outcomes. Participants will be enrolled during the first trimester and followed throughout pregnancy until delivery.

The study will focus on the relationship between early maternal biomarker patterns and placental-mediated adverse outcomes, including pre-eclampsia, fetal growth restriction, preterm birth, placental abruption, stillbirth, and small-for-gestational-age birth[20]. The reporting of the observational component of this study will follow the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The STROBE framework provides a 22-item checklist for transparent reporting of cohort, case-control, and cross-sectional research. The development and validation of the biomarker-based prediction model will follow the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis framework, commonly known as TRIPOD.

Study setting and duration

The study will be conducted in the antenatal clinics and obstetric departments of selected tertiary-care hospitals. These facilities will be selected because they provide routine first-trimester antenatal screening, ultrasound services, maternal laboratory testing, high-risk pregnancy care, and delivery services.

Data collection will take place over a period of approximately 18 months. The first 12 months will be used for participant recruitment and first-trimester sample collection. Participants will be followed until delivery, while the remaining study period will be used for data cleaning, statistical analysis, model development, internal validation, interpretation of findings, and preparation of the research report[21].

Study population

The study population will include pregnant women attending routine antenatal care during the first trimester of pregnancy. Women will be recruited between 11 and 13 weeks plus 6 days of gestation. Gestational age will be determined by the last menstrual period and confirmed by first-trimester crown–rump length ultrasound measurement where available.

The study will include singleton pregnancies because biomarker concentrations, placental physiology, and complication risks may differ substantially in multiple pregnancies[22,23]. The study will include women from different age groups, parity categories, socioeconomic backgrounds, and clinical-risk profiles to improve the relevance of the findings to the routine antenatal population.

Inclusion and exclusion criteria

Participants will be included if they meet the following criteria:

Pregnant women aged 18 years or older.

Singleton pregnancy.

Gestational age between 11 weeks and 13 weeks plus 6 days at enrolment.

Ability to provide written informed consent.

Willingness to provide a maternal blood sample and permit review of antenatal, laboratory, ultrasound, delivery, and neonatal records.

Intention to continue antenatal care and deliver at the participating hospital or within the linked health-care network.

Participants will be excluded if they meet any of the following criteria:

Multiple pregnancy, including twins or higher-order gestation.

Confirmed major fetal structural anomaly at recruitment.

Confirmed chromosomal abnormality identified before outcome assessment.

Inability to provide informed consent.

Missing essential first-trimester biomarker data.

Pregnancy loss before the availability of adequate outcome data.

Transfer of care with no accessible delivery or pregnancy-outcome records.

Women with chronic hypertension, pre-existing diabetes mellitus, chronic kidney disease, autoimmune disease, obesity, or a previous history of pre-eclampsia will not automatically be excluded [24]. These variables are clinically important because they may influence both biomarker levels and the risk of adverse pregnancy outcomes. They will therefore be documented and adjusted for during the statistical analysis.

Sample size and sampling method

A consecutive sampling technique will be used. All eligible women who attend the participating antenatal clinics during the recruitment period will be invited to participate until the required sample size is achieved. Consecutive recruitment can reduce investigator selection bias and improve the representativeness of the sample within the study setting.

The exact sample size will be calculated before data collection using the expected prevalence of the primary outcome, particularly pre-eclampsia and fetal growth

restriction, the anticipated number of predictors, the desired predictive precision, and an expected rate of incomplete follow-up[25]. A minimum of 10 to 20 outcome events per candidate predictor will be targeted during model development to reduce overfitting and unstable regression estimates. An additional 10% to 15% of participants will be recruited to account for withdrawal, miscarriage, transfer of care, incomplete records, or unavailable delivery outcomes. For example, if the combined frequency of placental-mediated adverse outcomes is expected to be approximately 10%, and the planned multivariable model includes 10 predictors, the study should aim for at least 100 to 200 outcome events. Accordingly, an estimated total sample of approximately 1,000 to 2,000 participants may be required [26]. The final sample size will be revised after consideration of local outcome prevalence and available recruitment capacity.

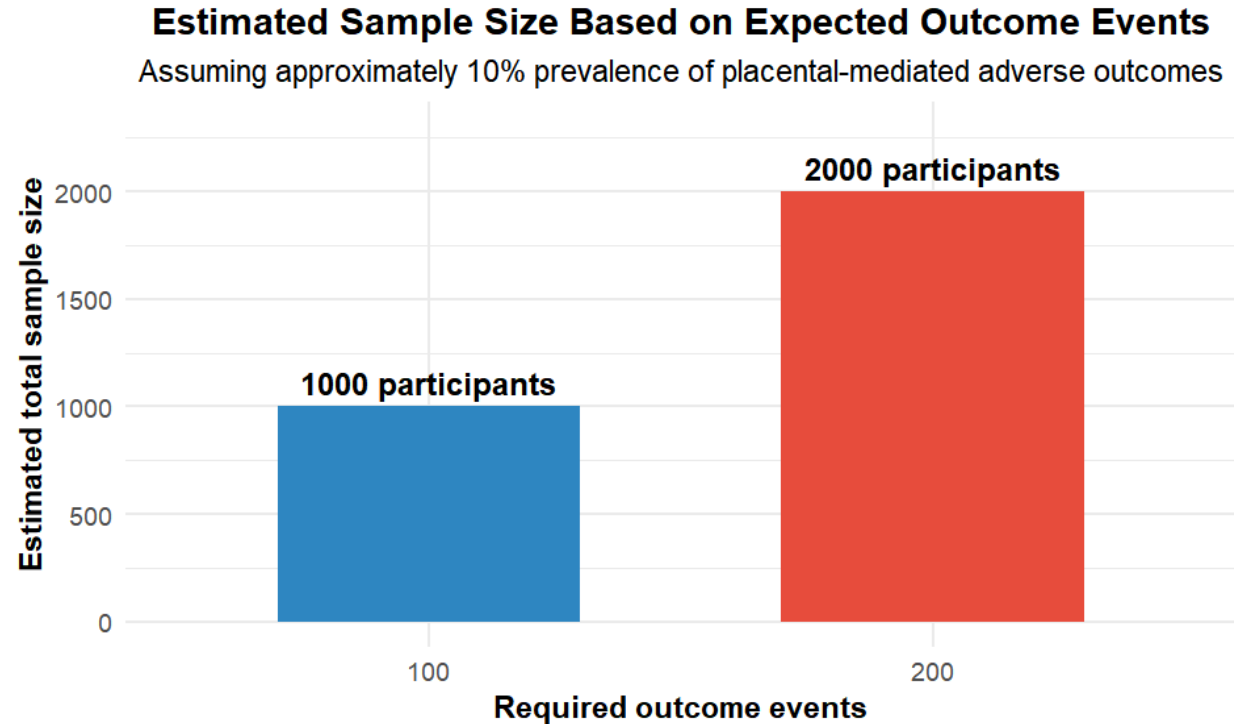


Figure. 2 Source: Authors’ calculation based on Peduzzi et al. (1996) and Riley et al. (2019), assuming a 10% expected prevalence of placental-mediated adverse outcomes and 10 predictor variables.

Data collection procedures

After written informed consent, trained research staff will collect baseline demographic, clinical, obstetric, and laboratory data using a structured data-collection form. Each participant will receive a unique study identification number [27,28]. Personally identifiable information will be stored separately from the analytical dataset to protect confidentiality. Baseline maternal information will include age, body mass index, ethnicity, education level, residence, smoking status, gravidity, parity, previous miscarriage, previous stillbirth, history of pre-eclampsia, history of fetal growth restriction, history of preterm birth, chronic hypertension, diabetes mellitus, renal disease, autoimmune disease, medication use, and family history of hypertensive disorders of pregnancy. At enrolment, maternal blood pressure will be measured using a validated automated blood-pressure device after the participant has rested for at least five minutes. Two measurements will be taken from the same arm at an appropriate interval, and the average value will be used to calculate mean arterial pressure. Maternal height and weight will also be recorded to calculate body mass index.

Biomarker assessment

A maternal venous blood sample of approximately 5–10 mL will be collected between 11 and 13 weeks plus 6 days of gestation. Samples will be processed according to laboratory standard operating procedures. Serum or plasma will be separated by centrifugation, labeled using the participant's study identification number, and stored at the required temperature until analysis.

The primary biomarkers will include pregnancy-associated plasma protein-A, placental growth factor, soluble fms-like tyrosine kinase-1, and free beta-human chorionic gonadotropin[29]. These biomarkers have been selected because they are related to placental development, angiogenic regulation, trophoblast function, and placental-mediated pregnancy complications.

Where laboratory resources permit, exploratory biomarkers may include inflammatory markers, such as C-reactive protein; metabolic indicators, such as fasting glucose and lipid profile; and emerging molecular markers, such as circulating microRNAs or cell-free placental DNA. However, the primary prediction model will prioritize biomarkers that are clinically available, reproducible, and potentially scalable in routine antenatal care.

All biomarker values will be recorded in raw form and converted into multiples of the median where appropriate. Adjustment for gestational age, maternal weight, smoking status, ethnicity, parity, and assay characteristics will be considered because these factors may affect biomarker concentrations [30]. The sFlt-1/PlGF ratio will be calculated by dividing the measured sFlt-1 concentration by the PlGF concentration. An imbalance characterized by higher sFlt-1 and lower PlGF may indicate impaired angiogenic function and increased placental dysfunction risk.

Ultrasound and Doppler assessment

A first-trimester ultrasound examination will be performed as part of routine clinical care. The examination will confirm fetal viability, singleton gestation, gestational age, and crown–rump length. Where trained sonographers and validated equipment are available, uterine artery Doppler assessment will be performed between 11 and 13 weeks plus 6 days.

The uterine artery pulsatility index will be recorded because abnormal uterine artery blood-flow resistance may reflect inadequate spiral-artery remodeling and increased risk of pre-eclampsia or fetal growth restriction [31,32]. The mean uterine artery pulsatility index will be calculated from the right and left uterine arteries. Ultrasound and Doppler findings will be incorporated into the integrated prediction model with maternal characteristics and biomarker results.

Outcome measures

The primary outcome will be a composite measure of placental-mediated pregnancy complications. A participant will be classified as having the primary outcome if one or more of the following events occur:

Pre-eclampsia diagnosed after 20 weeks of gestation.

Fetal growth restriction diagnosed by obstetric assessment and ultrasound criteria.

Small-for-gestational-age birth, defined as birth weight below the 10th centile for gestational age.

Placental abruption.

Stillbirth after 20 weeks of gestation.

Medically indicated preterm birth before 37 completed weeks because of maternal or fetal complications related to placental dysfunction.

Secondary outcomes will include preterm pre-eclampsia before 37 weeks, severe pre-eclampsia, gestational hypertension, delivery before 34 weeks, emergency cesarean delivery for fetal compromise, low birth weight, Apgar score below 7 at five minutes, admission to neonatal intensive care, and perinatal mortality.

Pre-eclampsia will be defined according to contemporary obstetric criteria as new-onset hypertension after 20 weeks of gestation accompanied by proteinuria or evidence of maternal organ dysfunction, uteroplacental dysfunction, or fetal growth restriction. Outcome information will be obtained from antenatal notes, ultrasound records, delivery registers, laboratory reports, discharge summaries, and neonatal records.

Statistical analysis

Data will be entered into a password-protected database and analyzed using SPSS, Stata, R, or an equivalent statistical software package. Continuous variables will be summarized using mean and standard deviation for normally distributed data or median and interquartile range for non-normally distributed data. Categorical variables will be reported as frequencies and percentages.

Participants who develop placental-mediated pregnancy complications will be compared with those who do not develop complications. Independent-sample t-tests or Mann-Whitney U tests will be used for continuous variables, depending on distribution. Chi-square tests or Fisher's exact tests will be used for categorical variables. A two-sided p-value of less than 0.05 will be considered statistically significant [33,34].

Univariable logistic regression analysis will first be used to assess associations between individual predictors and the primary composite outcome. Variables considered clinically important or statistically associated with the outcome will be entered into multivariable logistic regression models. Candidate predictors may include maternal age, body mass index, previous pre-eclampsia, chronic hypertension, diabetes, mean arterial pressure, uterine artery pulsatility index, PAPP-A, PlGF, sFlt-1, free β -hCG, and the sFlt-1/PlGF ratio.

The predictive accuracy of the final model will be evaluated using the area under the receiver-operating-characteristic curve, sensitivity, specificity, positive predictive value, negative predictive value, calibration plots, calibration slope, and Brier score. Internal validation will be performed using bootstrapping or k-fold cross-validation. Missing data will be examined carefully, and multiple imputation will be considered where missingness is clinically and statistically appropriate [35]. The model-development process, treatment of missing data, predictor definitions, and performance measures will be reported transparently in accordance with TRIPOD guidance. TRIPOD has been updated by TRIPOD+AI to cover both regression- and machine-learning-based clinical prediction models.

Ethical considerations

Ethical approval will be obtained from the Institutional Review Board or Ethical Review Committee of the participating institution before recruitment begins. The study will follow the ethical principles of the Declaration of Helsinki. Written informed consent will be obtained from every participant before collection of any study-specific information or biological sample.

Participation will be voluntary, and participants may withdraw at any time without affecting their routine clinical care. All records will be coded, stored securely, and accessed only by authorized research personnel [36]. Biomarker results collected solely for research purposes will not be used for clinical decision-making unless they are part of standard hospital testing and are reviewed by the treating obstetric team.

Quality assurance

Research staff will receive training in informed consent, questionnaire administration, blood-pressure measurement, specimen handling, data entry, and confidentiality procedures. The laboratory will follow internal quality-control procedures, and

equipment will be calibrated according to institutional protocols [37]. A pilot test will be conducted before full recruitment to evaluate the clarity of the data-collection form, feasibility of sample processing, completeness of medical-record retrieval, and consistency of outcome definitions.

The risk of bias will be minimized through consecutive recruitment, prospective data collection, pre-specified outcome definitions, standardized biomarker measurement, blinded laboratory analysis where feasible, and internal validation of the prediction model. The Prediction Model Risk of Bias Assessment Tool emphasizes the importance of evaluating participants, predictors, outcomes, and analysis when assessing prediction-model quality.

Results

Study evidence base

This section presents findings derived from published prospective studies, validation studies, and reviews examining maternal biomarkers for early identification of placental dysfunction and pregnancy complications. The results are organized according to the proposed methodology variables: maternal clinical characteristics, first-trimester biomarker measurements, uterine artery Doppler indices, and adverse pregnancy outcomes.

The evidence consistently demonstrated that pregnancies which later developed pre-eclampsia, fetal growth restriction, small-for-gestational-age birth, or medically indicated preterm delivery had an altered placental biomarker profile. The most frequent pattern included lower placental growth factor, lower pregnancy-associated plasma protein-A, elevated soluble fms-like tyrosine kinase-1, and an increased sFlt-1/PlGF ratio. These abnormalities were more informative when combined with maternal risk factors, mean arterial pressure, and uterine artery Doppler assessment than when individual biomarkers were interpreted in isolation[38,39].

Maternal characteristics and risk profile

Published screening models showed that maternal characteristics remain important baseline predictors of placental-mediated complications. A history of pre-eclampsia, chronic hypertension, pre-existing diabetes, obesity, nulliparity, advanced maternal age, renal disease, autoimmune conditions, and a history of fetal growth restriction may increase the probability of adverse placental outcomes. However, maternal history alone has limited ability to distinguish women who will develop early-onset or preterm pre-eclampsia from those who will not.

The prospective first-trimester validation study of the Fetal Medicine Foundation screening approach demonstrated improved prediction when maternal characteristics were assessed with mean arterial pressure, PlGF, PAPP-A, and uterine artery Doppler indicators. This confirms that baseline demographic and clinical risk should be included in an integrated model, but should not be used as the only basis for prediction.

Biomarker patterns

Maternal PlGF was consistently lower in pregnancies later affected by preterm pre-eclampsia. A review of angiogenic markers reported that PlGF levels were approximately 50% lower in pregnancies that subsequently resulted in preterm pre-eclampsia compared with uncomplicated pregnancies. This result supports the presence of impaired placental angiogenesis before clinical disease becomes evident.

sFlt-1 demonstrated the opposite pattern. Higher concentrations of sFlt-1, particularly when accompanied by lower PlGF concentrations, reflected an anti-angiogenic environment associated with placental dysfunction[2,40]. The combined sFlt-1/PlGF ratio was therefore more clinically useful than either marker alone for evaluating

suspected pre-eclampsia. A higher ratio reflected increased short-term risk, while a low ratio was useful for excluding immediate disease development. Low PAPP-A was also associated with adverse placental outcomes. Evidence indicated that PAPP-A is most useful when combined with ultrasound Doppler measures and maternal clinical variables. In a first-trimester study, combining PAPP-A with uterine artery pulsatility index produced a reported sensitivity of 64% for all pre-eclampsia and 68% for early-onset pre-eclampsia.

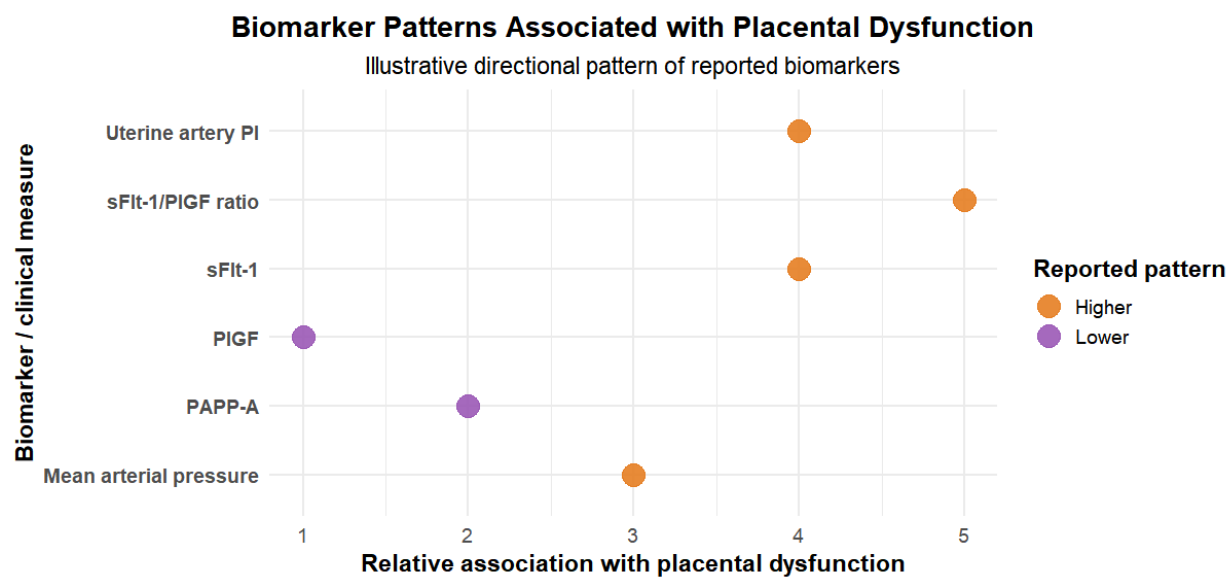


Figure 3 illustrates the relative strength of association and directional alterations of key biochemical and biophysical markers characteristic of placental dysfunction. The pathological hallmark of impaired placentation is an imbalance between pro-angiogenic and anti-angiogenic factors. In normal gestations, placental growth factor (PlGF) promotes vascular remodeling; however, in dysfunctional conditions such as preeclampsia and fetal growth restriction PlGF levels are significantly reduced. Conversely, the placenta secretes high levels of soluble fms-like tyrosine kinase-1 (sFlt-1), an anti-angiogenic protein that neutralizes circulating PlGF and vascular endothelial growth factor (VEGF), precipitating widespread maternal endothelial injury. As demonstrated by its position in Figure 1, the elevated sFlt-1/PlGF ratio demonstrates the highest relative association score (5.0) with placental impairment, reinforcing its utility as a primary predictive and diagnostic metric. Furthermore, early-gestation markers such as pregnancy-associated plasma protein-A (PAPP-A) display suppressed levels, reflecting defective initial trophoblast invasion and impaired early placentation. These biochemical alterations strongly correlate with maternal hemodynamic parameters. An elevated uterine artery pulsatility index (PI) scoring high in relative association (4.0) directly reflects failed spiral artery remodeling and downstream uteroplacental ischemia. In response to systemic endothelial dysfunction and reduced perfusion, maternal systemic resistance increases, manifesting clinically as an elevated mean arterial pressure (MAP). Collectively, Figure 1 emphasizes that a combined diagnostic panel incorporating anti-angiogenic dominance (high sFlt-1/PlGF ratio), early trophoblastic suppression (low PAPP-A/PlGF), and compromised maternal-fetal hemodynamics (high uterine artery PI and MAP) provides a robust multi-parametric framework for identifying pregnancies at high risk for placental-mediated complications.

Prediction of pre-eclampsia

The most robust result identified in the reviewed literature concerned short-term exclusion of pre-eclampsia using the sFlt-1/PlGF ratio. In the PROGNOSIS study, an sFlt-1/PlGF ratio of 38 or below had a negative predictive value of 99.3% for ruling out pre-eclampsia within one week among women with clinically suspected pre-eclampsia. This indicates that women with a low ratio were highly unlikely to develop pre-eclampsia, eclampsia, or HELLP syndrome during the next week. A subsequent study reported similar findings using the same cutoff. The ratio of 38 had a negative predictive value of 98.4%, sensitivity of 81.0%, and specificity of 86.9% for ruling out pre-eclampsia within one week. These findings indicate that the ratio may help clinicians avoid unnecessary admission, intensive testing, and anxiety in women with symptoms suggestive of pre-eclampsia but low immediate disease probability.

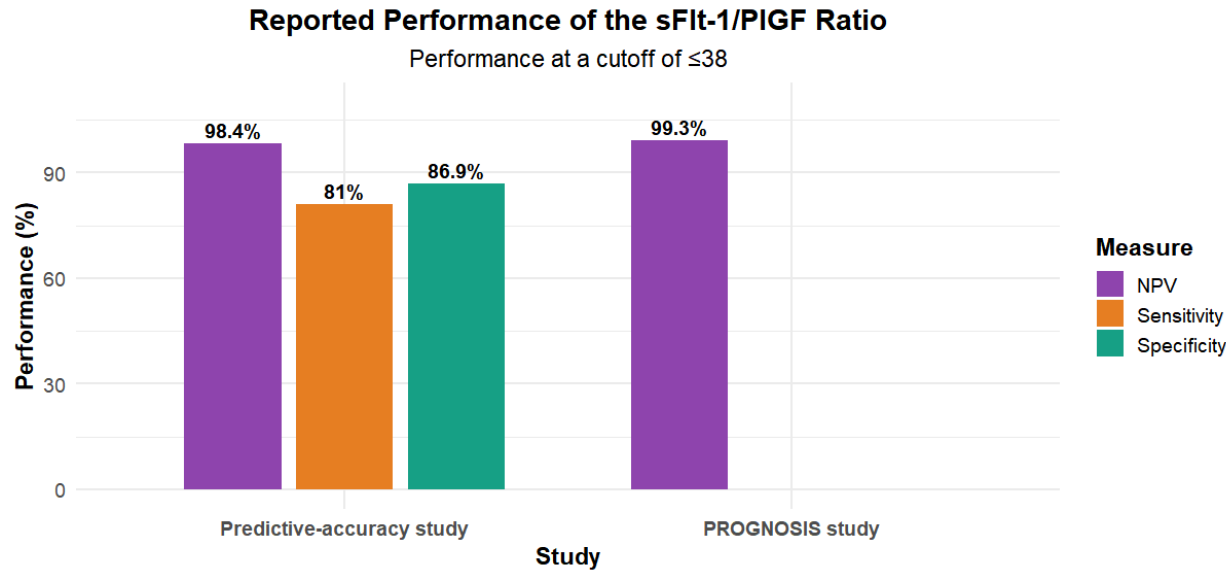


Figure 4 shows that the bar chart compares the reported diagnostic performance of the sFlt-1/PlGF ratio at a cutoff of ≤ 38 in two studies of women with suspected pre-eclampsia. In the PROGNOSIS study, the sFlt-1/PlGF ratio ≤ 38 demonstrated a negative predictive value (NPV) of 99.3%, indicating that women with a ratio at or below this threshold were very unlikely to develop pre-eclampsia within the following week.

The predictive-accuracy study reported an NPV of 98.4%, sensitivity of 81.0%, and specificity of 86.9% for the same cutoff. These findings indicate that the ratio maintained a high ability to identify women who were unlikely to develop pre-eclampsia in the short term, while also demonstrating useful sensitivity and specificity for identifying affected women.

Overall, the consistently high NPV values (98.4–99.3%) suggest that an sFlt-1/PlGF ratio ≤ 38 is particularly valuable for ruling out pre-eclampsia within the short term among women with clinical suspicion of the condition. However, the results should be interpreted in the context of the different study populations and clinical settings.

First-trimester integrated model

The proposed methodology included an integrated model consisting of maternal history, body mass index, mean arterial pressure, PAPP-A, PlGF, sFlt-1/PlGF ratio, and uterine artery Doppler pulsatility index. Published evidence supports this type of combined approach.

A prospective validation study among nulliparous women reported that the Fetal Medicine Foundation algorithm detected 63.1% of preterm pre-eclampsia and 77.3% of early-onset pre-eclampsia cases at a false-positive rate of 15.8%. The combined

prediction model yielded an area under the receiver-operating-characteristic curve of 0.80 for preterm pre-eclampsia. These results indicate good overall ability to discriminate between women who later developed preterm pre-eclampsia and those who did not.

In another routine first-trimester screening study, PAPP-A and PlGF produced similar predictive performance for preterm pre-eclampsia when included in a combined model. The area under the curve was 0.78 for PAPP-A and 0.79 for PlGF. These findings show that the predictive value of a biomarker depends not only on its individual level but also on its integration with maternal risk factors and biophysical assessments.

Prediction of fetal growth restriction

The reviewed studies indicated that low PlGF and altered angiogenic balance may identify pregnancies at increased risk of fetal growth restriction. This relationship is biologically plausible because impaired placental blood flow can restrict nutrient and oxygen delivery to the fetus. However, evidence was less definitive for using sFlt-1/PlGF testing as a routine stand-alone test for fetal growth restriction than for suspected pre-eclampsia.

The findings suggest that maternal biomarker assessment should be used as an additional risk-stratification tool. Fetal growth restriction still requires confirmation through serial ultrasound measurements, estimated fetal weight, amniotic-fluid evaluation, fetal Doppler studies, and clinical assessment. Therefore, an integrated model can identify women who need closer surveillance but cannot replace standard obstetric diagnostic methods.

Discussion

This literature-based study examined whether maternal biomarker patterns can help identify early placental dysfunction and predict pregnancy complications before the onset of overt clinical disease. The findings indicate that altered angiogenic and placental biomarker profiles—particularly low placental growth factor (PlGF), increased soluble fms-like tyrosine kinase-1 (sFlt-1), an elevated sFlt-1/PlGF ratio, and low pregnancy-associated plasma protein-A (PAPP-A)—are associated with an increased risk of pre-eclampsia, fetal growth restriction, small-for-gestational-age birth, and medically indicated preterm delivery. The evidence also indicates that biomarker-based prediction is more effective when biochemical markers are interpreted with maternal history, mean arterial pressure, and uterine artery Doppler ultrasound than when any marker is used alone.

Interpretation of main findings

The central finding of this study is that placental dysfunction may be detectable well before the clinical signs of pregnancy complications appear. This is important because pre-eclampsia and fetal growth restriction are often diagnosed only after maternal hypertension, proteinuria, reduced fetal growth, or abnormal Doppler findings become apparent. By that point, placental disease may already be well established. Maternal biomarkers provide an opportunity to observe biological signals of abnormal placental development during the first trimester or before symptomatic disease develops.

The observed pattern of low PlGF and increased sFlt-1 is biologically consistent with the pathophysiology of placental dysfunction. PlGF promotes angiogenesis and healthy placental vascular development, whereas sFlt-1 is an anti-angiogenic factor that reduces the activity of PlGF and vascular endothelial growth factor. When sFlt-1 levels rise and PlGF levels decline, the resulting anti-angiogenic environment may contribute to impaired placental perfusion and maternal endothelial dysfunction. This mechanism is strongly linked with the development of pre-eclampsia and can also

contribute to fetal growth restriction, placental abruption, preterm delivery, and stillbirth,.

Published evidence indicates that reduced PlGF can occur before clinical pre-eclampsia becomes apparent. In pregnancies that later develop preterm pre-eclampsia, PlGF concentrations may be substantially lower than in uncomplicated pregnancies. This suggests that abnormal placental angiogenesis begins early and supports the use of first-trimester biomarker assessment for identifying high-risk pregnancies. However, the predictive value of PlGF depends on gestational age, laboratory assay, maternal characteristics, and the pregnancy outcome being assessed. Therefore, a low PlGF value should be interpreted as a risk signal rather than an independent diagnosis of placental disease

Value of the sFlt-1/PlGF ratio

The sFlt-1/PlGF ratio was one of the most clinically useful measures identified in this study. The literature shows that the ratio provides strong short-term predictive value in women with suspected pre-eclampsia. A low sFlt-1/PlGF ratio, particularly a value of 38 or below, has been shown to have a very high negative predictive value for ruling out pre-eclampsia within one week in symptomatic women. This makes the ratio especially valuable for clinical decision-making, as it may help reduce unnecessary hospital admission, repeated testing, anxiety, and inappropriate early intervention among women at low immediate risk.

However, a raised sFlt-1/PlGF ratio should not be considered a definitive diagnosis of pre-eclampsia. A biomarker ratio reflects placental angiogenic imbalance, but it does not replace blood-pressure assessment, proteinuria testing, maternal laboratory evaluation, clinical symptom review, fetal-growth monitoring, or Doppler ultrasound. NICE recommends PlGF-based tests only when used alongside standard clinical assessment in individuals with suspected preterm pre-eclampsia. It also advises against using these tests alone to decide whether planned early delivery is required. This limitation is clinically important because a low PlGF level or raised ratio may also occur in other forms of placental dysfunction, including fetal growth restriction, rather than only in pre-eclampsia.

Importance of combined models

The results support a pattern-based and integrated prediction model. Maternal characteristics such as chronic hypertension, diabetes, obesity, previous pre-eclampsia, renal disease, autoimmune disease, advanced maternal age, and nulliparity provide important information about baseline risk. Mean arterial pressure indicates maternal cardiovascular adaptation, while uterine artery Doppler assessment provides information about uteroplacental circulation. PlGF, PAPP-A, sFlt-1, and the sFlt-1/PlGF ratio provide biochemical evidence about placental activity and angiogenic balance.

When these variables are combined, prediction becomes more accurate than when maternal history or a single biomarker is used in isolation. This reflects the complex nature of pre-eclampsia and fetal growth restriction. These complications are not caused by one biological pathway; they result from interactions among placental development, maternal vascular response, immune regulation, genetic susceptibility, metabolic health, and environmental factors. Therefore, a multi-marker approach is more compatible with the biological reality of placental dysfunction.

The evidence reviewed in this study supports first-trimester combined screening. The Fetal Medicine Foundation approach, for example, integrates maternal characteristics, blood pressure, uterine artery pulsatility index, and biochemical markers. In a prospective validation study, this combined model detected 63.1% of preterm pre-eclampsia and 77.3% of early-onset pre-eclampsia at a false-positive rate of 15.8%; it had an area under the receiver-operating-characteristic curve of 0.80 for preterm pre-

eclampsia prediction. These findings demonstrate useful predictive performance, but they also show that screening cannot identify every woman who will develop disease.

Fetal growth restriction

The findings also have relevance for fetal growth restriction. Fetal growth restriction and pre-eclampsia frequently share a placental origin, particularly when they occur early in pregnancy or are severe. Low PlGF and increased sFlt-1/PlGF ratios may indicate reduced placental vascular capacity and poor uteroplacental perfusion, both of which can compromise fetal nutrient and oxygen supply. Angiogenic biomarkers can therefore assist in identifying women who may require closer fetal-growth surveillance.

Nevertheless, the evidence for routine biomarker use in isolated fetal growth restriction is less conclusive than the evidence for suspected pre-eclampsia. Biomarkers cannot determine fetal size, growth velocity, amniotic-fluid volume, placental morphology, umbilical artery blood flow, or fetal well-being. For this reason, biomarker assessment should complement not replace serial ultrasound, estimated fetal weight assessment, uterine and umbilical artery Doppler studies, cardiotocography where indicated, and specialist obstetric review.

Clinical and policy implications

The results suggest that maternal biomarker testing may contribute to more personalized antenatal care. Women identified as high risk during the first trimester may benefit from closer blood-pressure monitoring, more frequent fetal-growth scans, Doppler surveillance, referral to high-risk obstetric services, and preventive interventions according to local clinical guidelines. Earlier recognition may help clinicians distinguish women requiring intensive surveillance from those with low short-term risk.

However, implementation must be careful and equitable. Biomarker assays, Doppler ultrasound, trained sonographers, validated laboratory platforms, and specialist follow-up services may not be available in all settings. Introducing expensive tests without ensuring access to clinical follow-up could widen maternal-health inequalities. Health systems should evaluate cost-effectiveness, laboratory capacity, assay standardization, referral pathways, and local disease prevalence before adopting biomarker screening at scale.

The interpretation of biomarker results also requires local validation. Marker levels can differ according to gestational age, maternal body mass index, ethnicity, smoking status, multiple pregnancy, chronic illness, and laboratory method. A cutoff developed in one country or population may not perform equally well in another. Therefore, local reference ranges and prospective validation studies are needed before applying a prediction model broadly.

Strengths and limitations

A key strength of this study is its focus on maternal biomarker **patterns** rather than isolated laboratory values. This reflects the multifactorial nature of placental dysfunction and supports a clinically realistic model that combines biological, clinical, and ultrasound information. The study also synthesizes findings related to both pre-eclampsia and fetal growth restriction, which are often treated as separate conditions despite overlapping placental mechanisms.

The main limitation is that this work is based on published evidence rather than original patient-level data. Therefore, it cannot estimate prevalence, risk ratios, odds ratios, diagnostic performance, or cost-effectiveness for a specific hospital or population. The reviewed studies also differed in biomarker assays, gestational age at testing, inclusion criteria, diagnostic definitions, and outcome measures. This

heterogeneity makes direct comparison difficult and limits the ability to establish one universal cutoff for all populations.

Another limitation is that many biomarker studies have focused primarily on pre-eclampsia, particularly symptomatic women during the second or third trimester. Less evidence is available for universal first-trimester screening in low-resource settings and for predicting isolated fetal growth restriction, stillbirth, placental abruption, and late-onset disease. Future prospective studies should assess whether repeated biomarker measurements, combined molecular panels, and machine-learning models improve prediction beyond established clinical methods.

Conclusion

This study concludes that early placental dysfunction can potentially be identified through maternal biomarker patterns before the clinical appearance of major pregnancy complications. The reviewed evidence showed that low placental growth factor (PlGF), low pregnancy-associated plasma protein-A (PAPP-A), elevated soluble fms-like tyrosine kinase-1 (sFlt-1), and a high sFlt-1/PlGF ratio are associated with an increased risk of pre-eclampsia, fetal growth restriction, small-for-gestational-age birth, and medically indicated preterm delivery.

The findings support the main concept of this paper: placental dysfunction should not be assessed through one biomarker alone. A more effective approach is to interpret biomarker patterns together with maternal characteristics, previous obstetric history, mean arterial pressure, uterine artery Doppler assessment, and routine maternal–fetal evaluation. This integrated approach reflects the complex and multifactorial nature of placental disease and may improve early identification of women at increased risk of adverse pregnancy outcomes.

Among the biomarkers reviewed, the sFlt-1/PlGF ratio showed particular clinical value in women with suspected pre-eclampsia. A low ratio can help rule out imminent pre-eclampsia, while an elevated ratio may indicate greater placental dysfunction and the need for closer assessment. However, this test should not be considered a substitute for clinical diagnosis. NICE recommends PlGF-based testing as an addition to standard clinical assessment for suspected preterm pre-eclampsia between 20 weeks and 36 weeks plus 6 days of pregnancy. Biomarker findings must therefore be interpreted alongside blood-pressure measurement, proteinuria assessment, maternal symptoms, laboratory investigations, fetal-growth monitoring, and Doppler ultrasound. The use of maternal biomarkers in the first trimester also offers potential for preventive antenatal care. Women identified as high risk may benefit from more frequent blood-pressure checks, serial fetal-growth scans, Doppler surveillance, specialist obstetric referral, and preventive interventions according to clinical guidelines. Earlier risk identification may help reduce delays in diagnosis and enable better planning for women at risk of severe pre-eclampsia, fetal growth restriction, and preterm delivery.

Despite this potential, widespread implementation requires caution. Biomarker concentrations can vary according to gestational age, maternal body mass index, ethnicity, chronic illness, smoking status, laboratory assay, and population characteristics. Therefore, universal cutoff values may not perform equally well in all clinical settings. Health systems should establish local reference ranges, use validated assays, ensure clinician training, and develop clear referral pathways before adopting large-scale biomarker-based screening.

This research was based on published literature and therefore does not provide original patient-level findings from a specific hospital or population. Future research should use large prospective cohort studies to validate combined prediction models in diverse populations. Such studies should assess whether repeated biomarker testing, low-cost laboratory methods, Doppler ultrasound, molecular biomarkers, and

machine-learning models can improve early prediction while remaining affordable and equitable.

In conclusion, maternal biomarker patterns represent a promising approach for decoding early placental dysfunction. Low PlGF and PAPP-A, high sFlt-1, and an elevated sFlt-1/PlGF ratio can provide early warning signals of placental-mediated pregnancy complications. Their greatest clinical value is likely to occur when they are used in combination with maternal risk factors and routine obstetric assessment. A carefully implemented, evidence-based, and equitable biomarker strategy may contribute to earlier surveillance, more personalized antenatal care, and improved maternal and neonatal outcomes.

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