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ORIGINAL ARTICLE

Combined prognostic value of first-trimester PAPP-A, placental volume and sFlt-1/PlGF ratio for early prediction of fetal growth restriction

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ABSTRACT

Background and Aim: This study aimed to evaluate the individual and combined prognostic value of first-trimester placental biomarkers, including PAPP-A, the sFlt-1/PlGF ratio, and placental volume calculated using the Harvey J. Kliman method, for early prediction of fetal growth restriction (FGR).
Methods: This retrospective analytical cohort study included 50 women with singleton pregnancies and known delivery outcomes. The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki. Birth weight percentiles were calculated according to gestational age and fetal sex using the INTERGROWTH-21st standards. FGR was defined as birth weight below the 10th percentile. First-trimester PAPP-A (MoM), sFlt-1/PlGF ratio, and ultrasound-based placental volume were analyzed. Diagnostic performance was assessed using ROC curve analysis, and optimal cut-off values were determined using the Youden index. Multivariate logistic regression was performed to evaluate independent and combined predictive effects.
Results: FGR was identified in 8 cases (16%); one intrauterine fetal death occurred. PAPP-A demonstrated high predictive performance (AUC = 0.842), while the sFlt-1/PlGF ratio showed moderate accuracy (AUC = 0.771). Placental volume had limited predictive value (AUC = 0.574). Optimal cut-offs were PAPP-A ≤ 0.69 MoM, sFlt-1/PlGF ≥ 122, and placental volume ≤ 74 cc. The combined biomarker model improved overall predictive performance (AUC = 0.807).

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Conclusions: Low first-trimester PAPP-A was the strongest early predictor of FGR. Combined assessment of biochemical and morphological placental markers improved diagnostic accuracy and may support early risk stratification in clinical practice. (www.actabiomedica.it)

Key words: Fetal growth restriction, PAPP-A, sFlt-1/PlGF ratio, placental volume, first trimester, placental dysfunction, biomarkers

Introduction

Fetal growth restriction (FGR) is a pathological condition characterized by the inability of the fetus to achieve its genetically determined growth potential and is most commonly associated with placental dysfunction. FGR was defined as a pathological condition associated with placental dysfunction and distinguished from small-for-gestational-age (SGA), which may represent constitutionally small but healthy fetuses. FGR remains one of the leading causes of perinatal morbidity and mortality worldwide and is strongly associated with adverse short-term neonatal outcomes as well as long-term adult health consequences, including metabolic syndrome, cardiovascular disease, and neurodevelopmental impairment (1–3). International clinical guidelines, including those issued by FIGO and ACOG, emphasize FGR as a major obstetric challenge requiring early risk identification and standardized management strategies (4,5). Despite its significant clinical impact, FGR is frequently diagnosed only in the second half of pregnancy, when placental insufficiency is already established and fetal growth deviation becomes evident on ultrasound examination. Current pathophysiological concepts identify defective early placentation as the central mechanism underlying FGR (6). Inadequate trophoblast invasion and incomplete spiral artery remodeling impair uteroplacental perfusion, resulting in chronic placental hypoxia and reduced placental functional capacity (6,7). These abnormalities originate in the first trimester, long before clinical manifestations of fetal growth restriction become apparent. Comprehensive reviews have highlighted that placental-origin cardiovascular programming may extend the impact of FGR into adulthood, reinforcing the importance of early detection (3). Among first-trimester biomarkers, pregnancy-associated plasma protein-A (PAPP-A) has been extensively investigated as an indicator of trophoblastic function. PAPP-A is a trophoblast-derived metalloproteinase synthesized by the placenta and routinely measured in maternal serum as part of the combined 11–13+6-week screening protocol together with nuchal translucency and β-hCG. Biologically, PAPP-A increases the bioavailability of insulin-like growth factors (IGF-I and IGF-II) by cleaving IGF-binding proteins (IGFBP-4). The IGF system plays a crucial role in trophoblast invasion, spiral artery remodeling, placental vascular development, and fetal nutrient supply (8,9). Low first-trimester PAPP-A levels, expressed as multiples of the median (MoM), reflect impaired placentation and reduced uteroplacental perfusion. Decreased PAPP-A levels (<0.5 MoM) have been consistently associated with subsequent placental insufficiency and represent one of the earliest and most sensitive predictors of FGR (10,11). Structural assessment of placental development provides complementary information regarding placental functional mass. Reduced placental volume reflects limited placental reserve and has been associated with adverse perinatal outcomes, including fetal growth restriction (12). Large prospective screening studies have demonstrated that integration of first-trimester biometry and biochemical markers improves early prediction of FGR (13). Ultrasound-based approaches allow early estimation of placental volume during the first trimester, enabling morphological assessment of placental development at a stage when functional disturbances may still be subclinical. The Merwin–Kliman method offers a practical two-dimensional alternative to three-dimensional volumetric techniques for early placental assessment (12). Angiogenic imbalance represents another fundamental mechanism of placental insufficiency. Placental growth factor (PlGF) is a pro-angiogenic molecule essential for placental vascular development and adequate perfusion. In contrast, soluble fms-like tyrosine kinase-1 (sFlt-1) acts as an anti-angiogenic factor by binding and neutralizing PlGF and vascular endothelial growth factor (VEGF). In the setting of placental hypoxia, sFlt-1 levels increase while PlGF levels decrease, leading to impaired angiogenesis and progressive placental dysfunction (14). Seminal work by Levine et al. first established the clinical relevance of angiogenic imbalance in placental disease (15). Subsequent studies confirmed the prognostic value of the sFlt-1/PlGF ratio in early-onset placental disorders, including FGR (16,17). In early-onset FGR (<32 weeks), markedly elevated sFlt-1/PlGF ratios may precede clinical and Doppler abnormalities by several weeks, highlighting their potential role in early risk stratification and pregnancy management. Although the sFlt-1/PlGF ratio is primarily used in the second and third trimesters, emerging evidence suggests that angiogenic imbalance may originate earlier in pregnancy. Therefore, assessment of this ratio in the first trimester may provide insight into early placental dysfunction, although its clinical application at this stage remains investigational.

Patients and Methods

Study design and setting

This observational, analytical cohort study was conducted between 2023 and 2026 at the Department of Obstetrics and Gynecology II of Azerbaijan Medical University. The study protocol was approved by the institutional ethics committee, and all procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Study population

A total of 50 pregnant women with singleton gestations were included in the study. All participants had completed delivery and had available first-trimester biochemical screening results, placental ultrasound measurements, and complete neonatal outcome data.

Inclusion and exclusion criteria

Inclusion criteria comprised singleton pregnancy, availability of first-trimester PAPP-A measurement, available serum sFlt-1 and placental growth factor (PlGF) concentrations, ultrasound measurements necessary for placental volume calculation, and complete delivery records including birth weight, length, Apgar score, and gestational age. Exclusion criteria included multiple pregnancy, chromosomal abnormalities, major structural fetal anomalies, severe maternal systemic disease, and incomplete laboratory or clinical data.

Maternal and gestational characteristics

Maternal age, gestational age at biochemical assessment, and gestational age at delivery were recorded. All biochemical and ultrasound assessments were performed between 11 and 14 weeks of gestation.

Biochemical assessment

Maternal venous blood samples were collected during the first trimester (11–13+6 weeks of gestation). Serum pregnancy-associated plasma protein-A (PAPP-A) levels were measured as part of routine prenatal screening and expressed as multiples of the median (MoM). Serum concentrations of soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) were measured in pg/mL using validated immunoassay methods. The sFlt-1/PlGF ratio was calculated for each participant as an indicator of angiogenic balance.

Placental volume assessment

Placental volume was estimated during first-trimester ultrasound examination (11–14 weeks of

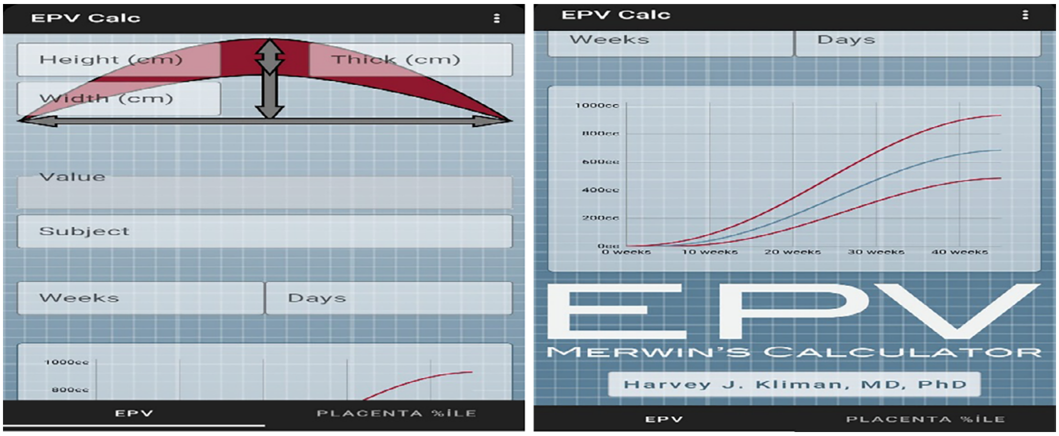

Figure 1. Merwin–Kliman method for estimating placental volume (EPV): formula (EPV = L × W × T × 0.52) and schematic illustration of measurement parameters.

gestation) using the Merwin–Kliman two-dimensional method.

Placental length (L), width (W), and thickness (T) were measured in centimeters, and estimated placental volume (EPV) was calculated using the formula:

$$EPV = L \times W \times T \times 0.52,$$

where 0.52 represents a geometric correction factor accounting for the ellipsoid morphology of the placenta (Figure 1).

Ultrasound assessment of placental volume

If the placenta had a crescent configuration, maximal placental width was measured with the ultrasound probe positioned perpendicular to the placental surface (Figure 2). Placental height was then measured from the highest convex point of the placenta perpendicular to the previously measured width axis (Figure 3). Placental thickness was measured along the same axis from the placental surface to its basal plate (Figure 4). In cases of a flat placental configuration without curvature, height and thickness measurements coincided and were obtained in a single measurement (Figure 5). For all measurements, the ultrasound probe was maintained perpendicular (90° angle) to the placental surface to ensure optimal echo reflection and measurement accuracy (Figure 6A-B). All ultrasound examinations were performed by

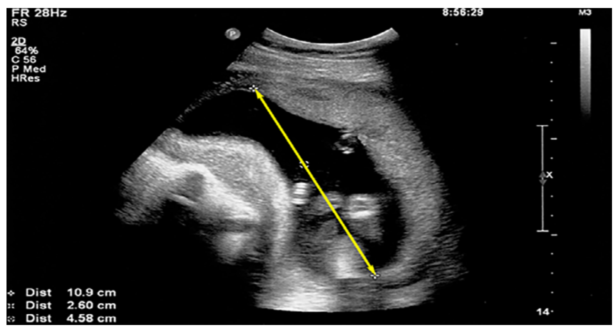

Figure 2. Measurement of maximal placental width (L) in crescent-shaped placenta with the ultrasound probe positioned perpendicular to the placental surface.

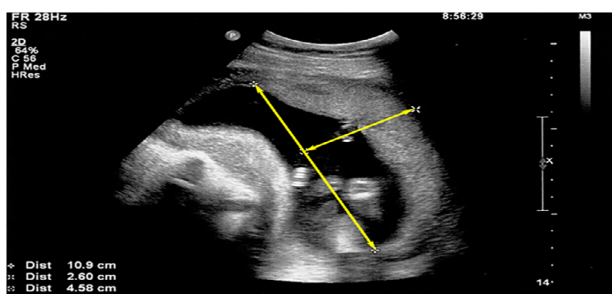

Figure 3. Measurement of placental height (W) from the highest convex point perpendicular to the previously measured width axis.

experienced obstetric sonographers using standardized scanning protocols. To minimize interobserver variability, measurements were obtained in duplicate, and the mean value was used for statistical analysis.

Although a formal assessment of intraobserver and interobserver variability was not performed, all measurements were conducted according to standardized protocols to minimize variability.

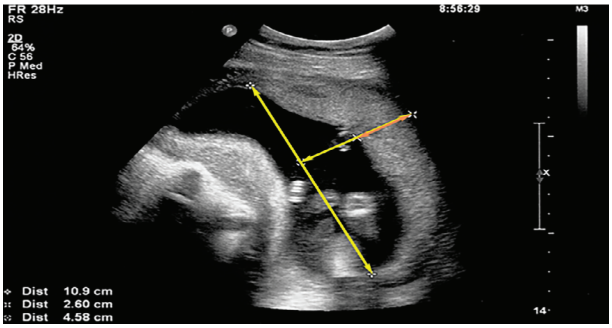

Figure 4. Measurement of placental thickness (T) from the placental surface to the basal plate along the defined measurement axis.

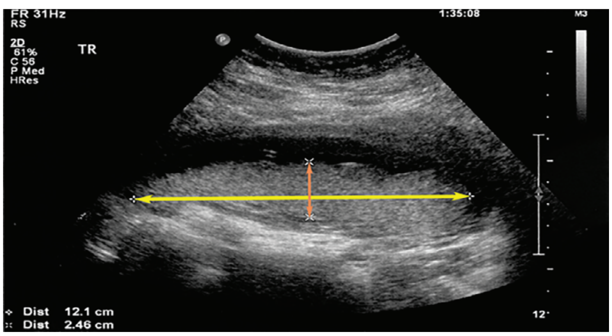

Figure 5. Measurement approach in a flat placental configuration where height and thickness coincide and are obtained in a single measurement.

Fetal growth assessment

Neonatal data, including gestational age at delivery, birth weight, birth length, Apgar score, and sex, were recorded. Birth weight percentiles were calculated according to gestational age and fetal sex using the INTERGROWTH-21st international standards (Villar et al., 2014). Fetal growth restriction (FGR) was defined as birth weight below the 10th percentile.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version XX). Data distribution normality was assessed using the Kolmogorov–Smirnov test. Continuous variables were presented as mean ± standard deviation or median (interquartile range), as appropriate. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance of individual biomarkers and the combined model. Optimal cut-off values were determined using the Youden index. Multivariate logistic regression analysis was conducted to assess the independent and combined effects of the biomarkers. A multivariable logistic regression model was constructed including PAPP-A (MoM), sFlt-1/PlGF ratio, and placental volume as continuous variables. The predicted probability of FGR was calculated for each participant based on the regression model. A P value <0.05 was considered statistically significant.

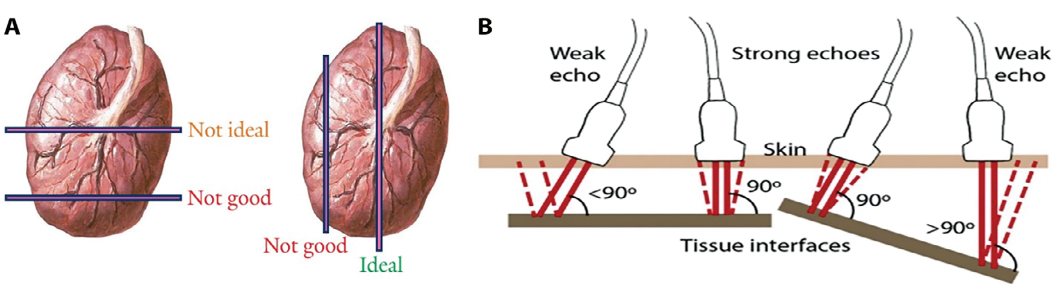

Figure 6. Ultrasound probe positioning and measurement orientation in placental volume assessment. (A) Effect of probe angulation on echo reflection: perpendicular (90°) positioning обеспечивает оптимальное отражение сигнала, тогда как отклонение <90° или >90° снижает точность измерений. (B) Examples of correct and incorrect orientation of measurement lines relative to placental curvature; vertical alignment perpendicular to the placental surface represents the ideal measurement technique.

Results

Characteristics of the study population

A total of 50 pregnant women with singleton pregnancies and completed deliveries were included in the analysis. Fetal growth restriction (FGR), defined as birth weight below the 10th percentile, was identified in 8 cases (16%), whereas 42 pregnancies (84%) demonstrated normal fetal growth. One case of intrauterine fetal demise (2%) was recorded in the subgroup characterized by severe placental dysfunction. Neonatal sex distribution was comparable: 24 female (48%) and 26 male (52%) newborns.

The median perinatal parameters were as follows (Table 1):

- Birth weight: 3220 g
- Birth length: 51 cm
- Gestational age at delivery: 39 weeks + 2 days
- 5-minute Apgar score: 8

Table 1. Baseline characteristics of the study population (n = 50)

Variable	Overall (n = 50)
Fetal growth restriction (<10th percentile), n (%)	8 (16 %)
Normal fetal growth, n (%)	42 (84 %)
Intrauterine fetal demise, n (%)	1 (2 %)
Female neonates, n (%)	24 (48 %)
Male neonates, n (%)	26 (52 %)
Birth weight (g), mean	3220
Birth length (cm), mean	51
Gestational age at delivery (weeks), mean	39.3
Apgar score at 5 min, median	8

Note: Data are presented as mean values or n (%), unless otherwise indicated. Continuous variables are presented as median values.

Overall, the study population demonstrated generally favorable perinatal outcomes, except for the subgroup affected by FGR.

Comparison between FGR and Non-FGR groups

Significant differences were observed between the FGR and non-FGR groups across key biochemical and clinical parameters (Table 2).

In the FGR group:

- First-trimester PAPP-A levels were significantly lower (0.41 vs 0.82 MoM, $p = 0.004$), reflecting impaired early trophoblastic invasion.
- The sFlt-1/PlGF ratio was markedly elevated (148 vs 38, $p = 0.006$), indicating pronounced angiogenic imbalance.
- Gestational age at delivery was significantly shorter (37+1 vs 39+3 weeks, $p = 0.03$), suggesting a tendency toward earlier delivery.
- Birth weight was substantially reduced (2330 g vs 3410 g, $p < 0.001$).

Placental volume was lower in the FGR group (54 cc vs 63 cc); however, this difference did not reach statistical significance ($p = 0.21$), supporting the limited predictive performance of placental volume when used as an isolated marker.

Correlation analysis

Birth weight percentile was used as a quantitative indicator of FGR severity (Table 3).

Table 2. Comparison between FGR and non-FGR groups

Variable	FGR (n = 8)	Non-FGR (n = 42)	P
PAPP-A (MoM), median	0.41	0.82	0.004
sFlt-1/PlGF ratio, median	148	38	0.006
Placental volume (cm³), mean	54	63	0.21
Birth weight (g), mean	2330	3410	<0.001
Gestational age at delivery (weeks), mean	37	39.4	0.03

Note: Data are presented as mean or median values, as appropriate. Continuous variables are presented as median values.

Table 3. Correlation analysis between biomarkers and birth weight percentile

Variable	Pearson's r	P value
PAPP-A (MoM)	0.44*	0.004
sFlt-1/PlGF ratio	−0.37*	0.006
Placental volume (cm³)	0.18	0.21

Birth weight percentile was used as an indicator of fetal growth. Asterisk indicates statistical significance (*p < 0.05).

The following correlations were identified:

- PAPP-A demonstrated a moderate positive correlation with birth weight percentile ($r = +0.44$, $p < 0.05$), indicating that lower PAPP-A levels were associated with lower percentiles and increased FGR risk.
- The sFlt-1/PlGF ratio showed a moderate negative correlation ($r = -0.37$, $p < 0.05$), suggesting that higher angiogenic imbalance was associated with greater placental dysfunction and reduced fetal growth.
- Placental volume exhibited a weak positive correlation ($r = +0.18$), which did not reach statistical significance.

These findings indicate that biochemical markers demonstrated stronger associations with impaired fetal growth than the structural placental parameter alone.

Clinical phenotype of FGR

Patients with FGR exhibited a characteristic biomarker pattern:

- PAPP-A < 0.4–0.5 MoM
- sFlt-1/PlGF > 120–150
- Placental volume < 50–60 cc

This triad reflects combined biochemical, angiogenic, and structural placental dysfunction.

Receiver operating characteristic curve analysis

Receiver operating characteristic (ROC) analysis demonstrated variable discriminative performance among the evaluated markers (Table 4):

- PAPP-A: AUC = 0.84 (95% CI 0.71–0.96, $p < 0.001$) — strong predictive performance.

Table 4. ROC analysis of biomarkers for prediction of fetal growth restriction

Marker	AUC	95% CI	P value
PAPP-A (MoM)	0.84	0.71–0.96	<0.001
sFlt-1/PlGF ratio	0.77	0.61–0.92	0.004
Placental volume (cm³)	0.57	0.39–0.75	0.28
Combined model (predicted probability)	0.81	0.68–0.94	<0.001

Abbreviations: AUC, area under the curve; CI, confidence interval. Diagnostic Performance and Cut-off Values

- sFlt-1/PlGF ratio: AUC = 0.77 (95% CI 0.61–0.92, $p = 0.004$) — moderate-to-strong performance.
- Placental volume: AUC = 0.57 (95% CI 0.39–0.75, $p = 0.28$) — weak predictive value.
- Combined model: AUC = 0.81 (95% CI 0.68–0.94, $p < 0.001$).

Although PAPP-A demonstrated the highest individual AUC, the combined model did not outperform PAPP-A but provided a clinically relevant integrative assessment of placental dysfunction.

Optimal cut-off values determined by the Youden index are presented in Table 5. The combined model cut-off (≥ 0.095) represents the optimal threshold of the predicted probability derived from the logistic regression model, as determined using the Youden index.

- PAPP-A ≤ 0.69 MoM demonstrated 100% sensitivity and 59% specificity (PPV 31%, NPV 100%).
- sFlt-1/PlGF ≥ 122 showed 75% sensitivity and 81% specificity (PPV 46%, NPV 94%).
- Placental volume ≤ 74 cc demonstrated high sensitivity (100%) but low specificity (31%).
- The combined model (≥ 0.095) yielded 100% sensitivity and 55% specificity.

The high negative predictive values observed across markers highlight their utility in ruling out FGR risk. The ROC curves illustrating the discriminative performance of the evaluated biomarkers are presented in Figure 7.

Table 5. Cut-off values and diagnostic performance of biomarkers for prediction of fetal growth restriction

Marker	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PAPP-A (MoM)	≤ 0.69	100	59	31	100
sFlt-1/PlGF ratio	≥ 122	75	81	46	94
Placental volume (cm³)	≤ 74	100	31	22	100
Combined model (predicted probability)	≥ 0.095	100	55	30	100

Note: Cut-off values were determined using the Youden index. *Abbreviations:* PPV, positive predictive value; NPV, negative predictive value.

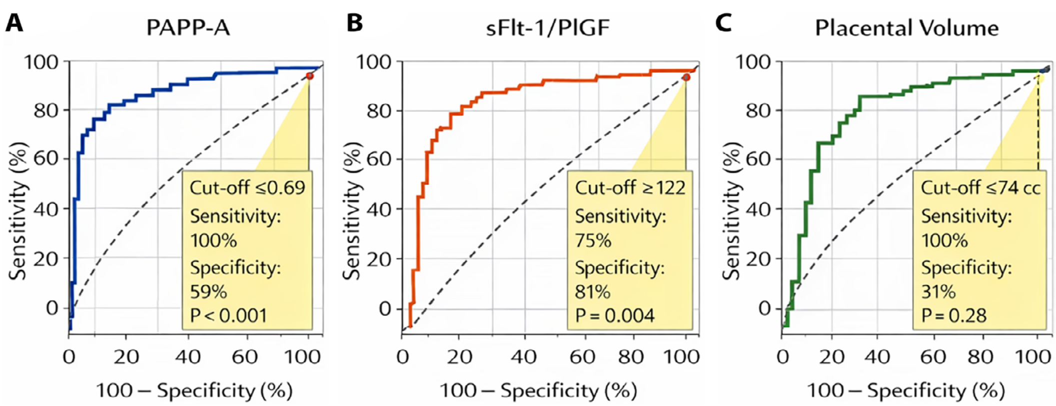

Figure 7. Cut-off values and diagnostic performance of biomarkers for prediction of fetal growth restriction.

Table 6. Multivariate logistic regression analysis for predictors of fetal growth restriction

Variable	OR	95% CI	P value
PAPP-A (MoM)	8.4	1.6–43.2	0.012
sFlt-1/PlGF ratio	5.6	1.2–26.1	0.027
Placental volume (cm³)	2.1	0.8–6.3	0.24
Combined model (predicted probability)	11.7	2.4–57.4	0.002

Abbreviations: OR, odds ratio; CI, confidence interval.

Multivariate logistic regression analysis

Multivariate logistic regression analysis was performed to identify independent predictors of fetal growth restriction (Table 6).

PAPP-A was independently associated with FGR (OR = 8.4, 95% CI 1.6–43.2, p = 0.012).

The sFlt-1/PlGF ratio also remained a significant predictor (OR = 5.6, 95% CI 1.2–26.1, p = 0.027).

Placental volume did not reach statistical significance in the adjusted model (OR = 2.1, p = 0.24).

The combined multimarker model demonstrated the highest prognostic strength (OR = 11.7, 95% CI 2.4–57.4, p = 0.002). The strength and precision of the associations are visually presented in Figure 8.

Discussion

This study evaluated the clinical utility of first-trimester biochemical and morphological placental markers—PAPP-A, sFlt-1/PlGF ratio, and placental volume calculated using the Merwin–Kliman method—for early prediction of fetal growth restriction (FGR). Our findings demonstrate that biochemical and angiogenic markers possess strong prognostic potential, and when integrated with structural parameters, improve early identification of pregnancies at risk for placental dysfunction.

PAPP-A and FGR

In the present study, first-trimester PAPP-A exhibited the strongest association with FGR (AUC = 0.84;

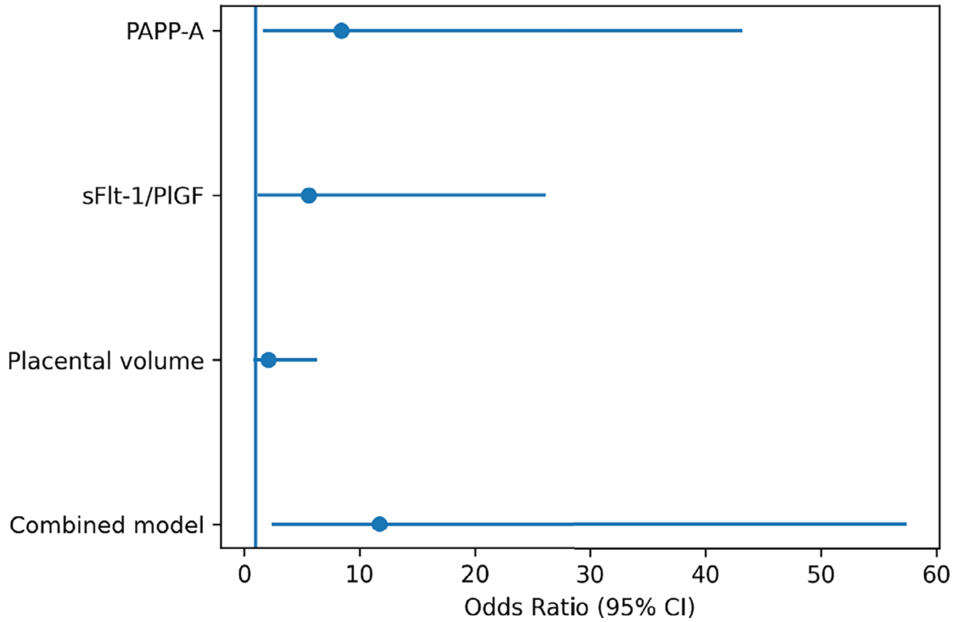

Figure 8. Forest plot of multivariate logistic regression analysis showing odds ratios (OR) and 95% confidence intervals for predictors of fetal growth restriction.

OR = 8.4). Reduced PAPP-A levels reflect impaired trophoblast invasion and defective early placental angiogenesis, which are central mechanisms in the pathogenesis of placental insufficiency (6,8). These findings are consistent with large cohort studies demonstrating that low PAPP-A levels are associated with reduced uteroplacental perfusion and subsequent fetal growth restriction (8,9). Moreover, previous investigations have emphasized that PAPP-A should not be considered solely as a chromosomal screening marker, but rather as an indicator of early placental function (10). Our data reinforce the concept that decreased PAPP-A (<0.5–0.7 MoM) represents an early biochemical signal of impaired placentation.

Angiogenic imbalance and the sFlt-1/PlGF ratio

The sFlt-1/PlGF ratio demonstrated moderate-to-strong predictive performance (AUC = 0.77; OR = 5.6). Angiogenic imbalance is a well-established hallmark of placental dysfunction. Excess sFlt-1 binds and neutralizes PlGF and VEGF, leading to endothelial dysfunction and reduced placental perfusion (14,15). While the angiogenic imbalance paradigm was initially described in preeclampsia (15), subsequent research has shown that similar mechanisms underlie early-onset FGR (16,17). Our findings support the expanding view that sFlt-1/PlGF is not exclusively a preeclampsia marker but also a valuable predictor of fetal growth restriction. It should be noted that the use of the sFlt-1/PlGF ratio in the first trimester is not yet part of routine clinical practice and should be interpreted as an exploratory approach requiring further validation. Importantly, elevated sFlt-1/PlGF ratios may precede clinical manifestations and Doppler abnormalities by several weeks (16), suggesting a potential role in early risk stratification and surveillance planning.

Placental volume as a structural marker

Placental volume, assessed using the Merwin–Kliman method, showed limited predictive value when analyzed independently (AUC = 0.57). The low AUC observed in our study suggests limited standalone predictive utility of placental volume. This may reflect the fact that structural parameters alone are insufficient to capture early functional placental impairment, which is better reflected by biochemical and angiogenic markers. This finding aligns with prior evidence indicating that structural parameters alone may lack sufficient sensitivity for early detection of FGR (12). However, placental surface area and volumetric estimations have been associated with adverse pregnancy outcomes in large observational studies (12).

Structural alterations may not fully capture early functional placental impairment, which is better reflected by biochemical and angiogenic markers. In addition, the absence of reproducibility analysis represents a methodological limitation that should be addressed in future studies.

Role of the combined model

Multivariate logistic regression demonstrated that the combined model was significantly associated with FGR (OR = 11.7; AUC = 0.81). The combined model did not outperform PAPP-A in terms of AUC; however, it integrates multiple pathophysiological pathways and may provide complementary clinical information. These findings support the concept that placental dysfunction is inherently multifactorial, involving structural, biochemical, and vascular components (3,6). Multimarker approaches have been shown to outperform single-parameter screening strategies (13). Our results are consistent with large prospective screening models integrating maternal characteristics, biochemical markers, and biophysical parameters to improve early prediction of placental-mediated disorders (13). Our findings are in line with recent evidence highlighting the importance of early placental biomarkers in predicting fetal growth restriction (18). Notably, the combined model exhibited a high negative predictive value, indicating clinical utility in safely identifying low-risk pregnancies and optimizing resource allocation.

Clinical implications

The clinical implications of our findings are substantial. Low first-trimester PAPP-A levels may serve as an early warning signal of impaired placentation and should prompt closer surveillance and individualized follow-up strategies. Elevated sFlt-1/PlGF ratios may reflect subclinical placental dysfunction even before Doppler abnormalities become apparent, allowing earlier risk stratification. The implementation of a combined screening model integrating biochemical, angiogenic, and structural markers may enhance early identification of pregnancies at high risk for fetal growth restriction and facilitate timely clinical intervention. Furthermore, the high negative predictive values observed in our study suggest that this multimarker approach may be particularly useful in safely identifying low-risk pregnancies, thereby reducing unnecessary interventions and optimizing healthcare resource allocation. Overall, such a strategy has the potential to improve perinatal outcomes through more precise and individualized risk assessment.

Strengths and limitations

This study has several strengths. It integrates biochemical, angiogenic, and structural placental markers within a unified analytical framework, reflecting the multifactorial nature of placental dysfunction. The use of multivariate modeling enhances the robustness of the predictive analysis. Additionally, birth weight percentiles were calculated using standardized INTERGROWTH-21st international criteria, and the study was based on real perinatal outcomes rather than surrogate markers, strengthening the clinical relevance of the findings. However, certain limitations should be acknowledged. The relatively small sample size and single-center design may limit the generalizability of the results. The absence of an external validation cohort restricts assessment of reproducibility across different populations. Moreover, longitudinal monitoring of biomarkers throughout pregnancy was not performed, and Doppler parameters were not systematically integrated into the predictive model. Future multicenter studies with larger cohorts and external validation are warranted to confirm the reproducibility and clinical applicability of the proposed multimarker screening strategy.

Limitations and future directions

This study has several limitations. The relatively small sample size and single-center design may limit the generalizability of the findings. In addition, the limited number of FGR events may increase the risk of overfitting in multivariable modeling, and the estimated effect sizes should therefore be interpreted with caution. Accordingly, the results of the multivariate analysis should be considered exploratory. Although statistically significant associations were identified, validation in larger and more diverse populations is required to confirm the stability of the proposed predictive model. Biomarkers were assessed at a single time point during the first trimester. Longitudinal evaluation throughout pregnancy may provide additional insight into the progression of placental dysfunction. Furthermore, Doppler parameters were not systematically incorporated into the predictive model, and their integration with biochemical and structural markers could potentially improve diagnostic accuracy. External validation of the multimarker model was not performed, and future multicenter prospective studies are needed to assess its reproducibility and clinical applicability. The use of advanced statistical approaches, including machine learning–based models, may further enhance individualized risk stratification in future research.

Conclusions

Low first-trimester PAPP-A levels represent the strongest early biochemical predictor of fetal growth restriction, reflecting impaired trophoblastic invasion and defective early placentation. The sFlt-1/PlGF ratio provides complementary functional information by capturing angiogenic imbalance, a central mechanism underlying placental insufficiency. In contrast, placental volume assessed as an isolated structural parameter demonstrates limited predictive capacity, likely due to the complex and multifactorial nature of placental dysfunction. Importantly, integration of biochemical and morphological markers within a combined predictive model enhances early risk stratification compared with single-marker approaches. The multimarker strategy demonstrated high negative predictive value, supporting its potential utility in safely identifying low-risk pregnancies while enabling targeted surveillance of high-risk cases. These findings highlight the importance of early placental assessment and may provide a basis for early risk assessment. However, they should be considered exploratory, and further validation in larger, multicenter studies is required before clinical application.

Ethical Approval: All study procedures were reviewed and approved by the Ethics Committee of Azerbaijan Medical University (protocol No. EC-2026-056, March 13, 2026). The protocol entitled "Combined prognostic value of first-trimester PAPP-A, placental volume and sFlt-1/PlGF ratio for early prediction of fetal growth restriction" was considered compliant with bioethical standards, and the research was authorized for implementation.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article

Authors' Contribution: US Conceptualization, study design, data collection, laboratory analyses, interpretation of results, and drafting of the manuscript, supervision of the research process, guidance in manuscript writing, and critical review of the final version, SG Methodology & Editing, statistical analysis, data visualization, and assistance with data interpretation. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Declaration on the Use of AI: None.

Consent for Publication: Written informed consent for participation and publication was obtained from all pregnant women included in the study. The participants were informed about the study objectives, research procedures, and the use of anonymized clinical and neonatal data for scientific purposes. No identifiable personal information is disclosed in this manuscript.

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