ORIGINAL ARTICLE

# First-trimester sFlt-1/PlGF ratio and oxidative stress markers in newborns: Biochemical associations and early risk stratification

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## ABSTRACT

**Background and Aim:** Early disturbances in placental angiogenesis contribute to adverse pregnancy outcomes; however, their biochemical impact on the newborn remains insufficiently understood. This study aimed to assess the association between first-trimester angiogenic markers (sFlt-1, PlGF, and the sFlt-1/PlGF ratio; MoM was calculated for normalization purposes) and oxidative stress parameters in newborns.

**Methods:** A total of 48 pregnant women at 11–13 weeks of gestation and their newborns were included. Maternal serum levels of sFlt-1, PlGF, and the sFlt-1/PlGF ratio were measured, and MoM values were calculated for the sFlt-1/PlGF ratio for normalization purposes. For neonatal outcome analysis, three angiogenic profile groups (normal, borderline, and high angiogenic profile group) were considered. Neonatal biochemical parameters included glucose, malondialdehyde (MDA), and dicarbonyl compounds (DK). Statistical analysis involved ANOVA with post hoc tests, correlation analysis, and visualization methods.

**Results:** Women in the high angiogenic profile group showed elevated sFlt-1 and sFlt-1/PlGF ratio and reduced PlGF ($p < 0.01$). Newborns of these mothers had higher MDA and DK levels ($p < 0.05$), indicating increased oxidative stress. A moderate positive correlation was found between maternal sFlt-1/PlGF ratio and neonatal DK ($r = 0.42$; $p = 0.031$), while MDA and DK were strongly correlated ($r = 0.89$; $p < 0.001$). The metabolic group showed a distinct profile with elevated MoM and intermediate angiogenic changes.

**Conclusion:** First-trimester angiogenic imbalance is associated with oxidative stress in newborns. Early angiogenic markers may serve as predictors of neonatal oxidative imbalance, supporting the concept of a

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maternal–placental–fetal axis. Integration of angiogenic and metabolic markers may improve the prediction of perinatal risks.

**Key words:** preeclampsia, placenta, oxidative stress, malondialdehyde, angiogenic factors, infant, newborn, sFlt-1/PlGF ratio

## Introduction

Preeclampsia and associated placental dysfunction remain major challenges in modern obstetric practice, accounting for up to 10–15% of maternal mortality worldwide and a substantial proportion of preterm births (1). A key role in the pathogenesis of pregnancy complications is played by an imbalance between pro-angiogenic and anti-angiogenic factors, which begins as early as the first trimester, long before the onset of clinical symptoms (2). It is well established that the soluble fms-like tyrosine kinase-1 (sFlt-1), a circulating anti-angiogenic factor, exerts its effects by binding vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), thereby reducing their bioavailability (3). Concurrently, decreased levels of PlGF, a critical regulator of trophoblast invasion and uteroplacental perfusion, contribute to impaired spiral artery remodeling, chronic placental hypoperfusion, and endothelial dysfunction (4). Numerous studies have demonstrated that the sFlt-1/PlGF ratio is not only a marker of early preeclampsia but also a useful indicator associated with adverse perinatal outcomes (5–7). Current clinical guidelines emphasize that first-trimester screening for preeclampsia should be based on a combined approach, including maternal risk factors, mean arterial pressure, uterine artery Doppler indices, and placental growth factor (PlGF), rather than the standalone use of the sFlt-1/PlGF ratio. The sFlt-1/PlGF ratio is primarily used in later stages of pregnancy, particularly for the evaluation of women with suspected preeclampsia, rather than for routine early screening in asymptomatic populations (8–10). In parallel, increasing attention has been paid to early biomarkers of neonatal adaptation. Oxidative stress indicators, such as malondialdehyde (MDA) and dicarbonyl compounds (DK), reflect the degree of perinatal hypoxia and metabolic stress in the fetus (11). Recent studies suggest that neonatal oxidative stress is closely linked to early placental dysfunction originating in the first trimester (12–14). Taken together, these findings indicate that a combined assessment of maternal angiogenic markers and neonatal oxidative stress parameters may provide additional insight into perinatal risk. Therefore, the present study aimed to evaluate sFlt-1, PlGF, and the sFlt-1/PlGF ratio in pregnant women at 11–13 weeks of gestation and to analyze oxidative stress-related biochemical parameters in their newborns, in order to explore the biochemical relationship between maternal angiogenic status and neonatal condition.

## 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, Azerbaijan Medical University. This study was based on the analysis of previously collected clinical and biological data. The study aimed to evaluate the relationship between first-trimester angiogenic markers and oxidative stress parameters in newborns. 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 had been obtained from all participants at the time of data collection.

### Study population

A total of 48 pregnant women at 11–13 weeks of gestation and their 48 newborns were included in the study. Eligible participants were women with singleton pregnancies within the specified gestational age and without severe somatic pathology or chronic inflammatory diseases. Women were excluded if they had a history of preeclampsia, type I or II diabetes mellitus, autoimmune diseases, multiple pregnancy, or use of antioxidant medications.

### Assessment of angiogenic markers

Venous blood samples were collected in the morning after overnight fasting. Serum levels of sFlt-1 and PlGF were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) with certified kits (Elabscience, USA) according to the manufacturer's instructions. Optical density was measured using a microplate reader at 450 nm with reference correction at 620 nm. The sFlt-1/PlGF ratio was calculated for each sample. MoM (multiples of the median) was calculated for the sFlt-1/PlGF ratio as the ratio of the measured value to the median reference value for the corresponding gestational age, based on regional reference data.

### Biochemical parameters in newborns

Glucose, malondialdehyde (MDA), and dicarbonyl compounds (DK) were measured in umbilical cord serum. Glucose levels were determined using the glucose oxidase method. MDA concentration was assessed by the thiobarbituric acid (TBA) reaction, while DK levels were determined using a colorimetric assay with dinitrophenylhydrazine. All measurements were performed using a semi-automated biochemical analyzer with double calibration.

### Group classification based on angiogenic and metabolic profiles

Participants were stratified based on their angiogenic and metabolic profiles. Four groups were initially defined. The normal group included women with angiogenic parameters (sFlt-1, PlGF, and sFlt-1/PlGF ratio) within established reference ranges. The borderline group comprised patients with moderate alterations in angiogenic balance, characterized by a slight increase in sFlt-1 and a decrease in PlGF levels. The high angiogenic profile group (preeclampsia risk) consisted of women with a markedly elevated sFlt-1/PlGF ratio (>150), indicating a pronounced anti-angiogenic state. The metabolic group included participants with elevated multiples of the median (MoM >1.3), reflecting increased metabolic load and potential subclinical metabolic dysregulation. For neonatal outcome analysis, participants were classified into three angiogenic profile groups (normal, borderline, and high angiogenic profile group) based on sFlt-1/PlGF ratio thresholds. These categories were used for intergroup comparisons of neonatal biochemical parameters. The metabolic group (MoM >1.3) was considered an overlapping phenotype and was analyzed separately without inclusion in comparative neonatal outcome analysis to avoid misclassification. The applied sFlt-1/PlGF ratio thresholds were used for analytical grouping within this study and should not be interpreted as clinically validated first-trimester cut-off values.

### Statistical analysis

Data normality was assessed using the Shapiro–Wilk test. Intergroup differences were analyzed using one-way analysis of variance (ANOVA) followed by Bonferroni post hoc correction. Correlations between angiogenic and biochemical parameters were evaluated using Pearson's correlation coefficient. Data visualization included raincloud plots and correlation heatmaps. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using Python (NumPy, Pandas, SciPy, and Matplotlib libraries). Data distribution was assessed for each variable prior to analysis. Due to the exploratory nature of the study and sample size, statistical results were interpreted with caution.

## Results

Angiogenic markers in pregnant women demonstrated substantial variability, reflecting heterogeneity in vascular adaptation during the first trimester

of pregnancy. In most participants, the values corresponded to a favorable angiogenic profile; however, a subset of women exhibited signs of an anti-angiogenic shift, suggesting potential impairment of placental perfusion. The contribution of metabolic factors, reflected by MoM values of the sFlt-1/PlGF ratio, was also significant, allowing the identification of a subgroup of patients with relative deviation from the expected angiogenic balance (Table 1).

The distribution of women across risk categories confirmed the presence of a clinically heterogeneous population. Although a normal angiogenic profile predominated, a considerable proportion of participants demonstrated borderline or pathological changes. The high angiogenic profile group was characterized by the most pronounced shift toward anti-angiogenic factors, whereas the metabolic subgroup represented a distinct risk phenotype combining moderate angiogenic alterations with a pronounced metabolic component (Table 2).

Visual analysis of angiogenic markers across angiogenic profile groups is presented in Figures 1–4 (mean ± SD). Figures 1–4 include all four initially defined groups (normal, borderline, high angiogenic profile group, and metabolic) to illustrate overall angiogenic and metabolic variability. A progressive pattern of angiogenic imbalance was observed across groups. Specifically, sFlt-1 levels were markedly elevated in the high angiogenic profile group compared to the normal group, whereas PlGF levels showed a pronounced decrease. The sFlt-1/PlGF ratio demonstrated the most distinct intergroup differences, highlighting its sensitivity to early placental dysfunction. The metabolic group exhibited intermediate angiogenic changes but was characterized by higher MoM values and greater variability, indicating a distinct metabolic phenotype. However, this group was not included in the comparative neonatal outcome analysis, as described above.

Biochemical parameters of newborns also demonstrated considerable interindividual variability (Table 3). While most values remained within physiological ranges, a subset of newborns exhibited elevated oxidative stress markers, suggesting increased oxidative burden potentially associated with intrauterine exposure to placental dysfunction, as well as maternal metabolic factors.

The metabolic group was not included in the comparative neonatal outcome analysis and was evaluated separately. Comparison of neonatal markers across maternal angiogenic groups revealed a clear gradient of increasing oxidative stress. Newborns from the high angiogenic profile group demonstrated significantly elevated MDA and DK levels and reduced glucose concentrations compared to the normal group ($p < 0.001$).

**Table 1.** Angiogenic markers and normalized sFlt-1/PlGF ratio (MoM) in pregnant women at 11–13 weeks of gestation (n = 48)

| Parameter | Mean ± SD | Median | Range |
|---|---|---|---|
| MoM (sFlt-1/PlGF ratio) | 0.93 ± 0.62 | 0.80 | 0.27–3.25 |
| sFlt-1 (pg/mL) | 2137.10 ± 1111.48 | 1555 | 919–4330 |
| PlGF (pg/mL) | 72.19 ± 44.95 | 63.45 | 12.7–176.8 |
| sFlt-1/PlGF ratio | 63.59 ± 75.41 | 22.85 | 7.2–341.5 |

*Note:* MoM values refer to the sFlt-1/PlGF ratio normalized to gestational-age-adjusted median values.

**Table 2.** Distribution of pregnant women according to angiogenic risk categories

| Risk category | Criteria | n | % |
|---|---|---|---|
| Normal | sFlt-1/PlGF ≤ 30 | 25 | 52.1 |
| Borderline | sFlt-1/PlGF 30–150 | 6 | 12.5 |
| High angiogenic profile group (preeclampsia) | sFlt-1/PlGF > 150 | 8 | 16.7 |
| Metabolic risk | MoM > 1.3 | 9 | 18.8 |

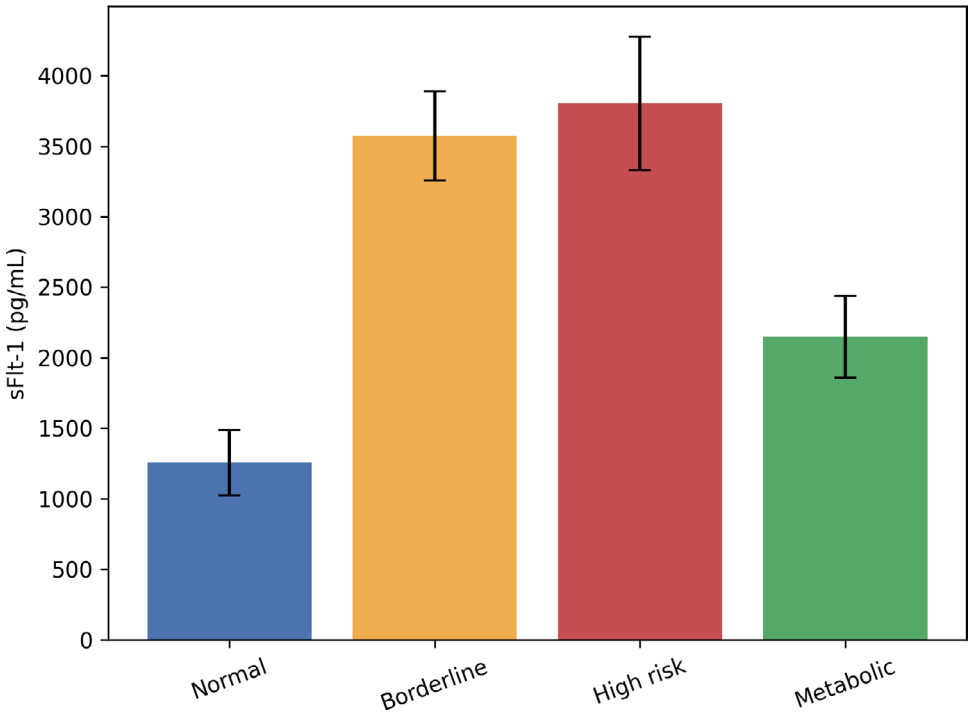


**Figure 1.** Maternal sFlt-1 levels across angiogenic groups in the first trimester of pregnancy.

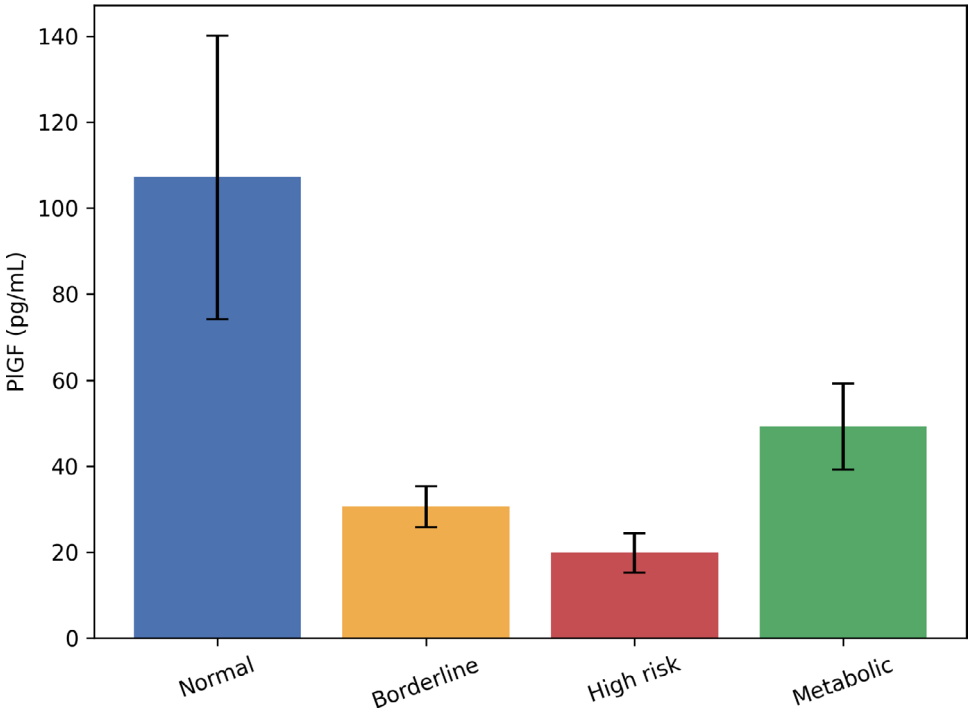


**Figure 2.** Maternal PLGF concentrations across angiogenic risk categories.

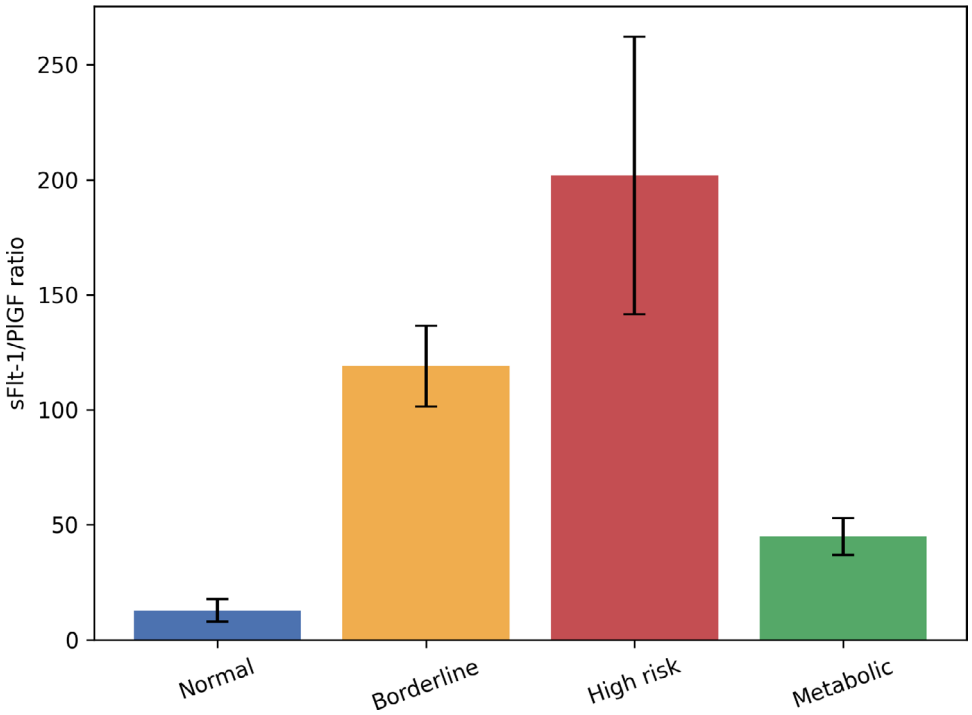


**Figure 3.** Distribution of the sFlt-1/PlGF ratio among angiogenic groups.

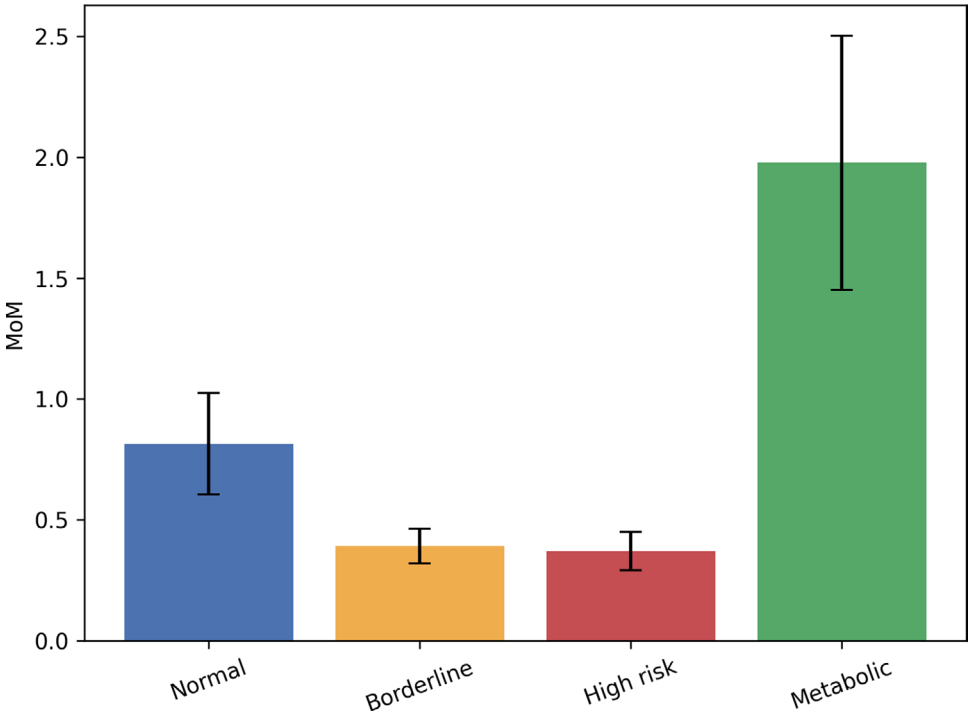


**Figure 4.** MoM values across maternal angiogenic and metabolic profiles.

**Table 3.** Comparison of oxidative stress markers in newborns across across angiogenic groups (n = 48)

| Parameter | Normal (n = 25) | Borderline (n = 6) | High angiogenic profile group (n = 8) |
|---|---|---|---|
| Glucose (mmol/L) | 4.33 ± 0.38 | 3.53 ± 0.39* | 3.02 ± 0.18*** |
| MDA (μmol/L) | 1.66 ± 0.30 | 2.24 ± 0.35** | 2.75 ± 0.33*** |
| DK (μmol/L) | 4.80 ± 0.51 | 6.70 ± 0.54*** | 8.53 ± 0.52*** |

*Note:* *p < 0.05, **p < 0.01, ***p < 0.001 vs normal group.

Borderline cases exhibited intermediate values, supporting a progressive relationship between maternal angiogenic imbalance and neonatal oxidative stress (Table 3). Correlation analysis revealed significant associations between maternal angiogenic markers and neonatal biochemical parameters, highlighting a pathophysiological link between placental dysfunction and oxidative stress in the newborn. Strong correlations among neonatal oxidative stress markers further reflect coordinated mechanisms of lipid peroxidation and carbonyl stress. Overall, these findings suggest that the angiogenic profile of pregnancy in the first trimester may be associated with the oxidative status of the fetus, highlighting the potential relevance of early biochemical assessment.

## Discussion

The results of the present study suggest the important role of angiogenic imbalance in the pathogenesis of early placental dysfunction and contribute to the current understanding of the relationship between maternal angiogenic disturbances and oxidative stress in newborns. The observed profile of elevated sFlt-1 and reduced PlGF in the high angiogenic profile group is consistent with previous studies demonstrating that an increased sFlt-1/PlGF ratio is strongly associated with early-onset preeclampsia (3,5). In our study, the ratio reached values of 150–450, indicating a pronounced anti-angiogenic shift already present at 11–13 weeks of gestation. These findings support the concept of an early "angiogenic window" of placental dysfunction described in recent studies (6,7). The metabolic group (defined by MoM >1.3) was analyzed as an overlapping phenotype and interpreted separately rather than as an independent category in neonatal outcome comparisons**.** Elevated MoM values of the sFlt-1/PlGF ratio in this subgroup reflect a relative deviation from the expected angiogenic balance rather than a directly measured metabolic state. Therefore, this group was interpreted as an overlapping phenotype with intermediate angiogenic characteristics rather than a distinct metabolic category. Our results are consistent with these findings, as women in the metabolic group demonstrated moderate increases in sFlt-1 with relatively preserved PlGF levels. Although this group was not included in direct neonatal comparisons, the observed biochemical profile suggests a potential contribution of additional regulatory factors influencing angiogenic balance and oxidative stress mechanisms. This expands current understanding of intrauterine stress mechanisms. The increase in MDA and DK levels in newborns from the high angiogenic profile group further supports the link between placental dysfunction and oxidative stress. Previous studies have demonstrated that impaired placental perfusion leads to enhanced lipid peroxidation and oxidative damage in neonates (11,12). More recent evidence indicates that oxidative stress originates in utero and may contribute to long-term metabolic programming in the offspring (15,16). Furthermore, carbonyl stress has been identified as a key mechanism linking oxidative damage with metabolic disturbances (11,17). Importantly, our study demonstrates an association between the maternal sFlt-1/PlGF ratio in the first trimester and neonatal dicarbonyl levels ($r = 0.42$; $p = 0.031$). This finding suggests that DK may represent a more sensitive marker of intrauterine oxidative stress compared to MDA, which is more closely associated with acute lipid peroxidation. The strong correlation between MDA and DK ($r = 0.89$; $p < 0.001$) confirms the coordinated activation of lipid peroxidation and carbonyl stress pathways, consistent with previous biochemical studies (13).

Importantly, our findings suggest that neonatal oxidative stress may be related to maternal angiogenic status in early pregnancy, a relationship that has not been previously reported. In comparison with global data, the proportion of women with angiogenic dysfunction in our cohort (17%) is within the range reported for early preeclampsia (8–20%), although this comparison is descriptive and does not imply equivalence between biomarker-defined groups and clinical diagnosis (1). However, the degree of angiogenic imbalance observed in our study appears more pronounced, which may reflect regional, genetic, or environmental influences, as suggested in previous population-based studies (14). The observed associations were not adjusted for potential confounding factors (such as maternal and perinatal characteristics) and should therefore be interpreted with caution. Overall, our findings indicate that first-trimester angiogenic imbalance is not only a marker associated with maternal risk but may also be associated with fetal biochemical status. This study suggests a potential integrative model linking maternal angiogenic factors with neonatal oxidative stress, highlighting the importance of early biomarker-based assessment and opening new perspectives for personalized prenatal care. However, the proposed stratification should be considered exploratory and requires further validation in larger prospective cohorts with adjustment for potential confounders. The relatively small sample size and subgroup distribution, as well as the absence of additional maternal and neonatal characteristics and adjusted analyses, should be taken into account when interpreting the results.

## Conclusion

The present study demonstrates a significant association between first-trimester angiogenic imbalance and increased oxidative stress in newborns. Elevated maternal sFlt-1/PlGF ratio was associated with higher levels of MDA and dicarbonyl compounds in neonates, indicating a link between early placental dysfunction and fetal oxidative status. These findings support the potential relevance of early angiogenic assessment for the evaluation of perinatal outcomes. The combined evaluation of angiogenic and metabolic markers may provide additional insight into perinatal outcomes and facilitate exploratory classification of maternal–fetal conditions. Overall, this study suggests a relationship between maternal angiogenic factors and neonatal oxidative stress, highlighting the potential value of integrated biomarker approaches. Further studies in larger cohorts with adjustment for confounding factors are required to confirm these findings.

**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 "First-trimester sFlt-1/PlGF ratio and oxidative stress markers in newborns: biochemical associations and early risk stratification" was considered compliant with bioethical standards, and the research was authorized for implementation. The term "risk stratification" in the protocol title reflects the original wording of the approved document and does not imply clinically validated stratification within the present study.

**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, ES Data collection, interpretation of results, and drafting of the manuscript, SV Supervision of the research process, guidance in manuscript writing, and critical review of the final version, GH Methodology & Editing, statistical analysis, data visualization, GJ Laboratory analyses, and assistance with data interpretation, GB Participation in data acquisition and contribution to manuscript revision, FG Assistance in data analysis, interpretation, and final editing of the manuscript. 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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