Placental and Maternal Serum Expression of sFlt-1 e15a and PlGF Reveal Distinct Angiogenic Patterns in Early-Onset Preeclampsia

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Abstract: *Background*: Early-onset preeclampsia (EOPE) represents a severe pregnancy disorder occurring before 34 weeks of gestation and is strongly associated with impaired placental angiogenesis. This condition is characterized by an imbalance between antiangiogenic and proangiogenic factors, particularly soluble fms-like tyrosine kinase-1 (sFlt-1) e15a and placental growth factor (PlGF). Despite their recognized roles, data regarding the concurrent expression of these biomarkers in maternal serum and placental tissue remain limited.

Methods: This analytical observational study used a comparative cross-sectional design involving 91 pregnant women with preeclampsia, categorized into EOPE (n=45) and late-onset preeclampsia (LOPE; n=46). Maternal serum and placental levels of sFlt-1 e15a and PlGF were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analyses were performed using independent t-tests or Mann–Whitney tests depending on the data distribution. Receiver operating characteristic (ROC) analysis and Spearman correlation were conducted to evaluate diagnostic performance and biomarker relationships.

Results: Serum sFlt-1 e15a levels were higher in EOPE than LOPE, although not statistically significant ($p=0.082$), while serum PlGF levels were significantly lower ($p<0.001$). Consequently, the serum sFlt-1/PlGF ratio was significantly elevated in EOPE ($p<0.001$). In placental tissue, sFlt-1 e15a levels were significantly lower, whereas PlGF levels were markedly reduced in EOPE compared to LOPE (both $p<0.001$), resulting in a higher placental sFlt-1/PlGF ratio ($p<0.001$). ROC analysis demonstrated good discriminative performance for both serum (AUC=0.772) and placental ratios (AUC=0.782). Significant correlations were observed between serum and placental biomarkers, particularly for the sFlt-1/PlGF ratio ($\rho=0.859$, $p<0.001$).

Conclusion: EOPE is characterized by a pronounced angiogenic imbalance in both maternal serum and placental tissue. The sFlt-1/PlGF ratio demonstrates strong diagnostic potential and may serve as a reliable biomarker for early identification and risk stratification of EOPE.

Keywords: Early-onset preeclampsia, angiogenesis, biomarker.

INTRODUCTION

Preeclampsia remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide, contributing substantially to adverse pregnancy outcomes [1, 2]. It is clinically classified into early-onset and late-onset types, with early-onset preeclampsia (EOPE) representing the more severe form of the disease, characterized by hypertension accompanied by proteinuria or organ dysfunction occurring before 34 weeks of gestation. EOPE accounts for approximately 10–15% of all maternal deaths globally and is a major cause of iatrogenic preterm delivery, which significantly worsens neonatal outcomes [3, 4].

The pathophysiology of EOPE is closely linked to abnormal placental angiogenesis and impaired vascular remodeling [5]. A critical mechanism underlying this disorder is an imbalance between pro-angiogenic and anti-angiogenic factors, which leads to poor placental perfusion and widespread maternal endothelial dysfunction [6, 7]. One of the central hypotheses in preeclampsia pathogenesis involves dysregulated placental expression of angiogenic factors, marked by increased soluble fms-like tyrosine kinase-1 (sFlt-1) and decreased placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) [3, 4, 6-8].

There are four known splice variants of sFlt-1: sFlt-1 i13, which is produced by multiple tissues including the placenta, endothelium, brain, heart, and kidney; sFlt-1 e15a, which is predominantly expressed in the placenta; and sFlt-1 v3 and sFlt-1 v4 [9, 10]. Among these isoforms, sFlt-1 e15a is considered the key placental variant and a potential mediator of endothelial dysfunction in preeclampsia. However, studies focusing specifically on this isoform remain limited [9, 10].

PlGF, a member of the VEGF subfamily, plays an essential role in angiogenesis and vasculogenesis, particularly during embryogenesis. During pregnancy, PlGF is primarily synthesized by placental trophoblasts, although it is also expressed in several other tissues [4, 9]. Consistent with its pro-angiogenic function, decreased maternal serum PlGF levels are a well-established finding in preeclampsia [4, 7, 9].

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Since 2010, the sFlt-1/PlGF ratio has been introduced into clinical practice, particularly during the second trimester, as a predictive biomarker for preeclampsia. The PROGNOSIS study demonstrated that an sFlt-1/PlGF ratio cutoff of 38 has a negative predictive value exceeding 99% for ruling out preeclampsia within one week and a positive predictive value of approximately 40% for diagnosing preeclampsia within four weeks [11-13].

However, most previous studies have measured total sFlt-1 levels without distinguishing between isoforms, potentially including contributions from non-placental sources such as the kidney and vascular endothelium. To date, limited data are available describing the specific expression of sFlt-1 e15a in placental tissue and its relationship with maternal serum concentrations. Based on these considerations, the present study aimed to explore the relationship between maternal serum and placental levels of angiogenic factors (sFlt-1 e15a and PlGF) in preterm pregnancies complicated by EOPE. The findings are expected to provide novel evidence regarding the correlation of angiogenic marker expression between serum and placental tissue, serving as a basis for developing standardized diagnostic protocols in hospitals across West Sumatra. Ultimately, such efforts may contribute to reducing iatrogenic preterm birth rates due to preeclampsia and improving neonatal outcomes. Furthermore, this research could establish foundational data for prognostic studies in preeclampsia with or without target organ involvement.

METHODS

Study Design and Setting

This study employed an analytical observational design with a comparative cross-sectional approach. The study was conducted at Dr. Cipto Mangunkusumo Hospital and Universitas Andalas Hospital. The clinical characteristics and biomarker measurements were assessed in pregnant women diagnosed with preeclampsia.

Study Population and Sample

The target population consisted of all pregnant women with preeclampsia who presented for evaluation at the participating centers. The study sample comprised 91 participants, including 45 women with early-onset preeclampsia (EOPE) and 46 women with late-onset preeclampsia (LOPE). Participants were selected using purposive sampling based on predefined inclusion and exclusion criteria. This approach was applied to ensure that the study groups were comparable and met the criteria required for analysis.

Biomarker Assessment

Maternal serum and placental levels of soluble fms-like tyrosine kinase-1 e15a (sFlt-1 e15a) and placental growth factor (PlGF) were measured using enzyme-linked immunosorbent assay (ELISA).

Statistical Analysis

Descriptive analyses were performed to summarize participants' demographic and clinical characteristics. Continuous variables were presented as mean ± standard deviation for normally distributed data or median with interquartile range (IQR) for non-normally distributed data, based on the Shapiro–Wilk test results. Categorical variables were expressed as frequencies and percentages and analyzed using the chi-square test or Fisher's exact test, as appropriate.

Comparative analyses between the EOPE and LOPE groups were conducted using the independent t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. To complement statistical significance testing, effect sizes were calculated. Cohen's d was used for normally distributed variables, while rank-biserial correlation was applied for non-normally distributed variables. Effect sizes were interpreted as small (0.2), moderate (0.5), and large (0.8).

Correlation analysis between maternal serum and placental biomarker levels was performed using Spearman's rank correlation coefficient (ρ), given the non-normal distribution of several variables. The strength of correlation was interpreted as weak ($\rho < 0.3$), moderate ($\rho = 0.3–0.6$), and strong ($\rho > 0.6$).

Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of angiogenic biomarkers in differentiating EOPE from LOPE. The area under the curve (AUC) was calculated with corresponding 95% confidence intervals (CI). Optimal cut-off values were determined using the Youden index (sensitivity + specificity − 1). Sensitivity and specificity were reported for each optimal threshold.

A post hoc power analysis was performed to assess whether the sample size was sufficient to detect meaningful differences between groups at a

significance level of α = 0.05. All statistical analyses were conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). A two-tailed p-value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 91 pregnant women with preeclampsia were included, comprising 45 cases of EOPE and 46 cases of LOPE. Baseline maternal characteristics are presented in Table **1**. Maternal age did not differ significantly between groups (31.02 ± 5.83 vs. 31.83 ± 4.86 years; p = 0.987). In contrast, gestational age at diagnosis was significantly lower in the EOPE group compared to the LOPE group (29.71 ± 1.95 vs. 35.96 ± 1.05 weeks; p < 0.001). Body mass index (BMI) was comparable between the two groups (29.26 ± 3.68 vs. 29.77 ± 4.03 kg/m²; p = 0.536). Mean arterial pressure (MAP) was significantly higher in the EOPE group compared to the LOPE group (126.64 ± 9.50 vs. 106.64 ± 9.05 mmHg; p < 0.001). Overall, maternal age and BMI did not differ significantly between groups, whereas gestational age at diagnosis and MAP did.

Comparison of Serum and Placental Angiogenic Biomarkers between EOPE and LOPE

Maternal serum and placental angiogenic biomarkers differed between the EOPE and LOPE groups. In the serum, sFlt-1 e15a was higher in the EOPE group than in the LOPE group, although the difference did not reach statistical significance (14,984.04 [IQR 12,063.60] pg/mL vs. 10,443.95 [IQR 5,045.95] pg/mL; p = 0.082). In contrast, serum PlGF levels were significantly lower in EOPE than in LOPE (24.97 [IQR 21.06] pg/mL vs. 46.11 [IQR 43.87] pg/mL; p < 0.001), and the serum sFlt-1/PlGF ratio was significantly higher in EOPE (506.70 [IQR 463.47] vs. 235.69 [IQR 226.19]; p < 0.001).

A similar pattern was observed in placental tissue. Placental sFlt-1 e15a levels were significantly lower in EOPE than in LOPE (7,091.56 [IQR 14,987.81] pg/mL vs. 24,280.38 [IQR 21,692.69] pg/mL; p < 0.001). Placental PlGF levels were also significantly reduced in EOPE (31.24 [IQR 36.21] pg/mL vs. 145.15 [IQR 123.48] pg/mL; p < 0.001), whereas the placental sFlt-1/PlGF ratio was significantly higher in EOPE than in LOPE (376.22 [IQR 165.87] vs. 166.74 [IQR 161.02]; p < 0.001).

Correlation between Serum and Placental Angiogenic Biomarkers

Spearman correlation analysis was performed to evaluate the relationship between serum and placental angiogenic biomarkers (Figure **1**). A significant positive correlation was observed between serum and placental sFlt-1 e15a levels (ρ = 0.268, p = 0.010). Similarly, serum PlGF levels showed a moderate positive correlation with placental PlGF levels (ρ = 0.493, p < 0.001).

In addition, a strong positive correlation was identified between the serum and placental sFlt-1/PlGF ratios (ρ = 0.859, p < 0.001). Serum sFlt-1 levels were

Table 1: Maternal Characteristics of Early-Onset and Late-Onset Preeclampsia

Variable	EOPE (n = 45)	LOPE (n = 46)	p-value
Maternal age (years)	32 (6)	31 (5)	0.987*
Gestational age at diagnosis (weeks)	30 (3)	36 (2)	<0.001*
Parity			0.586#
Nulliparous	18 (40%)	21 (45.7%)	
Multiparous	27 (60%)	25 (54.3%)	
Body Mass Index (kg/m²)	29.26 ± 3.68	29.76 ± 4.03	0.536&
History of preeclampsia			<0.01#
No	9 (20%)	29 (63.1%)	
Yes	36 (80%)	17 (36.9%)	
Mean Arterial Pressure (mmHg)	123.33 (10)	108.50 (15.67)	<0.001*

*Mann-Whitney U Test.
#Pearson Chi-Square.
&Independent T-Test.

Table 2: Comparison of Serum and Placental Angiogenic Biomarker Levels according to Preeclampsia Onset

Variable	EOPE (n=45)	LOPE (n=46)	p-value	Effect size (r)
Serum biomarkers				
sFlt-1 e15a (pg/mL)	14,984 (12,063.6)	10,276 (5,045.95)	0.082	0.18
PlGF (pg/mL)	22.97 (21.06)	46.12 (43.87)	<0.001	0.54
sFlt-1/PlGF ratio	506.70 (463.47)	235.69 (226.19)	<0.001	0.47
Placental biomarkers				
sFlt-1 e15a (pg/mL)	7,091.56 (14,987.81)	24,280.38 (21,692.69)	<0.001	0.46
PlGF (pg/mL)	31.24 (36.21)	145.15 (123.48)	<0.001	0.80
sFlt-1/PlGF ratio	376.22 (165.87)	166.74 (161.02)	<0.001	0.49

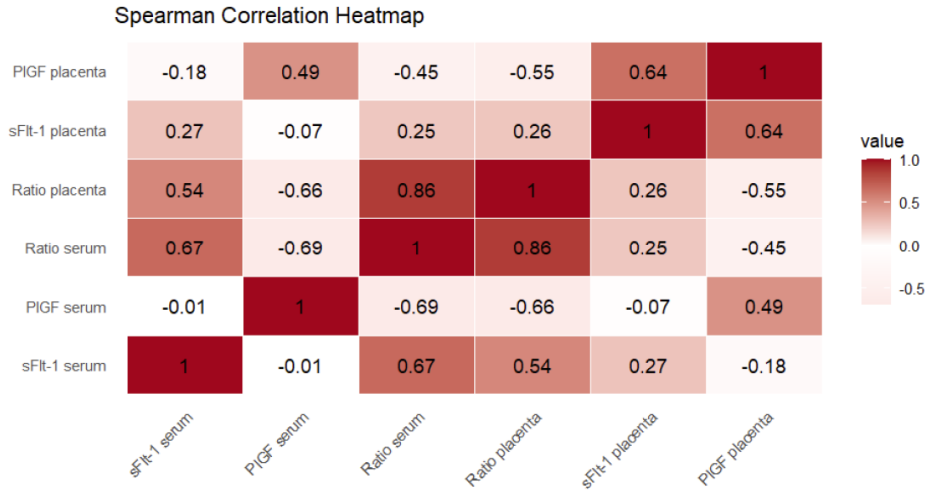

Figure 1: Heatmap of Spearman correlation coefficients among serum and placental angiogenic biomarkers in EOPE and LOPE.

also positively correlated with the placental ratio (ρ = 0.540, p < 0.001), whereas serum PlGF levels demonstrated a significant negative correlation with the placental ratio (ρ = −0.663, p < 0.001). Furthermore, the serum sFlt-1/PlGF ratio was negatively correlated with placental PlGF levels (ρ = −0.451, p < 0.001).

Overall, these findings demonstrate significant associations between circulating and placental angiogenic biomarkers, with both positive and negative correlations observed.

Diagnostic Performance of Angiogenic Biomarkers Based on ROC Analysis

Receiver operating characteristic analysis was conducted to evaluate the discriminative performance of maternal serum and placental angiogenic biomarkers in distinguishing EOPE from LOPE (Figure **2**). Among all evaluated parameters, the placental sFlt-1/PlGF ratio demonstrated the highest discriminative ability, with an AUC of 0.782 (95% CI: 0.684–0.880; p < 0.001), followed closely by the serum sFlt-1/PlGF ratio, which yielded an AUC of 0.772 (95% CI: 0.674–0.870; p < 0.001) (Tables **3** and **4**).

In contrast, individual biomarkers showed limited or inverse discriminative performance. The serum sFlt-1 level demonstrated poor discriminative ability (AUC = 0.606), whereas serum PlGF exhibited poor discriminative ability (AUC = 0.188), indicating that lower values were associated with EOPE. Similarly, placental sFlt-1 showed inverse discriminative performance (AUC = 0.235), and placental PlGF demonstrated marked inverse discrimination (AUC = 0.036).

Optimal cut-off values were determined using the Youden index. The optimal cut-off for the serum sFlt-1/PlGF ratio was 327, corresponding to a sensitivity of 75.6% and a specificity of 73.9%. For the placental sFlt-1/PlGF ratio, the optimal cut-off was 248, yielding a sensitivity of 82.2% and a specificity of 73.9%. Overall, ratio-based biomarkers demonstrated superior

discriminative performance compared with individual angiogenic markers.

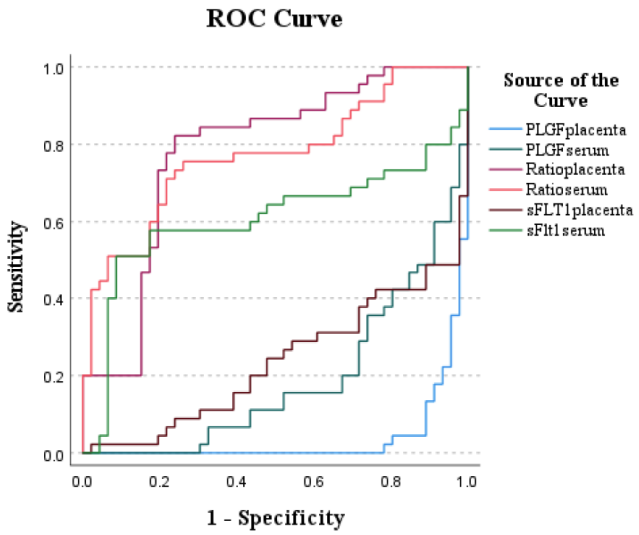

Figure 2: Receiver operating characteristic (ROC) curves of maternal serum and placental angiogenic biomarkers for distinguishing EOPE and LOPE.

Table 3: Area Under the Curve (AUC) of Angiogenic Biomarkers for Differentiating EOPE and LOPE

Biomarker	AUC
sFlt-1 serum	0.606
PlGF serum	0.188
sFlt-1/PlGF ratio (serum)	0.772
sFlt-1/PlGF ratio (placenta)	0.782
sFlt-1 placenta	0.235
PlGF placenta	0.036

DISCUSSION

The present study demonstrates that EOPE is characterized by a more pronounced angiogenic imbalance than LOPE, as reflected by lower serum PlGF, a higher serum sFlt-1/PlGF ratio, and a similarly adverse placental biomarker profile. Although the between-group difference in serum sFlt-1 e15a did not reach statistical significance, the observed trend still suggests a shift toward an antiangiogenic state in EOPE. This pattern is consistent with the established concept that preeclampsia is fundamentally driven by dysregulated placental angiogenesis, in which excess antiangiogenic signaling and reduced proangiogenic support contribute to endothelial dysfunction and impaired placental adaptation [3, 4, 6-8]. The literature also supports the clinical value of the sFlt-1/PlGF ratio as an integrated marker of angiogenic balance and disease severity, rather than relying on a single analyte in isolation.

A particularly relevant finding in this study is the discordance between serum and placental sFlt-1 e15a levels, with lower placental expression in EOPE despite a higher circulating tendency in serum [14]. This finding should not be interpreted as contradictory, because placental-specific sFLT-1 e15a is the dominant placental isoform and has been shown to be increased in both placental tissue and maternal circulation in preeclampsia, where it exerts antiangiogenic activity through VEGF signaling antagonism [9, 10, 15]. In the current analysis, the positive correlation between serum and placental sFlt-1 e15a ($\rho = 0.268$, $p = 0.010$) provides quantitative support for a linked, but not perfectly parallel, tissue-to-circulation relationship. This interpretation is strengthened by the strong positive correlation between the serum and placental sFlt-1/PlGF ratios ($\rho = 0.859$, $p < 0.001$) and the moderate positive correlation between serum and placental PlGF ($\rho = 0.493$, $p < 0.001$). Taken together, these findings are consistent with a compartmental release-distribution model in which the placenta remains the central source of angiogenic disturbance, while circulating and tissue levels reflect distinct yet dynamic biological processes [16].

The ROC findings further reinforce the superiority of ratio-based biomarkers over individual analytes in distinguishing EOPE from LOPE. In this study, both the serum and placental sFlt-1/PlGF ratios demonstrated good discriminative performance, with AUCs of 0.772 and 0.782, respectively, whereas individual biomarkers showed either weak or inverse discrimination. The inverse AUC values for PlGF and placental sFlt-1 indicate that lower values were associated with EOPE, which is biologically consistent with the disease's antiangiogenic phenotype, but these markers were less

Table 4: Diagnostic Performance of sFlt-1/PlGF Ratios in Differentiating EOPE and LOPE

Biomarker	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)
Serum ratio	0.772 (0.674–0.870)	327	75.6	73.9
Placenta ratio	0.782 (0.684–0.880)	248	82.2	73.9

informative than the composite ratio. The optimal cut-off values derived from the current cohort also suggest that the ratios provide clinically meaningful separation between the two disease phenotypes. This is in line with prior evidence that the sFlt-1/PlGF ratio is the most robust angiogenic marker in preeclampsia because it integrates both proangiogenic and antiangiogenic components into a single measurable index, thereby capturing the net biological balance more effectively than either factor alone [11, 15].

Several limitations should be considered when interpreting these findings. First, the cross-sectional design does not permit causal inference or temporal assessment of biomarker changes, and residual confounding by maternal factors such as obesity, parity, prior preeclampsia, and other obstetric characteristics may still be present despite group comparison Second, the sample size was modest, which means that the non-significant serum sFlt-1 e15a trend should be interpreted cautiously and the findings should be regarded as hypothesis-generating rather than definitive. Third, this analysis did not include multivariable regression or odds ratio modeling for clinical outcomes, so the prognostic implications of these biomarkers for complications such as preterm birth, disease severity, or maternal-fetal morbidity remain incomplete. Future studies should therefore use longitudinal designs, formal sample size justification or power analysis, and adjusted regression models to determine whether these biomarkers independently predict adverse outcomes and whether the observed correlations translate into clinically actionable risk stratification. Formal testing of complication rates between groups would also strengthen the clinical interpretation of the biomarker findings and help clarify their value beyond group discrimination.

CONCLUSION

EOPE is associated with a pronounced angiogenic imbalance, characterized by higher maternal serum sFlt-1 e15a, lower PlGF, and corresponding alterations in placental tissue. The sFlt-1/PlGF ratio demonstrated good diagnostic performance and may support early identification of EOPE in clinical practice. These findings suggest that angiogenic biomarkers could contribute to more targeted and individualized management of preeclampsia.

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