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Assessing the Prognostic Value of Serum PLGF, sFlt-1, and sFlt-1/PLGF Ratios in Predicting Adverse Pregnancy Outcomes in Preeclampsia: A Comprehensive Analysis

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Abstract

Objective: This study investigates the correlation between serum levels of placental growth factor (PLGF), soluble FMS-like tyrosine kinase-1 (sFlt-1), and the sFlt-1/PLGF ratio, and adverse pregnancy outcomes in preeclampsia (PE) patients. **Methods:** We analyzed data from 1,383 pregnant women diagnosed with preeclampsia at Xi'an People's Hospital (No. 4 Hospital of Xi'an) from July 2022 to June 2023. The participants were categorized into a PE group of 95 individuals, further divided into 53 with mild preeclampsia (mPE) and 42 with severe preeclampsia (sPE), and a control group of 1,288 individuals. The PE group was also subdivided based on pregnancy outcomes into a poor outcome subgroup (367 cases) and a normal delivery subgroup (1,015 cases). Serum PLGF, sFlt-1, and sFlt-1/PLGF levels were measured and analyzed in relation to pregnancy outcomes. **Results:** The PE group exhibited significantly lower PLGF levels and higher sFlt-1 and sFlt-1/PLGF levels compared to the control group. Within the PE group, the sPE subgroup had significantly lower PLGF and higher sFlt-1/PLGF levels than the mPE subgroup. Patients with adverse outcomes showed significantly higher sFlt-1 and sFlt-1/PLGF levels compared to those with normal delivery outcomes. Spearman correlation analysis indicated a negative correlation between PLGF levels and adverse pregnancy outcomes ($\rho = -0.057$, $P < 0.05$), and a positive correlation of sFlt-1 and sFlt-1/PLGF levels with adverse outcomes ($\rho = 0.075$ and 0.082, respectively; both $P < 0.01$). **Conclusion:** Lower serum PLGF and higher sFlt-1 and sFlt-1/PLGF levels are significantly associated with PE and adverse pregnancy outcomes, underscoring their potential as biomarkers for predicting pregnancy complications in PE patients.

Keywords

Preeclampsia, PLGF, sFlt-1, Pregnancy Outcome

1. Introduction

Preeclampsia (PE) is a hypertensive disorder that manifests after 20 weeks of gestation, characterized by elevated blood pressure and signs of damage to other organ systems, affecting approximately 5-7% of pregnancies globally

[1]. This condition is a leading contributor to intrauterine fetal growth restriction, neonatal malformations, and adverse pregnancy outcomes [2, 3]. Emerging research indicates that dysregulation in angiogenic factors plays a crucial role in the pathogenesis of PE [4-8]. Among these, Placental Growth Factor (PLGF) is pivotal in promoting endothelial cell proliferation, migration, and angiogenesis [9-11]. Conversely, Soluble Fms-Like Tyrosine Kinase-1 (sFlt-1) acts as an antagonist to Vascular Endothelial Growth Factor (VEGF) and PLGF, thereby hindering angiogenesis and contributing to endothelial damage [12], which, in turn, triggers hallmark symptoms of PE such as hypertension and proteinuria [13, 14].

Given this background, our study aimed to explore the correlation between serum levels of PLGF, sFlt-1, and the sFlt-1/PLGF ratio with pregnancy outcomes in PE patients. Herein, we present our findings, shedding light on the potential impact of these angiogenic factors on the disease's progression and outcomes.

2. Materials and methods

2.1 General Information

In this study, 1,383 pregnant women who underwent PE risk assessment at our hospital between July 2022 and June 2023 were selected. The cohort was divided into two groups: the PE group, consisting of 95 individuals (53 with mild preeclampsia (mPE) and 42 with severe preeclampsia (sPE)), and a control group of 1,288 individuals without PE. The demographic data for the control group were as follows: average age was 31.08 years (range: 29.10-33.98), height was 163 cm (range: 159-165 cm), and weight was 60 kg (range: 53-65 kg). For the PE group, the average age was 31.92 years (range: 29.96-34.94), height was 160 cm (range: 158-165 cm), and weight was 60 kg (range: 53-70 kg). The general characteristics of the patients—including age, height, and weight—between the control and PE groups were analyzed using a non-parametric test, revealing no statistically significant differences ($P > 0.01$), thereby confirming comparability between the groups.

2.2 Inclusion and Exclusion Criteria

The study focused on pregnant women undergoing preeclampsia risk assessment, incorporating strict inclusion and exclusion criteria to ensure a homogeneous and relevant sample. To be included, participants needed to meet diagnostic guidelines as per the 9th edition of Obstetrics and Gynecology, have a singleton pregnancy, and possess complete medical records with delivery conducted within our hospital, with all participants providing informed consent. Conversely, the study excluded individuals diagnosed with any organ-related, chronic, or mental health diseases, as well as those lacking comprehensive clinical data. Ethical approval was obtained from the Ethics Committee, underscoring the study's adherence to ethical standards and research integrity.

2.3 Detection methods

The study focused on pregnant women undergoing preeclampsia risk assessment, incorporating strict inclusion and exclusion criteria to ensure a homogeneous and relevant sample. To be included, participants needed to meet diagnostic guidelines as per the 9th edition of Obstetrics and Gynecology, have a singleton pregnancy, and possess complete medical records with delivery conducted within our hospital, with all participants providing informed consent. Conversely, the study excluded individuals diagnosed with any organ-related, chronic, or mental health diseases, as well as those lacking comprehensive clinical data. Ethical approval was obtained from the Ethics Committee, underscoring the study's adherence to ethical standards and research integrity.

3. Statistic analysis

Statistical analysis of the data was conducted using SPSS software, version 26.0. Measurements adhering to a normal distribution were presented as mean ± standard deviation (SD). The t-test was utilized for comparisons between groups with normally distributed data. For measurements that did not follow a normal distribution, data were expressed in quartiles, and the Mann-Whitney U test facilitated pairwise comparisons. The correlation between serum levels of sFlt-1, PLGF, and the sFlt-1/PLGF ratio with the onset severity of preeclampsia and adverse pregnancy outcomes was determined using Spearman's correlation coefficient. A P-value of less than 0.05 was considered statistically significant.

4. Results

4.1 Serum PLGF, sFlt-1, and sFlt-1/PLGF Levels in PE and Control Groups

The analysis revealed significant differences between the PE group and the control group in terms of serum levels of PLGF, sFlt-1, and the sFlt-1/PLGF ratio. Specifically, PLGF levels were significantly lower, whereas sFlt-1 and sFlt-1/PLGF levels were significantly higher in the PE group compared to the control group, with all differences achieving statistical significance ($P < 0.01$). These findings are summarized in Table 1, which presents a detailed comparison of sFlt-1, PLGF, and sFlt-1/PLGF levels between the two groups.

Table 1. The levels of sFlt-1, PLGF, and sFlt-1/PLGF were compared between the two groups

Detection indicators	control subjects (n=1288)	PE group (n=95)	Z-value	P-value
PlGF (pg/ml)	236.2(133.075-403.73)	111.7 (42-209)	-7.64	<0.01*
sFlt-1 (pg/ml)	1354.5 (938.35-1959.5)	1603 (1156-2462)	-3.87	<0.01*
sFlt-1/PlGF_	5.94 (2.97-11.93)	13.96 (6.92-79.99)	-7.38	<0.01*

Notes. *All tests were 2-sided. P<0 .01 was considered significant.

4.2 Comparison of Serum sFlt-1, PLGF, and sFlt-1/PLGF in Patients with Different Degrees of Disease in the PE Group

Upon comparing serum levels of sFlt-1, PLGF, and the sFlt-1/PLGF ratio between the mPE group and the sPE group, significant differences were observed. PLGF levels were notably lower, while the sFlt-1/PLGF ratio was significantly higher in the sPE group compared to the mPE group, with these differences being statistically significant ($P < 0.01$). Detailed comparisons are provided in Table 2, which outlines the distinctions in sFlt-1, PLGF, and sFlt-1/PLGF levels between the mPE and sPE groups.

Table 2. sFlt-1, PLGF, and sFlt-1/PLGF were compared between mPE group and sPE group

Detection indicators	mPE (n=53)	sPE (n=42)	z	p
PlGF (pg/ml)	159.8(60.5-261)	61.93(31.67-160.95)	-3.515	0.000*
sFlt-1 (pg/ml)	1527(1078.5-2378.5)	1645.5(1209-4827.25)	-1.154	0.248
sFlt-1/PlGF_	10.79 (4.15-33.83)	24.98(8.8-168.44)	-2.885	0.004*

Notes. *All tests were 2-sided. P<0 .05 was considered significant.

4.3 Comparison of PLGF, sFlt-1, and sFlt-1/PLGF in Different Pregnancy Outcome Groups

The analysis comparing serum levels of PLGF, sFlt-1, and the sFlt-1/PLGF ratio between the normal delivery group and the group experiencing adverse outcomes—such as fetal growth restriction, intrauterine distress, neonatal asphyxia, and intrauterine fetal death—revealed significant differences. Both sFlt-1 and sFlt-1/PLGF levels were significantly higher in the group with adverse outcomes compared to the normal delivery group ($P < 0.01$). These findings are detailed in Table 3, which showcases the comparison of these biomarkers between the two outcome groups.

Table 3. PLGF, sFlt-1, and sFlt-1/PLGF were compared between the two groups

Detection indicators	Normal delivery group(n=1015)	Adverse outcome group (n=367)	t	p
PlGF (pg/ml)	303.85±7.92	287.69±14.47	1.025	0.306
sFlt-1 (pg/ml)	1558±29.19	1991.35±121.08	-3.479	0.000*
sFlt-1/PlGF_	10.88±0.61	36.36±8.68	-2.928	0.004*

Notes. *All tests were 2-sided. P<0 .05 was considered significant.

4.4 Rison of Serum sFlt-1, PLGF, and sFlt-1/PLGF in Different Pregnancy Outcome Groups of PE Patients

Within the context of PE, our analysis revealed significant differences in biomarker levels between patients with adverse pregnancy outcomes and those who had a normal delivery. Specifically, PLGF levels were significantly lower, while the sFlt-1/PLGF ratio was significantly higher in the group with adverse outcomes, such as fetal growth restriction, neonatal asphyxia, or intrauterine fetal death, compared to the normal delivery group ($P < 0.05$). These critical findings are detailed in Table 4, illustrating the disparities in serum sFlt-1, PLGF, and sFlt-1/PLGF levels between the two outcome groups.

Table 4. Comparison of pregnancy outcomes in PE patients

Detection indicators	Normal delivery group (n=44)	Adverse outcome group (n=51)	z	p
PlGF (pg/ml)	140.85 (52.61-281.17)	72.97 (31.92-188.8)	-2.31	0.021*
sFlt-1 (pg/ml)	1512 (1087.75 - 2179)	1914 (1190-4452)	-1.702	0.089
sFlt-1/PlGF_	11.61 (4.47-25.5)	21.97 (7.92 - 164.92)	-2.358	0.018*

Notes. *All tests were 2-sided. P<0 .05 was considered significant.

4.5 Correlation Analysis of Pregnancy Outcome with PLGF, sFlt-1, and sFlt-1/PLGF

The correlation analysis between pregnancy outcomes and the biomarkers PLGF, sFlt-1, and sFlt-1/PLGF revealed significant relationships. Specifically, PLGF levels were found to be negatively correlated with adverse pregnancy outcomes ($\rho = -0.057$, $P < 0.05$), indicating that lower levels of PLGF are associated with a higher risk of adverse outcomes. Conversely, both sFlt-1 and sFlt-1/PLGF levels showed a positive correlation with adverse outcomes ($\rho = 0.075$ and 0.082, respectively; both $P < 0.01$), suggesting that higher levels of these biomarkers are associated with an increased risk of adverse pregnancy outcomes. These findings are detailed in Table 5, which presents the correlation coefficients and significance levels, illustrating the relationship between these biomarkers and pregnancy outcomes.

Table 5. Correlation of adverse pregnancy outcomes with PLGF, sFlt-1, sFlt-1/PLGF

norm	Pregnancy outcomes	
	ρ	p
PLGF (pg/ml)	-0.057	0.035*
sFlt-1 (pg/ml)	0.075	0.005*
sFlt-1/PLGF	0.082	0.002*

Notes. *All tests were 2-sided. P<0 .05 was considered significant.

5. Discussion

Previous research has consistently shown that PLGF levels in patients with PE are lower compared to those in normal pregnancies, with concentrations decreasing as the severity of PE increases [15]. Studies in animal models have demonstrated that sFlt-1 overexpression mimics PE symptoms such as hypertension and proteinuria, while in vitro removal of circulating sFlt-1 ameliorates these symptoms [16, 17]. A meta-analysis highlighted that alterations in the sFlt-1/PLGF ratio are among the earliest markers detectable in PE, possessing a higher negative predictive value for adverse pregnancy outcomes than either PLGF or sFlt-1 levels alone[18]. Furthermore, excessively low sFlt-1/PLGF ratios have been linked to an increased risk of adverse pregnancy outcomes [19, 20], and high sFlt-1 levels have been associated with a greater likelihood of preterm labor [21].

Our findings align with these observations, indicating significantly lower PLGF levels and higher sFlt-1 and sFlt-1/PLGF ratios in the PE group compared to the control group. Notably, patients with sPE exhibited lower PLGF levels and higher sFlt-1/PLGF ratios than those with mPE. Similarly, the adverse outcome group showed significantly higher levels of sFlt-1 and sFlt-1/PLGF compared to the normal delivery group. In PE cases, a significant negative correlation between PLGF levels and adverse pregnancy outcomes ($\rho = -0.057$, $P < 0.05$) was observed, alongside a positive correlation for sFlt-1 and sFlt-1/PLGF with adverse outcomes ($\rho = 0.075$ and 0.082, respectively, both $P < 0.05$).

In summary, our study underscores the critical role of decreased PLGF and increased sFlt-1 and sFlt-1/PLGF

levels in the pathogenesis of PE and their strong association with adverse pregnancy outcomes. Given that changes in PLGF and sFlt-1 precede the clinical manifestations of preeclampsia and related maternal-infant morbidities and complications, these biomarkers hold significant promise for the prediction, diagnosis, and management of PE.

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