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Association between elevated sFlt-1/PlGF ratio and obstetric outcomes in hospitalized patients with preeclampsia

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Abstract

Preeclampsia is a pregnancy-specific syndrome characterized by hypertension and proteinuria or hypertension and end-organ dysfunction with or without proteinuria after 20 gestational weeks. Maternal and fetal complications are a leading cause of maternal and neonatal death worldwide. Anti-angiogenic factor, soluble fms-like tyrosine kinase 1 (sFlt-1) and the pro-angiogenic factor, placental growth factor (PlGF) are markers of angiogenic disbalance and higher SFLT/PLGF ratio may correlate with adverse pregnancy outcome.To investigate the relationship between angiogenic biomarker levels and obstetric outcome parameters in hospitalized patients diagnosed with preeclampsia. This retrospective observational study was conducted over a two-year period at the University Clinic for Obstetrics and Gynecology. The study included 100 pregnant women diagnosed with preeclampsia who were admitted to the peripartal intensive care unit. All participants underwent testing for the sFlt-1/PlGF ratio using the Elecsys immunoassays. Based on their sFlt-1/PlGF ratio (<200 or ≥200), the women were equally divided into two groups. Maternal and neonatal outcomes were assessed at discharge using data obtained from the patients' obstetric records. No significant association of the group ratio to which the women belong and the vaginal birth (p=0,4489), induction of labor (p=0,6117), caesarean section (p=0,1582), and twins (p=0,7556) was found.Preterm labour and placental abruption were significantly associated with the group with ratio ≥200 for p=0,0001 and p=0,0302 respectively. There was significantly lower birth weight (p=0,00001) and birth length (p=0,00001), AS/ 1 min was significantly lower in the newborns of the mothers from the group with ratio ≥ 200 compared to the one from the group with ratio < 200 (p=0,00001). We found association with some form of unfavourable perinatal outcome in cases of preeclampsia with sFlt-1/PlGF ratio ratio≥ 200.

Keywords: sflt/plgf, Obstetric outcome

Introduction

Preeclampsia is a progressive multisystem disorder characterized by new-onset hypertension (≥140/90 mmHg) after 20 gestational weeks accompanied by either proteinuria (≥300 mg/24 hr) or end-organ dysfunction (elevated liver enzymes, thrombocytopenia, renal insufficiency, cerebral or visual symptoms), with or without proteinuria [1].

About 90% of cases appear during the late preterm period (from 34 to less than 37 weeks), at term, or after delivery, and typically lead to favorable outcomes for the mother, fetus, and newborn. However, there is still a potential for serious complications or even death.

The other 10% of cases occur before 34 weeks of gestation and are linked with a greater likelihood of severe outcomes, primarily due to the risks associated with moderately to extreme prematurity [2]. The clinical manifestations of preeclampsia result from microangiopathy of target organs- brain, liver, kidney and placenta. Fetal and neonatal sequeli include fetal growth restriction, oligohydramnios, induced premature labour and stillbirth.

The only definitive treatment is delivery to prevent maternal or fetal complications from disease progression. Timing of delivery is based on a combination of disease severity, both maternal and fetal condition, gestational age. It is necessary to balance the fetal benefits of expectant management (further growth and maturation) with the maternal and fetal risks of expectant management (progression to preeclampsia and possible sequelae like stillbirth or asphyxia) [3].

The pathophysiology of preeclampsia likely involves abnormalities in the development of placental vasculature in early pregnancy, relative placental underperfusion, progressive release of antiangiogenic factors into the maternal circulation that alter maternal systemic endothelial function and cause hypertension, vasospasm, platelet aggregation. However, the trigger for abnormal placental development and the subsequent cascade of events remains unknown.

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Soluble fms-like tyrosine kinase-1 (sFlt-1) is a circulating antagonist to vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). It is released by the abnormal placenta and is an important mediator of the maternal signs and symptoms of preeclampsia.

The sFlt-1/PlGF ratio in combination with other clinical assessments aids in predicting disease development and adverse outcomes [4].

Aims

Determining whether elevated Sflt/Plgf ratio is associated with adverse neonatal outcomes.

Study Design and Methodology

This retrospective observational study was carried out over a two-year period and included hospitalized patients diagnosed with either moderate or severe forms of preeclampsia. Upon admission, all participants underwent evaluation of the sFlt-1/PlGF ratio using the Elecsys immunoassays for sFlt-1 and PlGF. In certain cases, testing was repeated based on clinical necessity.

Participants were categorized into two equal groups according to their sFlt-1/PlGF ratio values:

Group 1: sFlt-1/PlGF ratio less than 200

Group 2: sFlt-1/PlGF ratio equal to or greater than 200.

Each group comprised 50% of the total study population.

Eligibility criteria

- Women aged between 18 and 45 years
- Confirmed clinical and laboratory findings consistent with preeclampsia.

Exclusive criteria

- Pregnancies complicated by major fetal anomalies
- Presence of amniotic infection syndrome
- Chronic inflammatory diseases

Data collection and outcomes

Information on maternal and neonatal outcomes was collected from obstetric records at the time of hospital discharge. The following outcomes were assessed:

Maternal and obstetric outcomes

- Type of delivery (spontaneous vaginal delivery, elective or emergency cesarean section)
- Labor induction (methods: Foley catheter, prostaglandins, or oxytocin)
- Multiple pregnancies (twins)
- Preterm birth
- Incidence of placental abruption

Neonatal and perinatal outcomes

- Stillbirth occurrence
- Evidence of fetal growth restriction
- Apgar scores at 1 and 5 min
- Neonatal weight and length at birth
- Umbilical cord blood pH value

Statistical analysis

The statistical analysis was conducted using SPSS software, version 22.0 for Windows. Measures of central tendency, including the mean, median, and interquartile range (IQR), along with measures of dispersion such as the standard deviation, were used to analyze ordinal and continuous variables. For categorical variables, the Pearson Chi-square test and Fisher's exact test were applied. Odds ratios (OR) were calculated to assess risks. The Shapiro-Wilk W test was employed to evaluate the normality of the frequency distribution of the studied variables. For analysis of ordinal and continuous variables, the Mann-Whitney U test was utilized for two independent parameters with non-normal distributions, while the Independent t-test was applied for two independent parameters with normal distributions. Statistical significance was determined using a two-sided analysis with a significance level of $p < 0.05$.

Results

The study initially enrolled 100 pregnant women who were hospitalized based on clinical criteria for moderate or severe preeclampsia. Following the application of exclusion criteria, a total of 86 women were included in the final analysis. All participants underwent clinical and laboratory assessments and were monitored until delivery. Based on their sFlt-1/PlGF ratio (< 200 or ≥ 200), the women were equally divided into two groups, with 43 participants

in each.

Mean sFlt-1/PIGF ratio

First group had mean sFlt-1/PIGF ratio 94,29+-53,65, min=2,71, max=192,60.

Second group had mean sFlt-1/PIGF ratio 463,21+-267, min=207,00, max=1219,13.

Labor parameters

1. Mode of delivery in preeclampsia based on sFlt-1/PlGF Ratio (< 200 vs ≥ 200)

Among women with a sFlt-1/PlGF ratio < 200, 8 (21.05%) had a vaginal delivery, compared to 5 (12.20%) in the group with a ratio ≥ 200. Induction of labor using a Foley catheter, oxytocin, or prostaglandins was performed in 7 cases (18.92%) in the < 200 group and in 5 cases (12.20%) in the ≥ 200 group. The majority of women in both groups underwent either elective or urgent caesarean section: 29 (76.32%) in the < 200 group and 38 (90.48%) in the ≥ 200 group.

No statistically significant association was found between sFlt-1/PlGF ratio group and mode of delivery—vaginal birth (p = 0.4489), induction of labor (p = 0.6117), or caesarean section (p = 0.1582) (see Table 1).

Table 1 Selective labour parametars and preeclampsia with sFlt-1/PlGF ratio (< 200 or ≥ 200)

Parameters	sFlt-1/PlGF ratio		p
	< 200 (N=43)	≥ 200 (N=43)	
Vaginal birth			
Yes	8 (21,05%)	5 (12,20%)	p=0,4489
No	30 (78,95%)	36 (87,80%)	
Induction of labor			
Yes	7 (18,92%)	5 (12,20%)	p=0,6117
No	30 (78,95%)	36 (87,80%)	
Caesarean section			
Yes	29 (76,32%)	38 (90,48%)	p=0,1582
No	9 (23,68%)	4 (9,52%)	

2. Preterm labour, twin pregnancies, and placental abruption in preeclampsia according to sflt-1/PlGF ratio (< 200 vs ≥ 200)

Preterm labour (defined as delivery between 22 and 37 weeks of gestation) occurred in 20 cases (52.63%) in the group with a sFlt-1/PlGF ratio < 200, compared to 40 cases (93.02%) in the group with a ratio ≥ 200. This difference was statistically significant (p = 0.0001).

Placental abruption, confirmed by clinical and ultrasound findings, was also significantly more frequent in the group with a ratio ≥ 200—8 cases (18.60%) compared to only 1 case (2.5%) in the < 200 group (p = 0.0302).

Twin pregnancies were observed in 7 women (16.28%) in the ≥ 200 group versus 5 women (11.63%) in the < 200 group. This difference was not statistically significant (p = 0.7556) (see Table 2).

Table 2-selective labour parametars and preeclampsia with sFlt-1/PlGF ratio < 200 or ≥ 200

Parameters	sFlt-1/PlGF ratio		p
	< 200 (N=43)	≥ 200 (N=43)	
Preterm labour			
Yes	20 (52,63%)	40 (93,02%)	p=0,0001*
No	18 (47,37%)	3 (6,98%)	
Twins			
Yes	7 (16,28%)	5 (11,63%)	p=0,7556
No	36 (83,72%)	38 (88,37%)	
Placental abruption			
Yes	1 (2,5%)	8 (18,60%)	p=0,0302*
No	39 (97,50%)	35 (81,40%)	

3. HELLP syndrome and stillbirth in preeclampsia based on sflt-1/PlGF ratio (< 200 vs ≥ 200)

HELLP syndrome and stillbirth were each observed in one case, both occurring in the group with a sFlt-1/PlGF ratio ≥ 200. No cases of HELLP syndrome or stillbirth were recorded in the group with a ratio < 200. Notably, the affected individual had the highest recorded ratio in the cohort (1219.1) (see Table 3).

Table 3- HELLP and stillbirth and preeclampsia with sFlt-1/PlGF ratio < 200 or ≥ 200

Parameters	sFlt-1/PlGF ratio		p
	< 200 (N=43)	≥ 200 (N=43)	
HELLP			
Yes	0 (0%)	1 (2,33%)	-
No	43 (100%)	42 (97,67%)	
stillbirth			
Yes	0 (0%)	1 (2,33%)	-
No	43 (100%)	42 (97,67%)	
*Significant for p<0,05			

4. Fetal/ newborn parameters in preeclampsia with sflt-1/PlGF ratio < 200 or ≥ 200

Fetal growth restriction

Fetal growth restriction (FGR) was observed in 8 cases (18.60%) in the group with a ratio < 200, and in 15 cases (36.59%) in the group with a ratio ≥ 200. However, this difference did not reach statistical significance, indicating no significant association between the incidence of fetal growth restriction and the ratio group (p = 0.1090).

Mean neonatal birth weight

In the group with an sFlt-1/PlGF ratio below 200, the average neonatal birth weight was 2265.27 grams with a standard deviation of 620.12 grams, while the median weight was 2290 grams (interquartile range: 1840–2755 g).

In contrast, neonates in the group with an sFlt-1/PlGF ratio of 200 or higher had a significantly lower mean birth weight of 1338.35 grams (±466.67 g), with a median of 1300 grams and an interquartile range of 1000–1670 g.

Mean neonatal birth length

In the group with an sFlt-1/PlGF ratio below 200, the mean birth length was 45.22 ± 4.26 cm, with a median of 46 cm and an interquartile range (IQR) of 43 to 48 cm. In contrast, the group with an sFlt-1/PlGF ratio of 200 or higher had a significantly lower mean birth length of 37.92 ± 5.11 cm, and a median of 38 cm with an IQR of 34 to 41 cm. Newborns born to mothers in the group with a ratio ≥ 200 had significantly lower birth weight (p = 0.00001) and birth length (p = 0.00001) compared to those born to mothers in the group with a ratio < 200.

AS in 1st minute

In the group with an sFlt-1/PIGF ratio below 200, the mean ± SD Apgar score at 1 minute was 7.40 ± 0.76, with a median (IQR) of 8 (7-8). In contrast, in the group with an sFlt-1/PIGF ratio of 200 or greater, the mean ± SD Apgar score at 1 minute was 5.92 ± 1.78, and the median (IQR) was 6 (5-7).
The Apgar score at 1 minute was significantly lower in newborns from mothers in the higher ratio group (≥ 200) compared to those in the lower ratio group (< 200), with a p-value of 0.00001.

AS in 5th minute

In the group with an sFlt-1/PIGF ratio < 200, the mean ± SD Apgar score at the 5th minute was 8.27 ± 0.90, with a median (IQR) of 9 (8-9). In contrast, in the group with an sFlt-1/PIGF ratio ≥ 200, the mean ± SD Apgar score at the 5th minute was 9.14 ± 14.61, and the median (IQR) was 7 (7-8). The opposite situation was found for the as/ 5 min which was significantly higher in the newborns from the group with ratio< 200 compared with the group with ration ≥ 200 (Table 4).

Umbilical artery mean pH

No significant differences between the groups was registered related to the umbilical artery mean ph of the newborns ±SD, 7,29±0,11 vs 7,28±0,09 (p=0,5901) (Table 4).

Table 4. Fetal/ Newborn parameters in preeclampsia with sFlt-1/PlGF ratio < 200 or ≥ 200

Parameters	Women with preeclampsia		p
	Mean±SD	Median (IQR)	
Birth weight			
sFlt-1/PlGF ratio < 200	2265,27±620,12	2290 (1840-2755)	Z=5,747; p=0,00001*
sFlt-1/PlGF ratio ≥ 200	1338,35±466,67	1300 (1000-1670)	
Birth length			
sFlt-1/PlGF ratio < 200	45,22±4,26	46 (43-48)	Z=5,570; p=0,00001*
sFlt-1/PlGF ratio ≥ 200	37,92±5,11	38 (34-41)	
AS/ 1min			
sFlt-1/PlGF ratio < 200	7,40±0,76	8 (7-8)	Z=-4,465; p=0,00001*
sFlt-1/PlGF ratio ≥ 200	5,92±1,78	6 (5-7)	
AS/5 min			
sFlt-1/PlGF ratio < 200	8,27±0,90	9 (8-9)	Z=-4,121; p=0,00004*
sFlt-1/PlGF ratio ≥ 200	9,14±14,61	7 (7-8)	
ph			
sFlt-1/PlGF ratio < 200	7,29±0,11	7,3 (7,2-7,4)	Z=-0,539; p=0,5901
sFlt-1/PlGF ratio ≥ 200	7,28±0,09	7,3 (7,2-7,3)	
*Significant for p<0,05			

Discussion

Preeclampsia is a condition marked by an imbalance in angiogenic factors. Measuring plasma levels of antiangiogenic markers, such as soluble fms-like tyrosine kinase-1 (sFlt-1), and proangiogenic markers, such as placental growth factor (PlGF), or calculating their ratio, has proven useful in several clinical scenarios. These include predicting short-term progression to preeclampsia with severe features, distinguishing preeclampsia from other hypertensive disorders of pregnancy, and guiding appropriate clinical management.

Verlohren et al. (2022) proposed a clinical framework for implementing the sFlt-1/PlGF ratio, emphasizing its value in risk stratification. A high ratio, particularly in women with suspected preeclampsia, may help identify those who would benefit from closer surveillance or timely intervention [1].

In our previous study, we observed that hospitalized patients with preeclampsia and an sFlt-1/PlGF ratio ≥200 had significantly worse clinical parameters. These included higher levels of proteinuria, abnormal liver function markers, and earlier gestational age at presentation—suggesting that extremely elevated ratios are associated with more severe or rapidly progressing forms of the disease that require intensive monitoring and care [2].

Building on this, our current study was designed to examine whether an sFlt-1/PlGF ratio >200 is also associated with worse perinatal outcomes. To ensure consistency, we included an equal number of patients who were hospitalized and delivered at our institution.

Kumar et al. [3] found that the sFlt-1/PlGF ratio correlates more strongly with adverse maternal and perinatal outcomes than other biochemical markers. In a cohort of 91 women with preeclampsia (mean gestational age: 30.63 ± 2.86 weeks), higher ratios were significantly associated with adverse outcomes—such as preterm birth, NICU admission, respiratory distress syndrome, intraventricular hemorrhage, hypoxic-ischemic encephalopathy, necrotizing enterocolitis, retinopathy of prematurity, and confirmed fetal infection. The mean sFlt-1/PlGF ratio in pregnancies with adverse outcomes was 378.45, compared to 30.63 in those without (P<.001), with an area under the curve of 0.88 (95% CI: 0.80–0.96).

Our findings further support this association: in patients with an sFlt-1/PlGF ratio >200, we found significantly higher rates of preterm delivery, lower neonatal birth weight and length, and reduced Apgar scores at 1 minute (P=0.0001).

Similarly, Leaños-Miranda et al. [4] reported higher rates of preterm delivery, delivery within 14 days, and small-for-gestational-age infants among patients with severe angiogenic imbalance (sFlt-1/PlGF >85) compared to those with mild or no imbalance (P<0.001).

Impaired placentation, abnormal trophoblast invasion, or trophoblast stress can lead to various complications collectively known as “placental syndromes”—including preeclampsia, fetal growth restriction (FGR), and placental abruption. These conditions are thought to share a common pathophysiology driven by angiogenic imbalance.

A recent study by Kaczyńska et al. (2025) found that maternal serum sFlt-1/PlGF ratios were elevated in cases of placental abruption, both in early and late pregnancy [5]. Consistently, in our study, placental abruption (based on ultrasound and clinical findings) was significantly associated with preeclamptic patients who had an sFlt-1/PlGF ratio ≥200 (P=0.0302).

Combinations of angiogenic biomarkers and clinical features have been explored as predictors not only for preeclampsia but also for its subtypes—such as preterm preeclampsia and preeclampsia with severe features—as well as for adverse maternal and fetal outcomes.

The INSPIRE trial [6] provided strong evidence that revealing the sFlt-1/PlGF ratio to clinicians significantly improves the detection and management of preeclampsia. Importantly, this approach optimized care without increasing the burden of hospital admissions.

Using the sFlt-1/PlGF ratio as a triage tool is particularly beneficial in identifying women at high risk for developing severe preeclampsia, especially in preterm gestations. This allows for early intervention and targeted monitoring [7].

A novel diagnostic strategy includes the addition of glycosylated fibronectin (GlyFn) measurement. According to Elbarbary et al. [8], GlyFn testing may offer sensitivity comparable to that of sFlt-1/PlGF in predicting preeclampsia, and thus may support faster and more accurate clinical decision-making.

Conclusion

We observed an association between a sFlt-1/PlGF ratio ≥ 200 and various unfavorable perinatal outcomes in cases of preeclampsia, including preterm delivery, placental abruption, lower birth weight and length, as well as reduced Apgar scores in the first minute.

The use of the sFlt-1/PlGF ratio in assessing and managing preeclampsia offers valuable insight into the severity of the condition and helps determine the appropriate timing for delivery. This biomarker significantly enhances clinical accuracy, enables more effective risk stratification, and supports the development of predictive models and clinical guidelines aimed at identifying adverse outcomes.

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