CASE STUDY

# PREGNANCY OUTCOMES IN WOMEN WITH EXTREMELY HIGH SFLT-1/PIGF RATIO: CASE SERIES

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**Viktor Oshovskyy[1], Svitlana Arbuzova[2], Marharyta Nikolenko[3], Kostyantyn Mylytsya[4]**
[1]UNIKLINIKA MEDICAL CENTRE, KYIV, UKRAINE
[2]CENTER OF MEDICAL GENETICS AND PRENATAL DIAGNOSIS, KYIV, UKRAINE
[3]MEDICO-BIOLOGICAL CENTER "GENOM", KYIV, UKRAINE
[4]MULTIDISCIPLINARY CLINIC OF THE ST. NICHOLAS, ZAPORIZHZHIA, UKRAINE

## ABSTRACT

Preeclampsia (PE) is a multisystem disorder, usually defined as the development of hypertension and proteinuria after 20 weeks of pregnancy. The sFlt-1/PlGF ratio has been widely studied as a diagnostic and prognostic marker of preeclampsia and other manifestations of placental dysfunction. A sFlt-1/PlGF ratio greater than 85 for early PE, <34 weeks of gestation suggests a high risk of PE requiring close clinical monitoring. Our main aim was to evaluate the maternal and perinatal outcomes of pregnancies with an extremely high sFlt-1/PlGF ratio.

The analysis included data on placental growth factor and soluble fms-like tyrosine kinase serum levels, measured during 2017–2020 in 128 pregnant women. Here we present 8 cases of women with a numerical ratio greater than 850.

In all 100% of cases, the signs of obstetric angiogenic catastrophe requiring imminent delivery developed soon.

We observed a trend for worsening perinatal outcomes in women with an extremely high sFlt-1/PlGF of ≥850.

**KEY WORDS:** placental dysfunction, preeclampsia, sFlt/PlGF ratio

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## INTRODUCTION

Pregnancy becomes a life-threatening condition for 10 million women annually. The most common complication is preeclampsia, which complicates 5 to 10% of pregnancies in the United States and up to 18% in some regions of Africa [1].

Preeclampsia is the leading cause of death for young women, particularly those living in resource-limited settings, and it leads to approx. 76,000 maternal deaths and 500,000 infant deaths worldwide each year [1].

Preeclampsia (PE) is a multisystem disorder, usually defined as the development of hypertension and proteinuria after 20 weeks of pregnancy [2]. Recent PE pathophysiology studies open up interesting prospects for screening for this disease.

As a sign of placental dysfunction, preeclampsia is associated with dysregulation of pro- and antiangiogenic factors[3]. Although the etiology of PE has not been fully understood, it is believed to occur due to impaired placentation in early pregnancy. Defective trophoblast invasion and abnormal remodeling of spiral arteries result in the placental hypoperfusion and, as a consequence, leads to oxidative stress[4]. Therefore, placenta releases a large number of antiangiogenic factors into the maternal circulation [5–7]During normal pregnancy, concentrations of antiangiogenic factor sFlt-1 (soluble fms-like tyrosine kinase-1) remains low, allowing accurate transmission of signals induced by proangiogenic factors such as VEGF (vascular endothelial growth factor) and PlGF (placental growth factor). This balance is crucial to maintain physiological vasodilation [8]. Secondary to hypoperfusion, placenta increases the synthesis of sFlt-1, trying to raise maternal blood pressure and increase placental perfusion. Consequently, levels of circulating proangiogenic factors are reduced and vascular homeostasis is altered, causing endothelial dysfunction, which leads to hypertension, proteinuria and other multiorgan manifestations of PE in mother [9].

Measurements of blood pressure and proteinuria are considered the gold standard for the diagnosis of preeclampsia, although they do not predict the adverse perinatal outcomes with adequate accuracy[10]. Clinically, hypertension and proteinuria do not always reflect the severity of the disease.

The sFlt-1/PlGF ratio has been widely studied since 2004 as a diagnostic and prognostic marker of preeclampsia and other manifestations of placental dysfunction [11]. To date, a large prospective clinical trial PROGNOSIS has clearly demonstrated that the sFlt-1/PlGF ratio ≤38 may be used to rule out PE within one week, independently of gestational age [12]. A sFlt-1/PlGF ratio greater than 85 (for early PE, <34 weeks of gestation) or 110 (for late PE, ≥ 34 weeks) suggests a high risk of PE requiring close clinical monitoring [13].

**Table I.** Baseline clinical characteristics of patients

| | Maternal age | Gestational age at enrolment | Preeclampsia | IUGR | sFlt-1/PlGF ratio | Time to delivery (days) | Indication for delivery | Adverse perinatal outcomes |
|---|---|---|---|---|---|---|---|---|
| 1 | 30 | 24 | Yes BP 160/100 | Yes | 1631 | 21 | Placenta abruption | Early neonatal mortality |
| 2 | 34 | 21 | No | Yes | 885 | 2 | Severe PE | Intrauterine demise |
| 3 | 24 | 29 | Yes BP 170/110 | No | 2048 | 1 | Eclampsia | No |
| 4 | 29 | 34 | Yes BP 140/100 | No | 1152 | 14 | Eclampsia | No |
| 5 | 34 | 32 | Yes BP 170/100 | No | 2312 | 1 | Placenta abruption | No |
| 6 | 26 | 21 | No | Yes | 2888 | 2 | Severe PE | Early neonatal mortality |
| 7 | 23 | 23 | No | Yes | 1992 | 7 | Severe PE | Early neonatal mortality |
| 8 | 27 | 26 | No | Yes | 1069 | 34 | Severe PE | Intrauterine demise |

Thus, estimated sFlt-1/PlGF ratio can be of great added value when used as an add-on to routine assessment methods. Accurate prediction of PE is important, since severe symptoms may worsen both maternal and fetal status.

The main objective of the expectant management of PE is to improve perinatal outcomes owing to delayed delivery, thereby reducing neonatal morbidity and mortality. In 2012, Verlohren et al. [14] reported that a sFlt-1/PlGF ratio above 655 identified women at high risk of imminent preterm delivery before 34 weeks of gestation, who therefore required close monitoring and medical care.

However, in a study by Stolz et al.,[2] a sFlt-1/PlGF ratio above 655 did not predict worsening of perinatal outcomes and was not reliable enough to predict results in cases with clinical signs of PE. Nevertheless, the data obtained suggest that an extremely high sFlt-1/PlGF ratio greater than 850 may be more helpful. Our main aim was to evaluate the maternal and perinatal outcomes of pregnancies with an extremely high sFlt-1/PlGF ratio.

## CASE REPORT

Detailed clinical profiles of patients are presented in Table I. The mean age of pregnant women was 28.4 ± 4 years. The mean gestational age was 26 ± 5 weeks throughout the study. The majority of pregnant women had signs of intrauterine growth restriction (IUGR) (62.5%) and/or preeclampsia (50%) throughout the study.

The mean sFlt-1/PIGF ratio was 1,747 pg/ml.

In all 100% of cases, the signs of obstetric angiogenic catastrophe requiring imminent delivery developed soon. The mean time to delivery was 10 days. In 50% of pregnant women, urgent delivery was required within 48 hours after analysis. Favorable neonatal outcomes were reported in 37.5% of women.

The analysis included data on placental growth factor (PlGF) and soluble fms-like tyrosine kinase (sfLT-1) serum levels, measured during 2017–2020 in 128 pregnant women at 18–39 weeks of gestation at the medical centers Genome and Uniclinic, Kyiv, Ukraine. The analysis was performed using the analytical method TRACE (Time Resolved Amplified Cryptate Emission) and test systems Thermo Fisher Scientific by BRAHMS Kryptor (Germany). The study was performed on an automatic BRAHMS Kryptor Compact Plus analyzer in full accordance with the manuals for the test kits. The variations in the concentrations of the studied analytes in the examined sample were 8 to 7,100 pg/ml (PlGF), 70 to 68,000 pg/ml (sfLT-1). These results were used to estimate the sFlt-1/PlGF ratio. Patients with a numerical ratio greater than 850 (exposure factor selected based on the literature) were included in the group for further research. Here we present 8 cases with an extremely high sFlt-1/PIGF ratio. All patients gave consent for the use of their data in a blinded manner.

Biochemical and biophysical parameters, routinely used to diagnose PE and determine its severity, such as proteinuria, blood pressure, transaminases, platelets, and serum creatinine, are of limited value in predicting adverse maternal and perinatal outcomes [9]. Finding parameters to stratify patients based on the severity of preeclampsia is a global problem. Except for those patients who are admitted to hospital with clinical signs of severe preeclampsia and/or imminent eclampsia (headache, abdominal pain, uncontrolled blood pressure), it is very difficult to assess the severity of the disease at the first examination [4].

The sFlt-1/PlGF ratio allows clinicians to predict the onset of PE not only in high risk but also in moderate risk patients and to stratify its level, in particular, by confirming or refuting threatening angiogenic profile[8].

In their study, Verlohren et al. reported that the sFlt-1/PlGF ratio was a reliable tool for identifying women at high risk of imminent iatrogenic delivery, demonstrating that the time to delivery was significantly shorter in women with a ratio above 655 [10].

However, recently Stolz et al. compared perinatal outcomes in a group of 30 patients with preeclampsia and sFlt-1/PlGF ratio >655 and 30 patients with preeclampsia and sFlt-1/PlGF ratio <655[2]. No significant differences in perinatal outcomes have been observed between the groups in this small study.

Currently, very little is known about the significance of exceeding the cut-off of 655 during pregnancy complicated by PE. Even less is known about pregnancies without preeclampsia, but with an extremely high sFlt-1/PIGF ratio. When placental dysfunction occurs in early pregnancy, expectative strategy or preventive intake of acetylsalicylic acid are routinely used, but the course of the disease is often difficult to predict.

In our case series, perinatal outcomes in women with signs of placental dysfunction and an extremely high sFlt-1/PlGF ratio have been analyzed. We sought to further demonstrate that the sFlt-1/PlGF ratio may be used to predict perinatal outcomes. This would determine the cut-off for iatrogenically induced delivery or justify expectative clinical strategy in relevant cases.

In our case series, 100% of women with an extremely high sFlt-1/PlGF ratio developed signs of obstetric catastrophe and required imminent delivery. We suggest that the extremely high sFlt-1/PlGF ratio (over 850 in our study) should be considered as a criterion for inpatient monitoring of mother and fetus to prevent obstetric catastrophes.

## CONCLUSIONS

The sFlt-1/PlGF ratio ≥655 does not appear to be a reliable cut-off for predicting adverse perinatal outcomes in women with clinical signs of preeclampsia and therefore has limited value for stratification of risk groups. However, we observed a trend for worsening perinatal outcomes in women with an extremely high sFlt-1/PlGF ≥850.

Our results also confirm that when an extremely high sFlt-1/PIGF ratio is detected, the pregnant woman should be closely monitored and the need for corticosteroids to accelerate fetal lung maturation should be considered.

Further studies are needed to confirm the prognostic role of sFlt-1/PlGF ratio, to determine the cut-off value, and to improve the clinical evaluation of patients with extremely high sFlt-1/PlGF ratios.

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**ORCID and contributionship:**

*Viktor Oshovskyy: 0000-0001-8334-3022* [A,B,D-F]
*Svitlana Arbuzova: 0000-0002-5846-1067* [B,F]
*Marharyta Nikolenko: 0000-0002-0231-7496* [B,F]
*Kostyantyn Mylytsya: 0000-0001-8187-8111* [B-F]


**Conflict of interest:**

*The Authors declare no conflict of interest.*


## CORRESPONDING AUTHOR

**Kostyantyn Mylytsya**
Multidisciplinary Clinic Of The St. Nicholas
53 St. Nicholas st., 69000 Zaporizhzhia, Ukraine
tel: +380502818399
e-mail: jenyapolyakova@gmail.com



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