Placental Angiogenic Markers In Pregnancies Complicated By Intrauterine Growth Restriction And Small For Gestational Age Fetuses

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***Abstract*— Introduction: Fetal growth restriction (FGR) is a condition of inadequate fetal growth and represents one of the leading causes of perinatal morbidity and mortality. Small fetuses are those whose ultrasound-estimated weight is below the 10th percentile. Some of these fetuses are constitutionally small, while others experience intrauterine growth restriction, failing to reach their genetic growth potential. Accurate diagnosis and monitoring of pregnancies with intrauterine growth restriction pose a challenge, requiring multiple ultrasound and Doppler assessments, which burden the healthcare system and cause anxiety and stress for patients. Angiogenic markers (sFlt-1/PlGF) in fetuses with intrauterine growth restriction are promising parameters that can significantly contribute to differentiating them from small-for-gestational-age fetuses, thereby improving the selection of fetuses at higher risk for adverse neonatal outcomes.**

Materials and Methods: This study is a pilot project for conducting a prospective, observational, cohort study involving pregnant patients with ultrasound-estimated fetal weight below the 10th percentile. The study included 20 patients with a gestational age beyond the 24th gestational week. The patients were divided into two groups: 10 patients with fetuses diagnosed with intrauterine growth restriction and 10 patients with small-for-gestational-age fetuses. The levels of angiogenic markers were analyzed in fetuses with intrauterine growth restriction and small-for-gestational-age fetuses.

Results: The analysis showed a significantly higher sFlt-1/PlGF ratio in patients with fetuses affected by intrauterine growth restriction.

Keywords*— *Intrauterine growth restriction, small for gestational age, angiogenic markers, PlGF, sFlt-1.

I. INTRODUCTION

Fetal growth restriction (FGR) is a condition characterized by inadequate fetal growth. It represents one of the leading causes of perinatal morbidity and mortality. [1,2,3,4,5] Fetal growth restriction is one of the main factors leading to intrauterine fetal death in highly and moderately developed countries and is associated with one-third of neonatal deaths in low-income countries. [6,7,8]

Small fetuses are those with an ultrasound-estimated fetal weight below the 10th percentile on the growth curve. Small for gestational age (SGA) refers to fetuses with an estimated fetal weight below the 10th percentile who show no Doppler abnormalities and are considered constitutionally small. Intrauterine growth restriction (IUGR) occurs when the fetus fails to reach its genetic growth potential and is accompanied by Doppler changes in the placental and maternal circulation.[9,10]

Despite advances in understanding the pathogenesis of IUGR, its diagnosis and proper management remain significant challenges in modern obstetric practice. Ultrasound assessment of fetal weight and Doppler evaluation of maternal and fetal circulation are standard methods for diagnosing and monitoring pregnancies with fetal growth restriction. However, universal third-trimester ultrasound screening has proven to be a weak predictor of perinatal morbidity and mortality. [11] As a result, ineffective antenatal diagnosis of IUGR is associated with a significantly increased risk of stillbirth, adverse perinatal outcomes, and a higher incidence of complications later in life. [3,4,5]

Placental insufficiency is one of the primary causes of intrauterine growth restriction. It results from inadequate trophoblastic invasion and abnormal remodeling of the spiral arteries—a pathophysiological process that underlies poor placental perfusion and placental insufficiency. [12,13] Chronic ischemia of the placental villi leads to decreased secretion of placental growth factor (PLGF) and increased secretion of sFlt-1, resulting in an elevated sFlt-1/PLGF ratio. The serum levels of these markers in the mother and their ratio correlate with the severity of placental insufficiency. [14]

Accurate diagnosis and monitoring of pregnancies with fetal growth restriction present a challenge, requiring multiple ultrasound and Doppler assessments. This places a burden on the healthcare system and causes anxiety and stress in patients. [15,16] Management of IUGR and SGA varies significantly across countries, as there is no clear consensus on the appropriate frequency of ultrasound growth assessments and Doppler evaluations. [15,16,17,18] The development of different percentile growth curves has introduced further uncertainty about

which curve best identifies small fetuses at high risk for adverse neonatal outcomes. [19,20,21]. The choice of diagnostic criteria significantly affects the identification of IUGR and its associated outcomes. [22] Hence, there is a need for additional diagnostic methods that can facilitate and complement the diagnostic approach for fetuses with growth restriction and significantly improve ongoing monitoring. Determining the values of angiogenic markers PLGF and sFlt-1 in maternal blood can significantly contribute to the early diagnosis and monitoring of pregnancies with fetuses affected by IUGR.

II. Objectives

To determine the serum levels of the angiogenic markers PLGF, sFlt-1, and their ratio (sFlt-1/PLGF) in pregnant women with fetuses affected by intrauterine growth restriction (IUGR) and in those with small for gestational age (SGA) fetuses.

III. Materials and Methods

This study is a pilot project for the development of a prospective, observational, cohort study involving pregnant women carrying fetuses with ultrasound-estimated fetal weight below the 10th percentile. The study was conducted at the University Clinic for Gynecology and Obstetrics (UCGO) in Skopje. A total of 20 participants were included and evaluated at the same clinic.

The participants were divided into two groups. The first group consisted of 10 patients with fetuses affected by intrauterine growth restriction (IUGR). The second group consisted of 10 patients with small for gestational age (SGA) fetuses.

Small for gestational age (SGA) was defined as fetuses with an ultrasound-estimated fetal weight between the 3rd and 10th percentile and no maternal or fetal Doppler abnormalities.

Intrauterine growth restriction (IUGR) was defined according to the Delphi consensus criteria for early and late onset growth restriction [23]:

- **Early-onset growth restriction** is defined as growth restriction occurring before 32 weeks of gestation, with an ultrasound-estimated fetal weight or abdominal circumference below the 3rd percentile, or a weight or abdominal circumference between the 3rd and 10th percentile accompanied by at least one of the following:
    - Umbilical artery pulsatility index above the 95th percentile, or
    - Uterine artery pulsatility index above the 95th percentile.
- **Late-onset growth restriction** is defined as growth restriction occurring after 32 weeks of gestation, with an ultrasound-estimated fetal weight or abdominal circumference below the 3rd percentile, or the presence of two out of the following three parameters:

1. Fetal weight or abdominal circumference between the 3rd and 10th percentile,
2. Drop of more than 50 percentiles in fetal weight or abdominal circumference on the growth chart,
3. Cerebroplacental ratio (CPR) < 5th percentile or uterine artery pulsatility index > 95th percentile.

Participants in the study met specific inclusion and exclusion criteria. **Inclusion criteria** included: patients over 18 years of age, pregnancies with an ultrasound-estimated fetal weight below the 10th percentile, gestational age of at least 24+0 weeks, patients available for follow-up during all phases of the study, and patients who provided written informed consent. **Exclusion criteria** included: patients with preeclampsia diagnosed before enrollment, pregnancies with prenatally or postnatally confirmed structural fetal anomalies, multiple pregnancies, patients with previously confirmed chromosomal or genetic abnormalities in the fetus, and patients in active labor.

Patient data were collected using a standard questionnaire, which included a medical history form with demographic data (age, body weight, height), obstetric history (number and outcomes of previous pregnancies, medical history of preeclampsia/eclampsia/HELLP or IUGR in a previous pregnancy), and pregnancy-related data (last menstrual period, gestational age, number of fetuses).

Gestational age was determined based on the crown-rump length (CRL) from 8+0 to 13+6 weeks of gestation [24]. If first-trimester ultrasound data were unavailable and there was a discrepancy of more than 10 days between menstrual age and fetal size, gestational age was determined based on head circumference (HC) between 14+0 and 21+6 weeks of gestation [24].

All patients underwent an ultrasound assessment for estimated fetal weight and Doppler parameters of the maternal and fetoplacental circulation. Ultrasound measurements were performed using transabdominal probes (4–6 MHz) on Voluson E8, Voluson E10, and Voluson E6 Ultrasound Systems (GE HealthCare), which support identical software platforms.

Standard fetal biometry included measurements of the biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). Measurements were performed in accordance with the recommendations of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) [25].

Estimated fetal weight (EFW) was calculated using the Hadlock formula [26] and evaluated against the Hadlock growth percentile chart [27].

The Doppler indices analyzed in the maternal and fetal circulation were: pulsatility index of the umbilical artery (UA PI), pulsatility index of the middle cerebral artery (MCA PI), and the cerebroplacental ratio (PI MCA/PI UA). Measurements were conducted

according to ISUOG guidelines for the use of Doppler velocimetry in obstetrics [28].

Oligohydramnios was defined as a maximum vertical pocket of less than 2 cm or an amniotic fluid index (AFI) of less than 5 cm.

Maternal blood samples were analyzed in the Biochemistry Laboratory at the Clinic for Gynecology and Obstetrics. Concentrations of sFlt-1, PLGF, and their ratio were determined using a fully automated ECLIA (electrochemiluminescence immunoassay) analyzer (Cobas e 411), employing immunoassay methodology and highly specific monoclonal antibodies for PLGF and sFlt-1. Quantitative determination of placental growth factor (PLGF) concentration in serum was performed using a sandwich immunoassay principle.

All patients with fetuses with IUGR and patients with angiogenic marker values predictive of preeclampsia [29] were examined and monitored for the development of the condition. Monitoring included measurement of systolic and diastolic blood pressure, analysis of AST, ALT, LDH, serum creatinine, platelet count, and proteinuria. Preeclampsia was defined as hypertension with blood pressure ≥ 140/90 mmHg measured on two occasions at least 4 hours apart, accompanied by significant proteinuria ≥ 300 mg/24h, renal insufficiency with serum creatinine > 97 µmol/L in the absence of preexisting renal disease, hepatic dysfunction with transaminase levels more than twice the upper limit (≥ 65 IU/L), thrombocytopenia (platelets < 100,000/µL), headache or visual symptoms, or pulmonary edema.

Indications for the timing and method of delivery were based on clinical guidelines for monitoring and delivering fetuses with growth restriction (abnormal Doppler parameters, cardiotocographic recordings showing signs of fetal distress, a positive stress test, a biophysical profile score < 4, or oligohydramnios).

The neonatal outcomes monitored included neonatal birth weight, Apgar score at 1 and 5 minutes, and neonatal mortality.

This pilot study will further develop by increasing the number of participants and correlating angiogenic marker values with neonatal outcomes.

IV Statistical Analysis

The statistical analysis of the data obtained from the study was performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois), version 25.0. The Shapiro-Wilk test was used to assess the normality of data distribution.

Qualitative variables are presented as absolute and relative frequencies. Quantitative variables are expressed as mean, minimum and maximum values, standard deviation, median, and interquartile range.

For comparison between the IUGR and SGA groups regarding qualitative data, Fisher's exact test was used. Quantitative variables were compared using the Student's t-test or Mann-Whitney U test, depending on the data distribution. Statistical significance was defined at $p < 0.05$.

V Results

A total of 20 pregnant women were analyzed, 10 with fetuses affected by intrauterine growth restriction (IUGR) and 10 with small for gestational age (SGA) fetuses. The mean age of women in the IUGR group was 33.4 ± 9.9 years, and in the SGA group 29.2 ± 5.8 years, with no statistically significant difference between the groups ($p = 0.265$).

There were no significant differences between the groups regarding maternal height (164.3 ± 5.8 cm vs. 160.0 ± 6.2 cm, $p = 0.126$) or weight (78.4 ± 14.6 kg vs. 73.6 ± 19.7 kg, $p = 0.54$). The average BMI was similar in both groups (23.78 ± 4.2 kg/m² in the IUGR group and 23.0 ± 5.8 kg/m² in the SGA group, $p = 0.735$).

At the time of the study, the mean gestational age was slightly lower in the IUGR group compared to the SGA group (31.2 ± 4.4 weeks vs. 34.5 ± 2.5 weeks), with this difference approaching statistical significance ($p = 0.056$).

Regarding obstetric history, half of the women in the IUGR group were nulliparous, and 40% had one previous delivery; in the SGA group, 60% had one previous delivery, and 30% were nulliparous.

Table 1. Maternal Baseline Characteristics

Baseline maternal characteristics of the study population			p-level
	IUGR	**SGA**	
Maternal age (mean ± SD)	33.4 ± 9.9	29.2 ± 5.8	t=1.15 p=0.265
Hight/см (mean ± SD)	164.30 ± 5.8	160.0 ± 6.2	t=1.6 p=0.126
Weight/кг (mean ± SD)	78.40 ± 14.6	73.60 ± 19.7	t=0.62 p=0.54
BMI (кг/м^2) (mean ± SD)	23.78 ± 4.2	23.0 ± 5.8	t=0.34 p=0.735
Gestational age et US (mean ± SD)	31.2 ± 4.4	34.5 ± 2.5	t=2.05 p=0.056
паритет n(%)			Fisher's exact test
0	5 (50)	3 (30)	p=0.37
1	4 (40)	6 (60)	
2	0	1 (10)	
3	1 (10)	0	

The placental growth factor (PLGF) was significantly lower in the group with intrauterine growth restriction (IUGR) fetuses (p = 0.00018). The mean and median PLGF levels in the IUGR group were 56.70 ± 24.8 pg/mL and 54.5 pg/mL, respectively. In the SGA group, the mean and median PLGF levels were 317.20 ± 267.1 pg/mL and 223 pg/mL, respectively.

The mean sFlt-1 values were 12,666.50 ± 9,454.4 pg/mL in the IUGR group and 5,003.70 ± 1,854.0 pg/mL in the SGA group. The median values were 9,121.5 pg/mL in the IUGR group and 4,522 pg/mL in the SGA group. The difference in sFlt-1 levels between the two groups was statistically significant (p = 0.0375), with significantly higher values in pregnant women with IUGR fetuses.

A significantly higher sFlt-1/PLGF ratio was also confirmed in the IUGR group (p = 0.00018). The median sFlt-1/PLGF ratio was 247.5 in the IUGR group compared to 22.8 in the SGA group. The mean values were 273.99 ± 217.2 for the IUGR group and 20.45 ± 10.9 for the SGA group.

The Doppler indices differed between the two groups. The mean pulsatility index (PI) of the umbilical artery was significantly higher in the IUGR group (1.45 ± 0.52) compared to the SGA group (1.07 ± 0.15), with a statistically significant difference of 0.38 (p = 0.039).The mean PI of the middle cerebral artery was significantly lower in the IUGR group (1.44 ± 0.32) than in the SGA group (1.79 ± 0.14), with a difference of 0.35 (p = 0.0064).

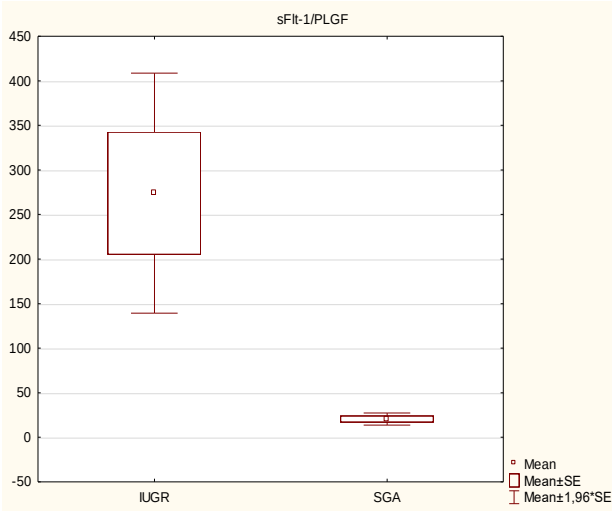


Table 2. PlacentaAngiogenic Markers

variable	Statistical parameters	IUGR	SGA	p-level
PLGF (pg/ml)	mean ± SD	56.70 ± 24.8	317.20 ± 267.1	Z=3.74 ***p=0.00018
	median (IQR)	54.5 (34 – 77)	223 (213 – 306)	
sFlt-1 (pg/ml)	mean ± SD	12666.50 ± 9454.4	5003.70 ± 1854.0	Z=2.08 *p=0.0375
	median (IQR)	9121.5(5976 – 17209)	4522(4314 – 6325)	
sFlt-1/PLGF	mean ± SD	273.99 ± 217.2	20.45 ± 10.9	Z=3.74 ***p=0.00018
	median (IQR)	247.5 (89 – 397)	22.8 (12.5 – 29.4)	

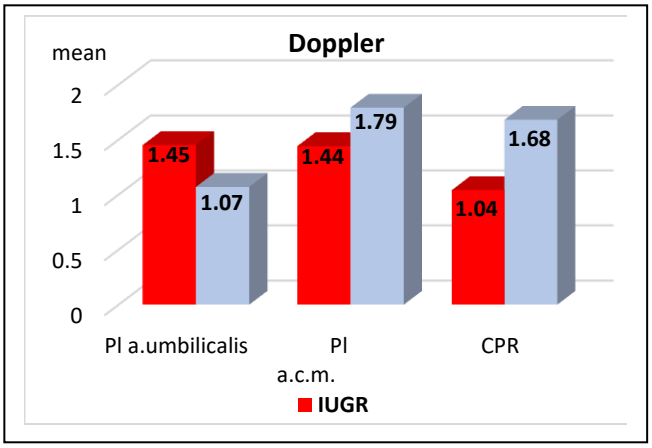
Z(Mann-Whitney U test)*sig p<0.05, ***sig p<0.0001

There was also a statistically significant difference in the cerebroplacental ratio (CPR), which was markedly lower in the IUGR group (1.04 ± 0.31) compared to the SGA group (1.68 ± 0.13), with a difference of 0.64 (p = 0.00001).

Table 3. Doppler Parameters

Variable	IUGR Group	SGA Group	p-level
PI a. umbilicalis	1. 45 ± 0.52	1.07 ± 0.15	t = 2.23, *p = 0.039
PI a. cerebri media	1.44 ± 0.32	1.79 ± 0.14	t = 3.08, **p = 0.0064
CPR	1.04 ± 0.31	1.68 ± 0.13	t = 6.08, ***p = 0.00001

*Student's t-test: *p < 0.05, **p < 0.01, ***p < 0.0001



6. DISCUSSION

This study demonstrated a statistically significant difference in the maternal serum sFlt-1/PLGF ratio, which was markedly elevated in patients with fetuses affected by intrauterine growth restriction compared to those with small for gestational age fetuses.The results suggest that an increased sFlt-1/PLGF ratio may assist in distinguishing between fetuses with IUGR due to chronic placental insufficiency and constitutionally small but otherwise healthy SGA fetuses with weights below the 10th percentile. These findings support more accurate antenatal diagnosis of IUGR and provide a foundation for improved prenatal monitoring and management.

The findings of our pilot study indicate a significant difference in serum levels of angiogenic markers—placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and their ratio (sFlt-1/PlGF)—between pregnancies complicated by intrauterine growth restriction (IUGR) and those classified as small for gestational age (SGA). Specifically, the IUGR group exhibited markedly lower PlGF levels, higher sFlt-1 concentrations, and a significantly elevated sFlt-1/PlGF ratio compared to the SGA group. These results underscore the potential utility of angiogenic markers in distinguishing between constitutionally small fetuses and those affected by placental insufficiency.

Our findings are consistent with previous studies demonstrating that low maternal PlGF levels are strongly associated with fetal growth restriction (IUGR) and placental dysfunction. For instance, a large prospective cohort study [30] found that PlGF concentrations below the 5th percentile for gestational age identified IUGR with a sensitivity of 98.2% and a positive predictive value (PPV) of 58.5%. In that study, low PlGF levels were more effective than fetal biometric measurements or Doppler indices in predicting IUGR due to placental insufficiency, suggesting that angiogenic markers provide a more direct reflection of underlying placental pathology.

The sFlt-1/PlGF ratio, a composite marker reflecting the balance between pro- and antiangiogenic signals, has been widely studied and is consistently reported to be elevated in IUGR [31–33]. Our data corroborate this association, showing significantly higher ratios in the IUGR group, particularly in early-onset cases. This is in line with evidence suggesting that early-onset IUGR is characterized by more severe placental dysfunction, as reflected by higher sFlt-1/PlGF ratios, compared to late-onset IUGR [33].

Several previous studies have investigated the levels of angiogenic markers in pregnancies with fetuses of appropriate growth and those with estimated fetal weight below the 10th percentile [34-36]. These findings support the identification of small fetuses under the 10th percentile as a high-risk group, although many of these fetuses, particularly those classified as SGA, may still have a favorable perinatal outcome.

A case-control study published in August 2021 evaluated the angiogenic sFlt-1/PLGF ratio in patients with fetuses classified via ultrasound as normally growing, constitutionally small, or with IUGR. The study found that patients with IUGR had significantly higher sFlt-1/PLGF ratios compared to those with normal or constitutionally small fetuses. The authors concluded that sFlt-1/PLGF levels in IUGR correlate with IUGR staging, Doppler parameters, and adverse outcomes, and may aid in disease classification and clinical management [33].

In an observational study published in 2020, sFlt-1/PLGF ratios were significantly higher in pregnancies with IUGR and adverse neonatal outcomes compared to those with normal fetal growth. Angiogenic markers were analyzed between 24–28+6 and 29–36+6 weeks of gestation in 530 patients. The study highlighted the potential utility of angiogenic markers as objective tools for identifying fetuses at risk of poor neonatal outcomes [34].

Our results align with previous studies reporting similar findings. In a retrospective study, Rajiv et al. analyzed angiogenic marker levels (PLGF, sFlt-1, and their ratio) in patients with IUGR and SGA fetuses and concluded that sFlt-1/PLGF ratios were significantly higher in the IUGR group than in the SGA group [37].

The sample size was relatively small, limiting the power to generalize the results. Our data suggest that angiogenic markers, particularly the sFlt-1/PlGF ratio, can serve as valuable tools in the antenatal distinction between IUGR and SGA. Their inclusion in clinical practice may improve risk stratification, enable individualized monitoring strategies, and ultimately enhance perinatal outcomes through timely intervention.

7. CONCLUSION

Patients with fetuses affected by intrauterine growth restriction (IUGR) exhibit higher levels of angiogenic markers compared to those with small for gestational age (SGA) fetuses. These markers can significantly improve the diagnosis of IUGR and placental insufficiency.

This pilot study demonstrates that the angiogenic markers PLGF and sFlt-1, as well as their ratio, have significant potential in differentiating between IUGR and SGA fetuses. Overall, our results reinforce the clinical relevance of angiogenic markers in differentiating pathologic from non-pathologic fetal smallness. Incorporating these markers into routine clinical assessment may enhance antenatal diagnostic accuracy, facilitate appropriate monitoring strategies, and ultimately improve perinatal outcomes. Further research with a larger sample size is necessary to confirm these findings and support the incorporation of these markers into clinical practice.

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