Open Journal of
Clinical & Medical
Case Reports

Volume 8 (2022)
Issue 22

Research Article ISSN: 2379-1039

Usefulness of the sFlt-1/PlGF ratio in the clinical management of preeclampsia

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Abstract

Introduction: An elevated soluble fms-like tyrosine kinase-1 (sFlt-1)/Placental Growth Factor (PlGF) ratio is associated with adverse perinatal outcome in women suspected of having preeclampsia (PE) and short time until delivery.

Methods: This is a retrospective, cohort study in a single center between February 2020 and June 2021. Angiogenic marker analysis were obtained from participants with hypertension.

Results: In total, 94 singleton pregnancies were included in the study. Median sFlt-1/PlGF ratio was significantly different in patients with adverse perinatal outcome compared to those without. The mean time until delivery was significantly negative correlated with sFlt-1/PlGF ratio.

Conclusion: In singleton pregnancies with PE, sFlt-1/PlGF ratio may be useful for decision-making regarding the exhaustive monitoring of high-risk patients. Our results emphasize the additive value of angiogenic biomarkers in clinical practice.

Keywords

Biomarkers; Gestational hypertension; Preeclampsia; Pregnancy outcome; Prediction; Hospitalization; sFlt/PlGF ratio; PlGF; sFlt-1; Preterm birth; Intrauterine Growth Restriction (IUGR).

Introduction

Hypertensive Disorders of Pregnancy (HDP) are a major cause of maternal and fetal morbidity and mortality, not only because of the effects of these conditions, but also because of the high rate of premature births, as they account for at least 15% of all preterm deliveries and up to 10% of pregnancy complications

worldwide [1]. Preeclampsia (PE) has classically been defined as new-onset hypertension during the second half of pregnancy (Blood Pressure [BP] levels >140/90 mmHg), together with the presence of edema and proteinuria (>300 mg in 24-h urine), all of which resolve twelve weeks after the delivery [2,3]. However, the International Society for the Study of Hypertension in Pregnancy has introduced a broader definition of this condition, which it currently described as gestational hypertension that is accompanied by one or more of the following new-onset conditions starting at 20 weeks of gestation: proteinuria (>0.3 g/24 h or protein/creatinine ratio >0.3 mg/mg), evidence of Target Organ Damage (TOD) (including acute kidney injury, liver involvement, neurological complications, and hematological complications) or uteroplacental insufficiency (Intrauterine Fetal Growth Restriction [IUGR] and Doppler abnormalities) (Table 1) [4,5].

Table 1: Classification of hypertensive disorders of pregnancy [5].

Preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome	New-onset hypertension (systolic blood pressure [SBP] ≥140 and/or diastolic blood pressure [DBP] ≥90 mmHg) associated with significant proteinuria (>300 mg/day or a protein/creatinine ratio >0.3 mg/mg) after the 20th week of gestation. In the absence of proteinuria, new-onset Arterial Hypertension (AHT) and signs of organ dysfunction, defined by the following: • **Thrombocytopenia** (less than 100,000 platelets/µl). • **Liver alterations** (elevated transaminase levels [2 x normal values]). • **Kidney failure** (creatinine levels >1.1 mg/dl or twice the basal value in the absence of kidney disease). • **Pulmonary edema, visual disturbances, or neurological symptoms.** **Eclampsia:** concomitant appearance of seizures in the absence of a neurological disorder.
	HELLP syndrome: hemolysis, elevated liver enzymes, and low platelet count.
Chronic hypertension (CHT)	Pregestational hypertension that diagnosed before the 20th week of gestation, or that persisting 12 weeks after the delivery.
Chronic hypertension with concomitant pre eclampsia (CHT + PE)	**a. Concomitant preeclampsia:** • New-onset or increased proteinuria; and or • Elevated BP levels or a greater need for antihypertensive medication **b. Concomitant preeclampsia meeting severity criteria:** • Severe HT (SBP ≥160 mmHg and/or DBP ≥110 mmHg) despite being under pharmacological treatment. • Thrombocytopenia (<100,000/µl). • Hypertransaminemia (twice the normal limits). • New-onset or exacerbated renal failure. • Neurological symptoms, such as headache and photopsia.
Gestational hypertension (GHT)	New-onset hypertension without associated proteinuria nor other signs or symptoms of preeclampsia after the 20th week of gestation and resolving less than 12 weeks after the delivery.

ATH: Arterial Hypertension; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure.

Although the etiopathogenesis of PE is not fully understood, it is known to be a multisystemic disease that predominantly presents with cardiovascular manifestations attributable to systemic inflammation, endothelial dysfunction, and generalized vasoconstriction, all of which result in hypertension and multiorgan hypoperfusion. This condition results in failed vascular remodeling of the uterine spiral arteries, thus leading to uteroplacental malperfusion and vascular endothelial dysfunction associated with an imbalance in the levels of circulating angiogenic factors [6]. Increased levels of antiangiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), have been found in patients with

preeclampsia, while proangiogenic factors, such as the placental growth factor (PlGF) are decreased, thus resulting in an elevated sFlt/PlGF ratio [7].

There is considerable scientific evidence on the prognostic value of this ratio in predicting the outcome and course of the disease [8-11] such that, when faced with a clinical suspicion of preeclampsia, a sFlt/PlGF angiogenic factor ratio <38 can be used to rule out the onset of PE within the following week owing to its high Negative Predictive Value (NPV), whereas a ratio >85 can be used to diagnose PE and a potential risk of shortening of the gestational length [12,13].

In a study carried out by Verlohren (2016), ratio values on the weeks of gestation were identified as associated with an imminent risk of pregnancy termination. In the group of patients at <34 weeks of gestation, only 29.4% of those with a sFlt/PlGF ratio greater than 655 continued to be pregnant within the following 48 h. In the group at >34 weeks of gestation, only 16.7% of the pregnant women with a ratio greater than 201 were still pregnant 48 h after the determination.

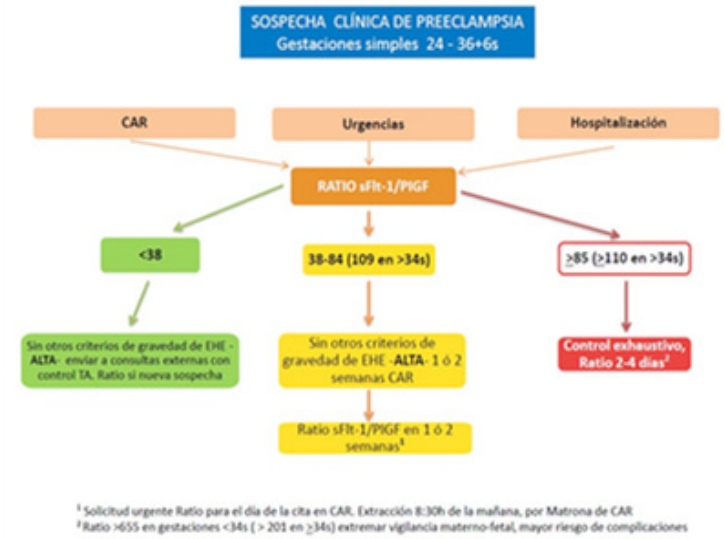
In February 2020, a protocol for determining the sFlt/PlGF angiogenic factor ratio in pregnant women with suspected preeclampsia was implemented in the Obstetrics and Gynecology Emergency Department in collaboration with the Clinical Analyses Department.

The aim of this study is to evaluate the impact of the implementation of this protocol on the diagnosis and follow-up of preeclampsia in our patient population, its influence on the admission and hospital stay of these patients, as well as on the early identification of complications and the optimization of the timing of the delivery.

Material and Methods

We carried out an observational, analytical, retrospective, cohort study on a total of 94 patients with singleton pregnancies and suspected preeclampsia (new-onset AHT +/proteinuria, worsening of preexisting AHT +/- proteinuria, signs and symptoms suggestive of this condition [epigastric pain, face-hand-foot edema, headache, visual disturbances, or sudden weight gain >1 kg/week during the third trimester], or early intrauterine growth restriction [IUGR]), who were attended at the Juan Ramón Jiménez hospital in Huelva (Spain) from February 2020 to June 2021, and for whom the sFlt/PlGF ratio was determined according to the specific protocol (Chart 1).

In cases of a high sFlt/PlGF ratio, the indication was to maximize maternal and fetal surveillance through hospitalization, repeat blood tests every 2-4 days, achieve fetal lung maturity <35 weeks of gestation, and monitor the maternal and fetal well-being.



HRC: High-Risk consultation.

Chart 1: Protocol for determining the sFlt/PlGF ratio in patients with suspected preeclampsia. BP: blood pressure. HDP: hypertensive disorder of pregnancy.

SOSPECHA CLÍNICA DE PREECLAMPSIA	CLINICAL SUSPICION OF PREECLAMPSIA
Gestaciones simples 24-36 + 6 s	Singleton gestations at 24–36 + 6 weeks
CAR	HRC
Urgencias	Emergency Department
Hospitalización	Hospitalization
RATIO SFlt-1/PlGF	SFlt-1/PlGF RATIO
38	38
38-84 (109 en >34 s)	38–84 (109 at >34 weeks)
≥85 (≥110 en >34 s)	≥85 (≥110 at >34 weeks)
Sin otros criterios de gravedad de EHE - ALTA- enviar a consultas externas con control de TA.	Without other HDP severity criteria - DISCHARGE- refer to outpatient follow-up with BP monitoring.
Ratio si nueva sospecha	Ratio determination in case of new suspicion.
Sin otros criterios de gravedad de EHE - ALTA- 1 0 2 semanas CAR	Without other HDP severity criteria - DISCHARGE- HRC in 1 or 2 weeks
Control exhaustivo, ratio 2-4 dias2	Close follow-up and ratio determination in 2–4 days[2]
Ratio sFlt-1/PlGF en 1 o 2 semanas1	sFlt-1/PlGF ratio determination in 1 to 2 weeks[1]
1 Solicitud urgente Ratio para el dia de la cita en CAR.	1 Urgent ratio determination on the day of the HRC appointment.
Extracción 8:30 h de la mañana por matrona de CAR	Blood collection at 8:30 h by the HRC midwife
2 Ratio >655 en gestaciones 34 x (>201 en ≥34 s) extremar vigilancia materno-fetal, mayor riesgo de complicaciones	2 Ratio >655 in gestations at 34 weeks (>201 at ≥34 weeks), close maternal and fetal monitoring, increased risk of complications

The results were analyzed after categorizing the pregnant women with singleton pregnancies at 24–36 + 6 weeks of gestation, to whom the protocol was applied, and the ratio of angiogenic factors determined into two groups: one group comprising patients with a ratio >85 and the other made up of those with a ratio <38.

We created a database in which the clinical characteristics and laboratory parameters of each pregnant woman, in addition to the occurrence of perinatal complications, the weeks of gestation at delivery, the type of delivery, any maternal complications, and any hospital stay were recorded as variables. The birth weight, Apgar score at 5 minutes, need for resuscitation, need for transfer to the Neonatal Intensive Care Unit (NICU), morbidity and mortality, as well as the days spent in the Children's Hospital were also recorded.

The gestational age was calculated based on the Craniocaudal Length (CCL) measured by ultrasonography during the first trimester of pregnancy. A small-for-gestational-age weight (SGAW) was considered to be a weight between percentiles p3 and p10, with normal Doppler findings, and a fetus with type-I IUGR at an estimated fetal weight <p3 or an estimated fetal weight <p10 with altered Doppler findings (mean uterine artery pulsatility index [mUAPI] >p95 or middle cerebral artery pulsatility index [MCAPI] <p5 or cerebroplacental ratio [CPR] <p5).

Quantitative determination of biochemical markers of preeclampsia: the presence of placental growth factor (PlGF) and the soluble fms-like tyrosine kinase-1 (sFlt-1) was determined in maternal serum samples by means of immunoanalyses carried out in Cobas®automated analyzers (Roche Diagnostics) following the manufacturer's instructions.

Both tests are sandwich Electrochemiluminescence Immunoassays (ECLIA) in which two specific monoclonal antibodies are used. Their total duration is 18 minutes, and their detection limits are 10 pg/ml and 3 pg/ml for the Elecsys sFlt-1 and the Elecsys PlGF test, respectively.

The sFlt-1 and PlGF quantifications were performed concomitantly in order to calculate the sFIt-1/PlGF ratio in women with suspected preeclampsia. This ratio has been shown to have a greater predictive value for preeclampsia than the separate measurement of each parameter. The laboratory information system calculates and reports the ratio and values of the two markers separately.

The sFIt-1/PlGF ratio cutoff point ≤38 has a NPV (with a 95% Confidence Interval [CI]) of 99.3%.

Statistical analysis

All data were analyzed using software IBM SPSS Statistics for Windows, version 24.0.

A descriptive analysis of the sociodemographic, clinical, and analytical variables was performed to describe these variables in our patient sample. Quantitative variables were described using a median and Interquartile Range (IQR), and categorical variables were described as frequencies and percentages. A bivariate analysis was carried out to determine potential differences between both groups (ratio ≥85 vs. ratio

<38). A proportions contrast test based on the chi-square ($\chi 2$) and Mann-Whitney U tests was used to carry out the statistical comparison between both groups, with a statistical significance of 5% ($p < 0.05$) being required in all cases.

Ethical aspects

All patient information collected was treated confidentially for all purposes according to the provisions of Spanish Organic Law 14/2007, of July 7th, governing biomedical research. The protection of personal data according to European General Data Protection Regulation (GDPR) 2016/679 of the European Parliament and the Council, dated 27 April 2016, as well as Spanish Organic Law 3/2018, of December 5th, will be guaranteed. Furthermore, the patient's rights will be ensured at all times (updated 2013 Helsinki declaration).

Results

In this study we included a total of 94 patients, 57 of whom corresponded to women with singleton gestations, a gestational age of 24–36 + 6 weeks, and a sFlt/PlGF ratio <38, hereafter referred to as group 1; and 37 of whom corresponded to women with singleton gestations, a gestational age of 24–36 + 6 weeks, and a ratio ≥85 (above 110 if the gestational age was over 34 weeks), who comprised group 2.

In 13 patients with a ratio of 38-84 (109 in the case of gestations >34 weeks), a new ratio was determined one week later according to the protocol (Chart 1): ten of these patients had a ratio below 38 and were consequently added to group 1, whereas three patients had a ratio above 85 and were categorized into group 2.

The characteristics of the patients included in the analyzed population, such as their full gestational age (weeks) at diagnosis, maternal age, ethnicity, body mass index

(BMI) ≥35 (type-2 and -3 obesity), number of pregnancies, smoking history, prior history of PE, current prophylactic treatment with Acetylsalicylic Acid (ASA) 150 mg starting before 16 weeks of gestation, history of chronic AHT, history of gestation achieved through an egg donation, and/or history of maternal autoimmune disease (Systemic Lupus Erythematosus [SLE], Antiphospholipid Syndrome [APS], Hemolytic Uremic Syndrome [HUS], hypothyroidism, and pregestational diabetes) are listed in Table 2.

Regarding the degree of hypertension (mild 140–149/90–99 mmHg, moderate 150– 159/100–109 mmHg, and severe >160/110 mmHg), almost 90% of the pregnant women with an elevated sFlt-1/PlGF ratio had consulted for moderate or severe hypertension. When analyzing the need for hypotensive treatment to control the patients' BP levels (Table 3), we found that 43% of the patients included in group 1 did not require treatment. The number of patients requiring oral medication was similar in both groups. However, more patients from group 2 required intravenous treatment with labetalol and hospitalization ($p < 0.001$).

Table 2: Population characteristics. ASA: acetylsalicylic acid. IQR: interquartile range. The statistical comparisons were performed using the chi-square and Mann-Whitney U tests.

		Ratio <38 (N= 57)	Ratio >85 (N= 37)	*P*
		% - median (IQR)	% - median (IQR)	
Maternal age		33 (8)	34 (11)	*0.991*
Race	White	70.2%	78.4%	
	Caucasian Maghrebi	19.3% 8.8%	10.8% 5.4%	*0.476*
	Black	1.8%	5.4%	
Weeks of gestation		33 (5)	33 (4)	*0.393*
Obesity		22.8%	2.7%	*0.007*
History of pregnancies	Nulliparous Multiparous	50.9% 49.1%	54.1% 45.9%	*0.763*
Smoking habit		28.1%	29.7%	*0.862*
Previous history of preeclampsia		7.0%	10.8%	*0.520*
Prophylaxis with ASA		31.6%	18.9%	*0.175*
Chronic AHT		36.8%	18.9%	*0.063*
Type-1 diabetes		5.3%	2.7%	*0.548*
Maternal autoimmune disease		5.3%	0.0%	*0.156*
Egg donation		1.8%	13.5%	*0.002*

Table 3: Need for treatment and hospitalization according to the sFlt/PlGF ratio.

		Ratio <38	**Ratio >85**	**P**
		(N = 57) %	(N = 37) %	
AHT	Mild	38.60%	10.80%	0.003
	Moderate/severe	61.40%	89.20%	
Hospitalization		21.10%	89.20%	<0.001
Treatment administered	None	42.90%	10.80%	<0.001
	Oral antihypertensive	48.20%	48.60%	
	Intravenous antihypertensive	8.90%	40.50%	
Oral antihypertensive	Labetalol	27.60%	50.00%	0.232
	Alpha-methyldopa	51.70%	30.00%	
	Both	20.70%	20.00%	

Maternal and perinatal outcomes

Table 4 shows data on the weeks of gestation at delivery, the delivery route, and Newborn (NB) outcomes. The mean gestational age at delivery was lower among the patients of group 2 compared with those of group 1. Regarding the delivery route, the percentage of cesarean sections among the patients of both groups exceeded the usual percentage of cesarean sections performed at our site of 19%, reaching 65.7%

in the group with the highest ratio.

With respect to the newborns' weight, the mean weight, expressed in grams, was lower among the newborns of group 2, and almost half (48.6%) of the newborns of this group were born with a SGAW compared with only 18.5% of those of group 1. Differences in the 5-minute Apgar score were also evidenced between both groups (Apgar ≤7 in 1.7% vs. 13.5% of the newborns of group 1 and 2, respectively).

When analyzing the need for admission to the NICU and the length of stay at said unit, we observed that 75% of the NBs of group 2 had to be admitted to this unit with a mean stay of 16 days.

Patients of group 2 experienced the most severe complications, including one case of premature detachment of normoinsert placenta [PDNP] in a hospitalized, pregnant woman with a gestational age of 26 + 3 weeks, PE, type-2 IUGR (CPR <p5), and a very high ratio (2.722), who gave birth to a 620-g male whose clinical evolution was favorable, thus being discharged after 80 days of hospitalization. Group 2 also included one early neonatal death, at three days of life, due to a premature delivery (emergency cesarean section secondary to a loss of fetal well-being at 27 weeks of gestation); one case of bronchopulmonary dysplasia; one case of sepsis; and one case of severe hypoxic-ischemic encephalopathy.

One case of extraclinical, antepartum fetal death was recorded in group 1, associated with PDNP and disseminated intravascular coagulation (DIC) on admission, in a pregnant woman who was under study for a suspected Immunoglobulin A (IgA) nephropathy.

An analysis of maternal complications revealed an episode of thromboembolic disease in a patient of group 1 (deep vein thrombosis and pulmonary thromboembolism) during the postpartum period. In group 2, five patients developed HELLP syndrome (hemolysis, elevated liver enzymes, and thrombocytopenia), and another patient had to undergo a subtotal hysterectomy in the context of severe postpartum hemorrhage (PPH). One patient of group 2 presented with generalized focal seizures secondary to thrombosis of the cortical veins during the postpartum period, following an induced, oxytocic delivery due to presenting with PE.

When focusing on the number of days elapsed between the first measurement of elevated sFlt/PlGF ratio value (group 2) and the delivery, we calculated (Chart 2) a median of 4 days. The box plot reflects the ratio scores, showcasing how lower ratio values correspond to longer intervals until the delivery, and higher values are associated with pregnancy termination within 24-72 h as a result of the onset of maternal and fetal complications.

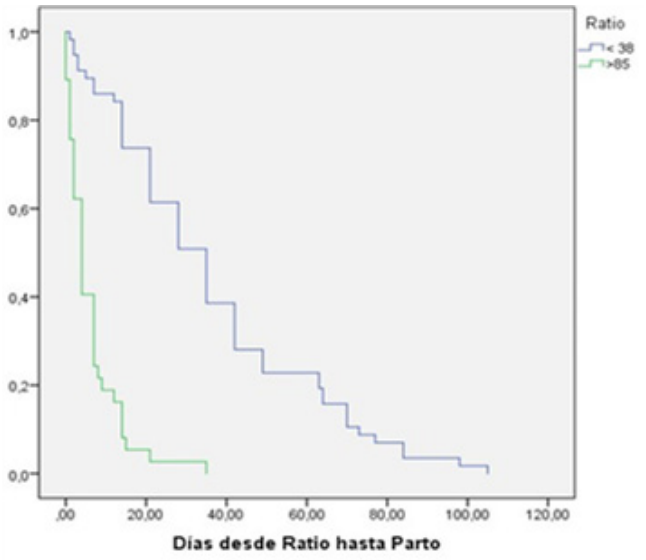
Calculation of the cumulative likelihood of delivery as a function of the weeks elapsed after obtaining a high ratio value revealed that, in the sample analyzed, 40% of the pregnancies ended within the first week of obtaining the first high ratio value and 80% ended by the end of the second week (Chart 3).

Chart 4 refers to the ratio variable divided into its four quartiles (from a lower to a greater ratio, where Q1 corresponds to the group with the lower ratio and Q4 to that with the greater ratio: Q1: 0–6.84, Q2: 6.85–35.45, Q3: 35.46–178.31, and Q4: 178.32–2722). The cumulative percentage (in weeks) between

the admission of the pregnant woman to the delivery is also shown. It is clear that less time elapses between the admission and the delivery in group Q4 corresponding to a greater ratio value.

Table 4: Maternal and perinatal outcomes. AGA: Adequate for Gestational Age. DVT: Deep Vein Thrombosis; HGA: High for gestational Age; IUGR: Intrauterine Growth Restriction. NB: Newborn. NICU: Neonatal Intensive Care Unit; PDNP: Premature Detachment of Normoinsert Placenta; PTE: Pulmonary Thromboembolism; SGAW: Small-for-Gestational-Age Weight.

	Ratio <38 (N = 57)	**Ratio >85 (N = 37)**	*p*	
	% - median (IQR)	% - median (IQR)		
Weeks of gestation at delivery	37 (3)	33 (5)	*<0.001*	
Delivery	Spontaneous	26.30%	5.70%	
	Induced	45.60%	28.60%	*0.001*
	Cesarean section	28.10%	65.70%	
IUGR		17.50%	32.40%	*0.096*
5-min NB Apgar ≤7		1.70%	13.50%	*0.002*
NICU transfer		17.30%	75.00%	*<0.001*
Length of neonatal stay		2.5 (2)	16 (26)	*<0.001*
NB weight		2755	157900.00%	*<0.001*
(quantitative)		-1120	-1227	
NB weight	SGAW	18.50%	48.60%	*0.006*
	AGA	77.80%	51.40%	
	HGA	3.70%	0.00%	
Neonatal	No	89.40%	61.50%	*0.045*
morbidity	Respiratory distress	10.60%	26.90%	
	Bronchopulmonary dysplasia	0.00%	3.80%	
	Severe hypoxic-ischemic	0.00%	3.80%	
	encephalopathy			
	Sepsis	0.00%	3.80%	*0.756*
Neonatal mortality		1.80%	2.70%	
Maternal	No	95.60%	87.00%	*0.311*
morbidity	PDNP	2.20%	4.30%	
	Cerebral cortical vein thrombosis	0.00%	4.30%	
	PTE + DVT	2.20%	0.00%	
	Postpartum hemorrhage and hysterectomy	0.00%	4.30%	
	HELLP syndrome	0.00%	13.50%	*0.005*
Length of maternal stay		3 (1)	5 (5)	*0.001*



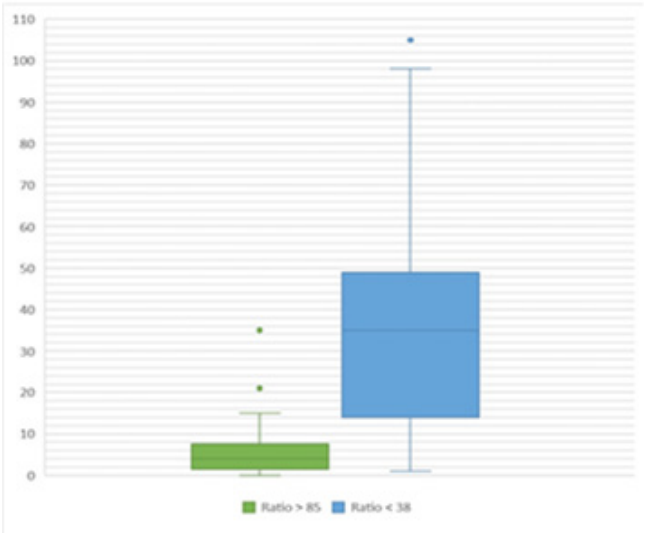


Chart 2: Days elapsed between the first sFlt/PlGF ratio termination and the delivery.

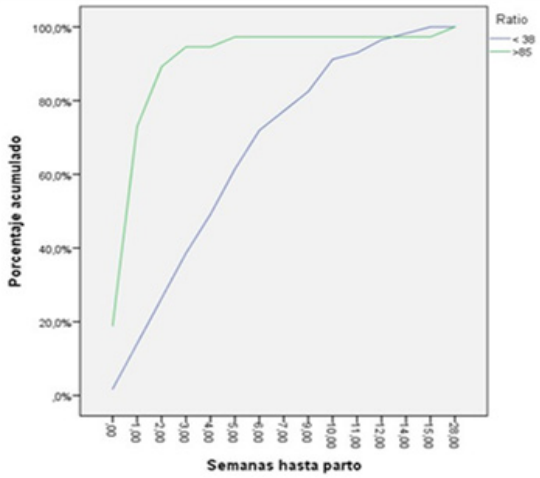


Chart 3: Number of weeks elapsed between the first ratio determination and the delivery on the abscissa axis. Q1: lower ratio sFlt-1/PlGF, Q4: greater ratio.

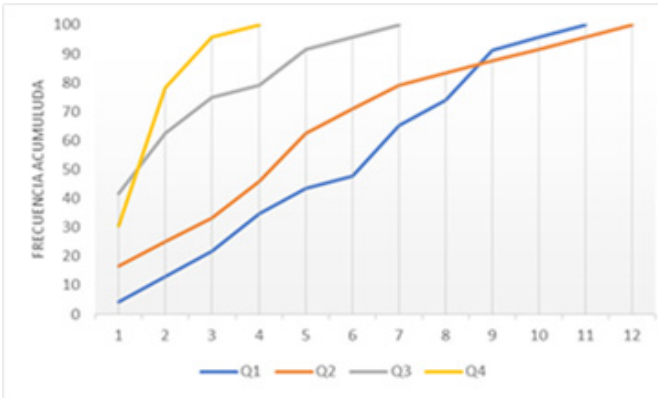


Chart 4: Number of weeks elapsed between the first ratio determination and the delivery on the abscissa axis. Q1: lower ratio sFlt-1/PlGF, Q4: greater ratio.

Discussion

The severity criteria for preeclampsia do not always correlate with the maternal and fetal clinical presentation, and the onset of certain complications, such as fetal death, growth retardation, or PDNP often precede the diagnosis by days or weeks [14].

The difficulties associated with the diagnosis and the often unpredictable course of preeclampsia hamper the early identification of patients at an increased risk, and other pregnant women who present with clinical signs of preeclampsia and consult for these manifestations do not always develop the disease. It is for this reason that a marker with such a high negative predictive value is a good tool for predicting and managing preeclampsia.

The findings of our study confirm the clinical usefulness of the sFlt/PlGF ratio in predicting adverse maternal and perinatal outcomes. Our data were obtained retrospectively from a cohort of women seen in the Obstetrics and Gynecology Department due to presenting with a wide range of specific and/or non-

specific signs and symptoms of preeclampsia. Over a third (39.3%) of the women for whom a determination of the sFlt/PIGF ratio was indicated developed preeclampsia, and pregnant women with higher ratio values had earlier and more severe maternal and fetal complications.

The characteristics of the study population were similar in both patient groups, with significant differences only being found in the percentage of obese women (22.8% in group 1 and 2.7% in group 2) and the percentage of pregnancies achieved through an egg donation (1.8% in group 1 and 13.5% in group 2). The relationship between obesity and PE seems to involve the immune cells of the maternal adipose tissue and placenta, which contribute to the onset of more severe placental disorders, as described by some authors [15,16]. However, in our sample only one patient with grade-2 obesity developed PE, which could be explained by the fact that half of the patients with a BMI ≥35 had chronic hypertension and were under prophylactic treatment with ASA from the first trimester of gestation. An immune theory based on the allogeneic nature of the fetus with respect to the mother has also been proposed to explain the relationship between PE and pregnancies achieved through an egg donation [17], a circumstance that was also observed in the population analyzed in our study.

Differences that did not reach statistical significance were also observed in the percentage of patients with chronic AHT, which was twice as high in the group with lower ratios (36.8% vs. 18.9%), as well as in the prophylactic treatment with ASA consumed by the patients of both groups: 31.6% in group 1 and 18.9% in group 2, thus emphasizing the importance of administering a low dose of ASA in selected patients at a high risk of developing PE [18].

Since the implementation of the protocol described in this study and coinciding with the published literature [19], the ratio of circulating angiogenic markers sFlt/PlGF has allowed us to discriminate between pregnant women who required hospitalization (21% in group 1 and 89.2% in group 2) and those who could continue to be followed on an outpatient basis, thus avoiding admission in 33.8% of the pregnant women who consulted for hypertension. Similarly, higher levels were associated with preeclampsia of greater severity [20], thus enabling pregnant women to be stratified according to their risk of developing complications and adverse effects.

The data presented in this paper demonstrate that altered sFlt-1/PlGF ratio values (group 2) are associated with a worse control of BP levels, as well as a greater need for antihypertensive treatment administered intravenously, a greater number of hospitalizations, and greater costs associated with these. In this group, deliveries mostly took place through a cesarean section (up to 65.7%).

With respect to maternal complications, severe maternal complications occurred in up to 26.4% of the patients of group 2, such as the HELLP syndrome, placental detachment, and severe obstetric hemorrhage, all linked with a greater length of hospital stay, with these complications occurring in patients with the highest sFlt-1/PlGF ratio values according to the extent and intensity of the damage to the systemic vascular endothelium, as also described in previous studies [21].

According to our data on newborns, and coinciding with the findings reported by other authors

[22,23], the angiogenic factor ratio also correlates with an increase in adverse perinatal outcomes, such as preterm delivery and a small-for-gestational-age weight, thus resulting in a greater length of hospital stay and more neonatal complications.

The findings of our study demonstrate that, in the group of pregnant women with a high ratio, the delivery occurred at earlier gestational ages (33 vs. 37 weeks) and there was a greater number of newborns with a SGAW (48.6% vs. 18.5%), which has immediate repercussions on neonatal morbidity and mortality, as well as the length of stay in the NICU (16 vs. 2.5).

Conclusion

The ratio of angiogenic factors sFlt-1/PlGF is a useful tool for predicting and diagnosing preeclampsia, even more so since the inclusion of uteroplacental dysfunction by the International Society for the Study of Hypertension in Pregnancy. After a year and a half of analyses, our data support that this ratio has the potential to predict adverse pregnancy outcomes caused by placental disorders, thus allowing for optimizing pregnancy termination before the onset of severe symptoms and achieving fetal lung maturity through the administration of corticosteroids and close maternal and fetal monitoring.

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Manuscript Information: Received: October 17, 2022; November 21, 2022; Published: November 30, 2022

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Citation: Yera M, Núñez P, Cabanillas C, Sánchez J, Buezas B, et al. Usefulness of the sFlt-1/PlGF ratio in the clinical management of preeclampsia. Open J Clin Med Case Rep. 2022; 1940.