ORIGINAL RESEARCH ARTICLE

The sFlt1/PlGF ratio predicts faster fetal deterioration in early fetal growth restriction: A historical cohort study

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Abstract

Introduction: The velocity of fetal deterioration in fetal growth restriction is extremely variable, which makes monitoring and counseling very challenging. The soluble fms-like tyrosine kinase to placental growth factor (sFlt1/PlGF) ratio provides a readout of the vasoactive environment that correlates with preeclampsia and fetal growth restriction and that could be useful to predict fetal deterioration. Previous studies showed a correlation between higher sFlt1/PlGF ratios and lower gestational ages at birth, although it is unclear whether this is due to the increased incidence of preeclampsia. Our goal was to evaluate whether the sFlt1/PlGF ratio predicts faster fetal deterioration in early fetal growth restriction.

Material and methods: This was a historical cohort study in a tertiary maternity hospital. Data from singleton pregnancies with early fetal growth restriction (diagnosed before 32 gestational weeks) confirmed after birth monitored between January 2016 and December 2020 were retrieved from clinical files. Cases of chromosomal/fetal abnormalities, infection and medical terminations of pregnancy were excluded. The sFlt1/PlGF ratio was acquired at diagnosis of early fetal growth restriction in our unit. The correlation of log10 sFlt1/PlGF with latency to delivery/fetal demise was assessed with linear, logistic (positive sFlt1/PlGF if >85) and Cox regression excluding deliveries for maternal conditions and controlling for preeclampsia, gestational age at time of ratio test, maternal age and smoking during pregnancy. Receiver-operating characteristic (ROC) analysis tested the performance of sFlt1/PlGF ratio in predicting delivery for fetal reasons in the following week.

Results: 125 patients were included. Mean sFlt1/PlGF ratio was 91.2 (SD 148.7) and 28% of patients had a positive ratio. A higher log10 sFlt1/PlGF ratio predicted shorter latency for delivery/fetal demise in linear regression after controlling for confounders, β = −3.001, (−3.713 to −2.288). Logistic regression with ratio positivity confirmed these findings (latency for delivery 5.7 ± 3.32 weeks for ratios ≤85 vs 1.9 ± 1.52 weeks

for ratios >85); β = −0.698 (−1.064 to −0.332). Adjusted Cox regression showed that a positive ratio confers a significantly positive hazard ratio (HR) for earlier delivery/ fetal demise, HR 9.869 (5.061–19.243). ROC analysis showed an area under the curve of 0.847 (SE±0.06).

Conclusions: sFlt1/PlGF ratio is correlated with faster fetal deterioration in early fetal growth restriction, independently of preeclampsia.

KEYWORDS
fetal deterioration, fetal growth restriction, sFlt1/PlGF ratio

1 | INTRODUCTION

Impaired placentation is the basis of the proposed pathophysiology for some conditions referred to as "placental syndromes", such as preeclampsia[1–3] and fetal growth restriction (FGR).[3] In these syndromes, the anti-angiogenic environment that follows an impaired placentation is a crucial mediator for its clinical sequelae.[1–3] Two mediators have emerged as being particularly relevant: placental growth factor (PlGF), an angiogenic factor, and soluble fms-like tyrosine kinase 1 (sFlt1), that acts as an anti-angiogenic factor.[4]

In preeclampsia, circulating levels of sFlt1 levels are increased and free PlGF is decreased[5]; the magnitude of change in both sFlt1 and PlGF levels correlates with adverse outcomes.[6] Consequently, the sFlt1/PlGF ratio is increasingly used in clinical practice, assisting with diagnosis in cases where preeclampsia is suspected and for risk-stratification of preeclamptic patients.[7,8]

In FGR, clinical management is currently limited to serial fetal ultrasound monitoring; and close maternal surveillance (given the risk of preeclampsia). The addition of computerized cardiotocography monitoring to surveillance algorithms has been shown to improve outcomes in this setting.[9] However, it is unfortunately not available in all centers. Fetal Doppler monitoring allows for risk stratification in these fetuses and, according to most guidelines, indicates the timing for the next assessment and for delivery.[10–15] However, the rates of clinical deterioration are extremely variable among patients, which makes counseling very challenging.[16]

Previous studies have demonstrated that the sFlt1/PlGF ratio is elevated in FGR pregnancies, even in the absence of preeclampsia.[17–20] The elevation of the sFlt1/PlGF ratio appears to be higher in cases of FGR with superimposed preeclampsia than in cases of isolated FGR.[21] In addition, an increased sFlt1/PlGF ratio has been shown to correlate with adverse outcomes in early FGR[22,23] and to predict shorter intervals to delivery in patients with preeclampsia or FGR.[24] Other studies have shown that higher sFlt1/PlGF ratios predict a shorter interval to delivery in early FGR.[25–27] However, those studies did not control for the occurrence of preeclampsia and thus it is not clear whether this correlation is due to the known association between preeclampsia and FGR, or whether the sFlt1/ PlGF ratio can predict fetal clinical deterioration even in the absence of this complication. Additionally, previous publications have shown that other variables such as maternal age and smoking during

> **Key message**
>
> A higher sFlt1/PlGF ratio at diagnosis of early fetal growth restriction predicts faster fetal deterioration after controlling for maternal-indicated deliveries, preeclampsia, gestational age at time of ratio test, maternal age and smoking.

pregnancy are associated with changes in the sFlt1/PlGF ratio.[28] Since both are also risk factors for preterm delivery, the assessment of the association between sFlt1/PlGF ratio and interval to delivery should account for these confounders.

Our goal was to investigate whether a higher sFlt1/PlGF ratio predicts a faster fetal clinical deterioration of FGR even after controlling for preeclampsia and other confounders, such as gestational age at time of ratio sampling, maternal age and smoking during pregnancy. This could be a potentially useful tool for risk stratification and patient counseling in FGR.

2 | MATERIAL AND METHODS

This was a historical cohort study conducted in a tertiary maternity center in Lisbon, Portugal (Maternidade Dr. Alfredo da Costa, Centro Hospitalar Universitário Lisboa Central). The hospital identification number for all patients followed in our FGR clinic from January 2016 to December 2020 was retrieved from electronic appointment records, and all files were reviewed to select singleton pregnancies diagnosed with early FGR and confirmed after birth. Data pertaining to those patients were retrieved from clinical notes.

Pregnancy was dated according to crown–rump length obtained from first trimester ultrasound (performed between 11 and 13+6 weeks of gestation) or when this result was not available, according to biparietal diameter between 14 and 21+6 weeks of gestation.

Early FGR was diagnosed according to international guidelines[29] in the presence of one solitary criterion or two or more contributory criteria. Solitary criteria were estimated fetal weight (EFW) or abdominal circumference <3th centile for a given gestational age, and umbilical artery absent end-diastolic flow

(UA-AEDF). Contributory criteria were EFW or abdominal circumference <10th centile combined with umbilical artery pulsatility index (UA-PI) >95th centile or mean uterine artery pulsatility index >95th centile.

FGR was classified as early when diagnosed before 32 gestational weeks, and as severe in the presence of an EFW <3rd centile by ultrasound scan. The periodicity of maternal and fetal evaluation complied with international guidelines[10]: fetuses with an EFW <10th centile but >3rd centile with normal fetal Dopplers were monitored every 10–15 days; fetuses with an EFW <3rd centile with normal fetal Dopplers were monitored weekly. In cases of UA-PI >95th centile or middle cerebral artery pulsatility index (MCA-PI) <5th centile, patients were monitored weekly. When there was UA-AEDF, patients were monitored every 48 hours, and in cases of absent umbilical artery end-diastolic flow or Doppler venosus changes, patients were admitted to the hospital and monitored every 12–24 hours.

Criteria for delivery also complied with these guidelines[10]: delivery was initiated at any gestational age for maternal indications (HELLP syndrome or severe preeclampsia) or if the fetal biophysical profile score was <4/8 (after fetal viability was established; defined in our center at 24 gestational weeks and an EFW >500 g, after patient counseling). In addition, delivery was implemented at 28–32 weeks in cases of absent or reversed a-wave in the ductus venosus; 32–34 weeks for reversed end-diastolic flow in the umbilical artery; 34–38 weeks for absent end-diastolic flow in the umbilical artery; 37 weeks for cerebroplacental ratio or MCA-PI <5th centile; and, for the remaining cases, between 37 and 39 weeks.

Vaginal delivery was preferred whenever possible. FGR-specific cesarean section indications included altered umbilical artery or ductus venosus Doppler, non-reassuring fetal status, gestational age <32 weeks (after patient counseling) or maternal conditions.

As part of the initial evaluation, all women were tested for infections (syphilis and cytomegalovirus in addition to the routine pregnancy serology) and invasive testing was offered in cases of early and severe FGR (EFW <3rd centile by ultrasound scan), maternal infection or malformations, or at the request of the couple. Cases of infection, chromosomal abnormalities, fetal malformations and medical interruptions of pregnancy were excluded from this analysis.

Maternal blood was collected at diagnosis of FGR in our clinic for assessment of the sFlt1/PlGF ratio. Some cases were diagnosed in other centers and referred to our unit; in these cases, blood was collected after the first appointment in our clinic. The maximum time-lapse for ratio collection after the confirmation of diagnosis in our unit that was accepted for this study was 15 days. This assessment aimed to stratify the patients in terms of risk of developing preeclampsia, with a positive ratio potentially influencing the next clinical evaluation (patients could be booked an earlier appointment at the clinician's discretion if the ratio was high). Ratio values did not interfere with the previously described indications for delivery (a positive ratio was not a reason to expedite delivery or for hospital admission). The samples were processed using an automatic analysis system (Roche Cobas e41). According to the literature, the sFlt1/PlGF ratio was considered positive if ≥85.[30]

Preeclampsia was defined and managed according to the American College of Obstetrics and Gynecology guidelines.[31] All ultrasound scans were performed by fetal medicine consultants accredited by the Fetal Medicine Foundation. Smoking was codified as a binary variable (yes or no) according to reported tobacco use during pregnancy.

2.1 | Statistical analyses

STATA statistical software 13.0 was used for all calculations. Continuous data are reported as means and standard deviations or median and interquartile range. Categorical data are reported as numbers and proportions. Proportions were compared with Chi-square test, and means were compared using Student's t-test (parametric) or Mann–Whitney U-test (non-parametric).

A variable called "latency for delivery" was generated (gestational age at birth or fetal demise minus gestational age at measurement of sFlt1/PlGF ratio).

Since the sFlt1/PlGF ratio exhibited a non-parametric distribution in our cohort, a Box Cox transformation was performed ($\lambda = 0$). Consequently, a decimal logarithm of the sFlt1/PlGF ratio was generated as a variable to test in the regression models.

Multiple linear regression models analyzed the correlation of the decimal logarithm of the sFlt1/PlGF ratio and both gestational age at birth and latency for delivery, excluding deliveries for maternal indication; and controlling for preeclampsia, gestational age at time of ratio test, maternal age and smoking during pregnancy. A multiple logistic regression model was also built, using ratio positivity as a binary variable and controlling for the previously described confounders. Survival analysis was performed, defining delivery or fetal demise as the failure event and analyzing latency for delivery/fetal demise as the time-to-event data. Adjusted Cox regression was performed, analyzing the correlation of a positive sFlt1/PlGF ratio with latency to delivery while controlling for the previously described confounders. Kaplan–Meier curves were obtained from this model.

A receiver operating characteristic (ROC) analysis tested the performance of the sFlt1/PlGF ratio in predicting delivery for fetal reasons in the following week (excluding cases of delivery for maternal reasons).

Two-sided $P < 0.05$ were used for statistical significance, and two-sided confidence intervals of 95% are reported.

2.2 | Ethics statement

Local ethics committee approval was obtained (Comissão de Ética do Centro Hospitalar Universitário Lisboa Central, process number 1150/2021) on November 26, 2021.

3 | RESULTS

The flowchart of participants included in the study is presented in Figure 1.

Our study sample characteristics are described in Table 1. Mean maternal age at delivery was 31.9 ± 5.9 years and the majority were primipara (45.6%). Preeclampsia complicated 12.8% of these pregnancies.

Mean gestational age at diagnosis of FGR was 27.2 weeks; 80.8% of cases were severe.[29] The main indications for delivery were gestational age >37 weeks (28%), fetal biophysical profile score <4/8 (16.8%), maternal indications (13.6%) and changes in the ductus venosus (10.4%). Infants with early FGR were born at a mean gestational age of 34.8 ± 3.7 weeks and 49 cases (42.2%) were admitted to the NICU in the first 28 days of life.

In our cohort, there were six cases of fetal demise (survival rate was 95.2%). Mean maternal age in these cases was 33.3 ± 5.5 years. Half the women ($n = 3$) were primipara, and 50% ($n = 3$) reported smoking during pregnancy. In all cases, fetuses had been diagnosed with severe FGR (EFW <3rd centile). Median gestational age at diagnosis of FGR in this setting was 29.28 weeks (interquartile range [IQR] 28.28–31.43) and median birthweight was 670 g (IQR 500–960). There was one case of preeclampsia in this group of patients, and in all of these patients ($n = 6$) the sFlt1/PlGF ratio was positive. Median sFlt1/PlGF ratio was 321.5 (IQR 176–661). Only one patient consented to neonatal autopsy, and in this case the main finding was pulmonary hypoplasia.

Mean sFlt1/PlGF ratio in our overall cohort was 91.2 (SD 148.7) with 35 (28%) positive ratios.

We analyzed the correlation between the logarithm of the sFlt1/PlGF ratio and timing of delivery/fetal demise, using linear regression. Considering that our goal was to correlate the sFlt1/PlGF ratio with deliveries secondary to fetal deterioration, deliveries for maternal indications were excluded ($n = 17$). Preeclampsia, gestational age at the time of ratio test, maternal age and smoking during pregnancy were included in the model as possible confounders.

Graphical results can be found in Figure 1A (for absolute gestational age at delivery/fetal demise), showing that higher values of the sFlt1/PlGF ratio are associated with earlier gestational ages at delivery/fetal demise; and Figure 1B (for latency to delivery/fetal demise), showing that higher values of the sFlt1/PlGF ratio are associated with shorter latencies to delivery/fetal demise.

The statistical model for Figure 1A can be found in Table S1A. Both in the crude model and in the multivariate model adjusted for preeclampsia, gestational age at ratio test, maternal age and smoking during pregnancy, there is a significant decrease in gestational age at birth/fetal demise for higher values of the ratio. In the adjusted analysis, the β coefficient for the decimal logarithm of the sFlt1/PlGF ratio is −3.001 (−3.715 to −2.288). The statistical model for Figure 1B can be found in Table S1B, showing a significant decrease in latency to delivery/fetal demise for higher values of the ratio in both the crude and the multivariate model (adjusted for the previously described confounders). In the adjusted analysis, the β coefficient for the decimal logarithm of the sFlt1/PlGF ratio is −3.001 (−3.713 to −2.288).

The results with logistic regression using ratio positivity (controlling for the previously described confounders), were similar to those described with linear regression (Table S2). Mean gestational age at birth/fetal demise with a positive ratio was 31.72 ± 2.52 vs 35.98 ± 3.36 weeks in cases with negative ratio ($P<0.001$). Mean latency for delivery was 5.7 ± 3.32 weeks for ratios ≤85 vs 1.9 ± 1.52 weeks for ratios >85. In the adjusted logistic regression model for the outcome latency for delivery/fetal demise (controlling for preeclampsia, gestational age at time of ratio test, maternal age and smoking during pregnancy) the β coefficient for a positive sFlt1/PlGF ratio was −0.698 (−1.064 to −0.332).
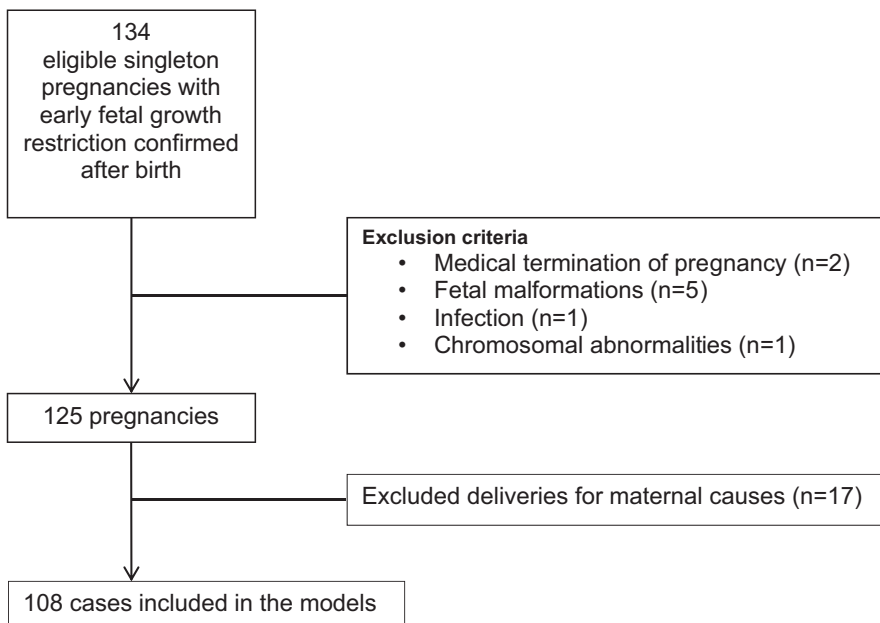
FLOWCHART 1 Patients included in the study.

TABLE 1 Description of the study population (early FGR pregnancies) regarding maternal, pregnancy, delivery and newborn characteristics.

	Early FGR (n = 125)
Maternal characteristics	
Age at delivery (years), mean (SD)	31.9 (5.9)
Primipara, n (%)	57 (45.6)
Chronic hypertension, n (%)	9 (7.2)
Pregnancy characteristics	
Tobacco smoking during pregnancy, n (%)	18 (14.4)
Gestational diabetes, n (%)	13 (10.4)
Gestational hypertension, n (%)	8 (6.4)
Preeclampsia, n (%)	16 (12.8)
Gestational age at FGR diagnosis mean (SD)	27.2 (3.7)
Severe FGR, n (%)	101 (80.8)
sFlt1/PlGF ratio, mean (SD)	91.2 (148.7)
Positive sFlt1/PlGF ratio, n (%)	35 (28)
Gestational age of sFlt1/PlGF ratio, mean (SD)	30.4 (3.6)
Delivery characteristics	
Gestational age (in weeks), mean (SD)	34.8 (3.7)
Spontaneous onset of labor, n (%)	15 (12)
Indication to terminate pregnancy, n = 110	
Fetal demise	6 (4.8)
Fetal BPS <4/8	21 (16.8)
Maternal cause	17 (13.6)
Absent or reversed a-wave in DV	13 (10.4)
Reversed UA-EDF	2 (1.6)
Absent UA-EDF	8 (6.4)
CPR <5th centile	5 (4)
MCA-PI <5th centile	3 (2.4)
Gestational age >37 weeks	35 (28)
Type of delivery, n (%)	
Vaginal	53 (42.4)
Cesarean	72 (57.6)
Newborn characteristics	
Live-born	120 (95.2)
Sex, n (%)	
Male	58 (47.5)
Female	64 (52.5)
Birthweight (g), median (IQR)	1922 (1070)
Birthweight percentile, mean (SD)	1.8 (2.24)
Admission to the NICU, n (%)	49 (42.2)
Neonatal death, n = 126, n (%)	5 (5.7)

Abbreviations: BPS, biophysical profile score; CPR, cerebroplacental ratio; FGR, fetal growth restriction; IQR, interquartile range; MCA-PI, middle cerebral artery pulsatility index; NICU, neonatal intensive care unit; PlGF, placental growth factor; sFlt1, soluble fms-like tyrosine kinase 1; UA-EDF, umbilical artery-end diastolic flow.

Analyzing time to event data (latency for delivery/fetal demise) with adjusted Cox regression, early FGR with a positive ratio confers a significantly positive HR for earlier delivery or fetal demise with a hazard ratio of 9.869 (5.061–19.243), even after controlling for the previously described confounders. This survival model is described in Table S3. The respective Kaplan–Meier curve is represented in Figure 2 according to ratio positivity showing significantly shorter survival times (time for delivery/fetal demise) for the positive ratio group.

A receiver operating characteristic (ROC) analysis for the outcome of delivery for fetal reasons in the following week shows that the sFlt1/PlGF ratio has a good predictive value for this outcome, with an area under the curve (AUC) of 0.847 ± 0.06 (95% CI 0.731–0.962) (Figure 3).
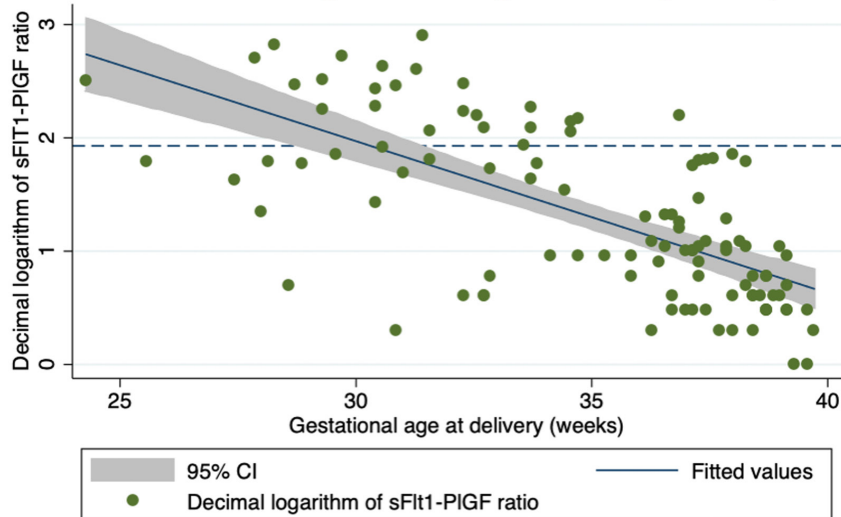
4 | DISCUSSION

In this study, a higher sFlt1/PlGF ratio at diagnosis of early FGR was correlated with a shorter latency to delivery and an earlier gestational age at delivery, even after controlling for confounders such as preeclampsia, gestational age at ratio sampling, maternal age and smoking during pregnancy.

In terms of population characteristics, as seen in Table 1, our unit has a higher proportion of severe (80.8%) vs non-severe (19.2%) cases of early FGR since it is a tertiary reference center for this condition, and most non-severe FGRs are managed successfully in other centers.

The link between early FGR and hypertensive complications of pregnancy is well established and has been attributed to the common pathophysiology of both syndromes.[3] Despite this, our cohort had a low absolute incidence of hypertensive complications (6.4% incidence of gestational hypertension and 12.8% incidence of preeclampsia) when compared with other studies that report incidences of preeclampsia of around 50%.[26] Our results are closer, although still lower than the 26% incidence of preeclampsia described in a cohort of early FGR pregnancies without absent/reverse umbilical artery-end diastolic flow (UA-EDF) and without ductus venosus changes at diagnosis.[27] The reason for this low incidence of hypertensive complications of pregnancy in FGR when compared with previous reports is not completely clear. Some studies have reported a particularly low incidence of preeclampsia in Mediterranean countries, questioning the influence of the Mediterranean climate or diet in decreasing the risk for this condition.[33] Additionally, in our cohort, in 35 pregnancies the decision to deliver was made due to gestational age >37 gestational weeks (with normal fetal Dopplers). In these cases, although diagnostic criteria were compatible with early FGR (EFW <3rd centile or mean uterine artery PI >95th centile) the fetuses might have behaved more like small-for gestational age than early FGRs, which might explain the lower incidence of preeclampsia.
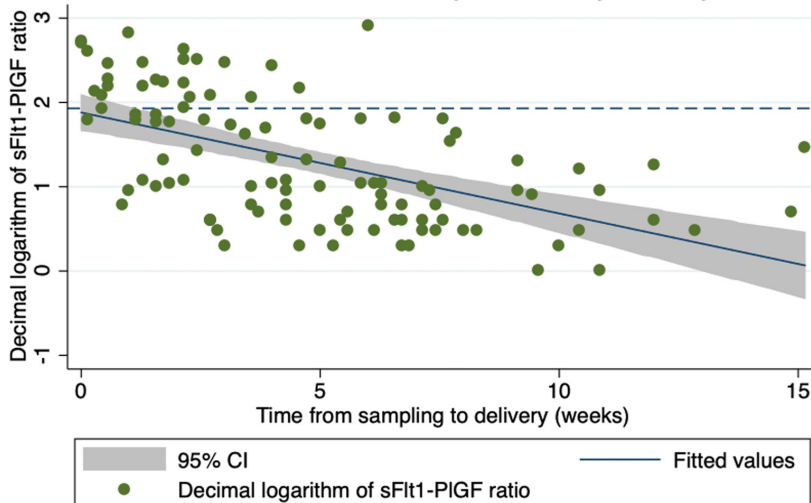
Mean gestational age at diagnosis of FGR in our cohort (27.2 gestational weeks) was similar to previous reports.[26,27] In agreement with

FIGURE 1 (A) Decimal logarithm of the sFlt1/PlGF ratio and gestational age at delivery in early fetal growth restriction (FGR). Adjusted linear regression with 95% confidence interval (excluding delivery for maternal indication). (B) Decimal logarithm of the sFlt1/PlGF ratio and latency to delivery in early FGR. Adjusted linear regression with 95% confidence interval (excluding delivery for maternal indications).

previous studies, newborns with early FGR were born prematurely (mean gestational age at delivery 34.8 ± 3.7 weeks), with low birthweight (median 1922 g, IQR 1070) and had a significant probability of being admitted to the NICU (42.2%). Comparing these neonatal outcomes with a study by Garcia-Manau et al.[27] that looks at outcomes of early FGR stratified by fetal Doppler findings at diagnosis, they were similar to what is described for patients in their stage I (fetuses without absent or reverse UA-EDF or ductus venosus changes); these results are also concordant to what is described in terms of neonatal outcomes in another cohort of early FGR pregnancies by Quezada et al.[26] The incidence of fetal demise in our cohort was 4.8% ($n = 6$), which is similar to other studies.[12] Reasons for planning a preterm delivery (through induction of labor or cesarean section) were concordant with previous literature, with maternal indications, changes in ductus venosus and fetal BPS <4/8 being the most common causes.[10]

Latency from ratio sampling to delivery was significantly lower in the group with a ratio >85 (13.3 vs 39.9 days), which is very similar

to what was previously reported in the study from Quezada et al. mentioned above.[26]

The sFlt1/PlGF ratio at diagnosis of FGR was positive in around one-quarter of our population (28%), which is consistent with previous studies.[23] In particular, the study from Garcia-Manau et al.[27] reports a positive ratio in 21.5% of patients with early FGR in stage I. Quezada et al.,[26] however, in a cohort of early FGR pregnancies, reported an even higher rate (75% positive sFlt1/PlGF ratios), with a mean ratio value of 196 (whereas in our cohort, mean sFlt1/PlGF was 91.2). We hypothesize that our population is more similar to the stage I population described in the former study by Garcia-Manau et al.[27]

Looking at the correlation between sFlt1/PlGF ratio and latency to delivery/fetal demise, it was clear that a higher ratio predicts a faster fetal deterioration and an earlier delivery/fetal demise for early FGR fetuses, even after excluding deliveries for maternal indications and controlling for confounders (occurrence

of preeclampsia, gestational age at time of ratio test, maternal age and smoking during pregnancy) (Figures 1A,B and 2, Tables S1A,B and S3). When considering the cut-off described in the literature for ratio positivity, a positive ratio significantly correlates with an earlier delivery/fetal demise and shorter latency to delivery/fetal demise (Table S2). Additionally, the sFlt1/PlGF ratio seems to be a good predictor of delivery for fetal deterioration in the following week (Figure 3).

This can be explained by the phenotype of early FGR and its association with severely impaired placentation, vasculopathy and an anti-angiogenic environment.[3,16,32] We hypothesize that a higher sFlt1/PlGF ratio represents a more marked anti-angiogenic environment, translating to a more severely impaired placenta. This would mean less oxygen and nutrients being available to the fetus, with a consequent decrease in fetal reserve and faster clinical deterioration measurable through

FIGURE 2   Kaplan–Meier survivor function for delivery or fetal demise in early fetal growth restriction, by positive sFlt1/PlGF ratio. Adjusted survival analysis (excluding delivery for maternal indication). Log rank test: $P<0.001$.

fetal Doppler changes (organ-sparing mechanisms) and ultimately fetal demise.

The counseling and monitoring of patients with FGR can be very challenging, particularly in pregnancies complicated by early FGR, where the velocity of fetal deterioration is hard to predict.[16] The sFlt1/PlGF ratio could be a useful tool to predict fetal deterioration in this setting.

It should be noted that this study has some important limitations. First, this is a retrospective cohort study with a limited sample size; on the other hand, clinicians were not blinded to the results of the sFlt1/PlGF ratio. Although these results should not change the management of these pregnancies and they were not an indication to expedite delivery according to the unit's protocol, they could have introduced a potential bias in the clinicians towards more intensive surveillance of these patients and consequently earlier identification of fetal deterioration. Additionally, we were unable to control for two other important confounders – maternal obesity, and fetal status at the time of diagnosis. The latter is particularly relevant, since it is unclear whether the sFlt1/PlGF ratio improved the predictive value for shorter latency to delivery/fetal demise when compared with or added to fetal status at diagnosis.

Lastly, and although in this study we controlled for the occurrence of preeclampsia to try to isolate the accuracy of the sFlt1/PlGF ratio in predicting fetal deterioration, we are aware that this can be seen as an artificial division, since some authors postulate that FGR and pre-eclampsia are part of a single angiogenic placental syndrome.[33]

Despite these limitations, this is, to the authors' knowledge, the first study to assess the influence of the sFlt1/PlGF ratio in fetal deterioration in FGR (controlling for confounders).

Further studies are needed to test sFlt1/PlGF ratio incorporation in clinical algorithms, particularly for early FGR monitoring. Future studies focusing on the influence of sFlt1/PlGF ratio in fetal deterioration should control for preeclampsia and other maternal indications for delivery.
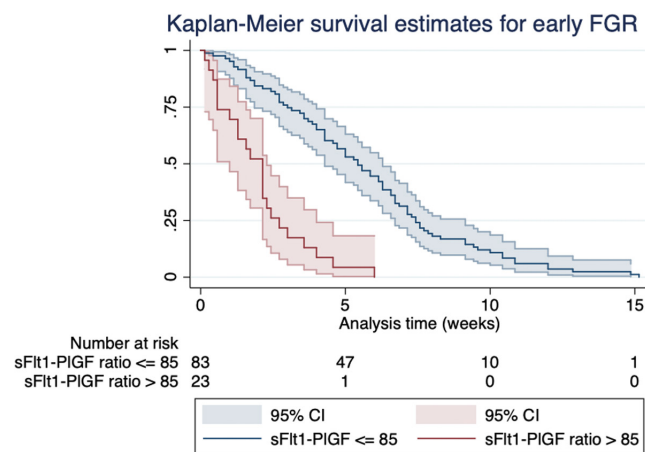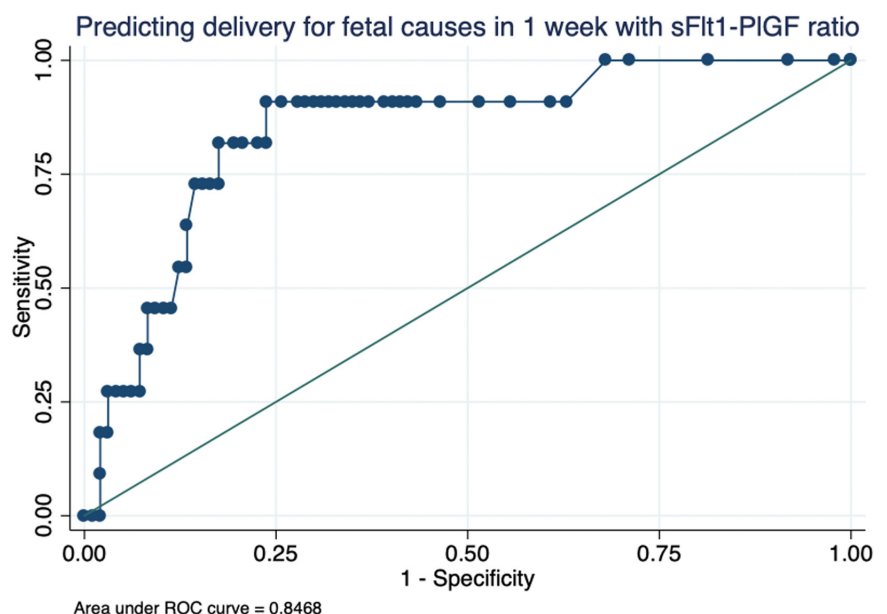
FIGURE 3   Receiver-operating characteristic analysis testing the performance of sFlt1/PlGF ratio in predicting delivery for fetal reasons in the following week.

5 | CONCLUSION

This study shows that a high sFlt1/PlGF ratio at the time of diagnosis of FGR is correlated with a significantly faster fetal deterioration rate in early FGR. Consequently, the ratio could be a useful tool to incorporate in clinical algorithms for the management of this syndrome.

AUTHOR CONTRIBUTIONS

CR, MV, AC and AM were responsible for the conception and planning of the article. CR, SB and TM contributed to literature review, data acquisition and drafting of the article. CR performed the statistical analysis. MV, AC and AM revised the article critically for important intellectual content. All co-authors reviewed and approved the final article.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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REFERENCES

1. Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of preeclampsia. *Obstet Gynecol Annu*. 1972;1:177-191.
2. Labarrere C, Althabe O. Chronic villitis of unknown etiology and maternal arterial lesions in preeclamptic pregnancies. *Eur J Obstet Gynecol Reprod Biol*. 1985;20:1-11.
3. Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. *Br J Obstet Gynaecol*. 1986;93:1049-1059.
4. Luttun A, Carmeliet P. Soluble. VEGF receptor Flt1: the elusive preeclampsia factor discovered? *J Clin Invest*. 2003;111:600-602.
5. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med*. 2004;12(350):672-683.
6. Kulkarni AV, Mehendale SS, Yadav HR, Kilari AS, Taralekar VS, Joshi SR. Circulating angiogenic factors and their association with birth outcomes in preeclampsia. *Hypertens Res*. 2010;33:561-567.
7. Verlohren S, Herraiz I, Lapaire O, et al. New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia. *Hypertension*. 2014;63:346-352.
8. Cerdeira AS, O'Sullivan J, Ohuma EO, et al. Randomized interventional study on prediction of preeclampsia/eclampsia in women with suspected preeclampsia: INSPIRE. *Hypertension*. 2019;74:983-990.
9. Ganzevoort W, Thornton JG, Marlow N, et al. Comparative analysis of 2-year outcomes in GRIT and TRUFFLE trials. *Ultrasound Obstet Gynecol*. 2020;55:68-74.
10. Seravalli V, Baschat AA. A uniform management approach to optimize outcome in fetal growth restriction. *Obstet Gynecol Clin North Am*. 2015;42:275-288.
11. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics, Society for Maternal-Fetal Medicine Publications Committee. Fetal growth restriction: ACOG practice bulletin, number 227. *Obstet Gynecol*. 2021;137:e16-e28.
12. Ganzevoort W, Mensing van Charante N, Thilaganathan B, et al. How to monitor pregnancies complicated by fetal growth restriction and delivery below 32 weeks: a post-hoc sensitivity analysis of the TRUFFLE-study. *Ultrasound Obstet Gynecol*. 2017;49:769-777.
13. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. *Fetal Diagn Ther*. 2014;36:86-98.
14. Lees CC, Stampalija T, Baschat AA, et al. ISUOG practice guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol*. 2020;56:298-312.
15. Melamed N, Baschat AA, Yinon Y, Athanasiadis A, Mecacci F, Figueras F. FIGO (International Federation of Gynecology and Obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. *Int J Gynecol Obstet*. 2021;152(Suppl. 1):3-57.
16. Turan OM, Turan S, Gungor S, et al. Progression of Doppler abnormalities in intrauterine growth restriction. *Ultrasound Obstet Gynecol*. 2008;32:160-167.
17. Schoofs K, Grittner U, Engels T, et al. The importance of repeated measurements of the sFlt1/PLGF ratio for the prediction of preeclampsia and intrauterine growth restriction. *J Perinat Med*. 2014;42:61-68.
18. Li SW, Ling Y, Jin S, et al. Expression of soluble vascular endothelial growth factor receptor-1 and placental growth factor in fetal growth restriction cases and intervention effect of tetramethylpyrazine. *Asian Pac J Trop Med*. 2014;7:663-667.
19. Sovio U, Goulding N, McBride N, et al. A maternal serum metabolite ratio predicts fetal growth restriction at term. *Nat Med*. 2020;26:348-353.
20. Gaccioli F, Sovio U, Cook E, Hund M, Charnock-Jones DS, Smith GCS. Screening for fetal growth restriction using ultrasound and the sFLT1/PlGF ratio in nulliparous women: a prospective cohort study. *Lancet Child Adolesc Health*. 2018;2:569-581.
21. Herraiz I, Quezada MS, Rodriguez-Calvo J, Gómez-Montes E, Villalaín C, Galindo A. Longitudinal change of sFlt-1/PlGF ratio in singleton pregnancy with early-onset fetal growth restriction. *Ultrasound Obstet Gynecol*. 2018;52:631-638.
22. Sharp A, Jackson R, Cornforth C, et al. A prediction model for short-term neonatal outcomes in severe early-onset fetal growth restriction. *Eur J Obstet Gynecol Reprod Biol*. 2019;241:109-118.
23. Lobmaier SM, Figueras F, Mercade I, et al. Angiogenic factors vs Doppler surveillance in the prediction of adverse outcome among late-pregnancy small-for-gestational-age fetuses. *Ultrasound Obstet Gynecol*. 2014;43:533-540.
24. Graupner O, Lobmaier SM, Ortiz JU, Karge A, Kuschel B. sFlt-1/PlGF ratio for the prediction of the time of delivery. *Arch Gynecol Obstet*. 2018;298:567-577.
25. Shinohara S, Uchida Y, Kasai M, Sunami R. Association between the high soluble fms-like tyrosine kinase-1 to placental growth factor ratio and adverse outcomes in asymptomatic women with early-onset fetal growth restriction. *Hypertens Pregnancy*. 2017;36:269-275.
26. Quezada MS, Rodríguez-Calvo J, Villalaín C, Gómez-Arriaga PI, Galindo A, Herraiz I. sFlt-1/PlGF ratio and timing of delivery in early-onset fetal growth restriction with antegrade umbilical artery flow. *Ultrasound Obstet Gynecol*. 2020;56:549-556.
27. Witwicki J, Chaberek K, Szymecka-Samaha N, Krysiak A, Pietruski P, Kosińska-Kaczyńska K. sFlt-1/PlGF ratio in prediction of short-term

neonatal outcome of small for gestational age neonates. *Children (Basel)*. 2021;8(8):718.

28. Jääskeläinen T, Heinonen S, Hämäläinen E, et al. Angiogenic profile in the Finnish genetics of pre-eclampsia consortium (FINNPEC) cohort. *Pregnancy Hypertens*. 2018;14:252-259.

29. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol*. 2016;48:333-339.

30. Stepan H, Herraiz I, Schlembach D, et al. Implementation of the sFlt1/PlGF ratio for prediction and diagnosis of preeclampsia in singleton pregnancy: implications for clinical practice. *Ultrasound Obstet Gynecol*. 2015;45:241-246.

31. American College of Obstetricians and Gynecologists. *Hypertension in Pregnancy*. American College of Obstetricians and Gynecologists; 2018:89.

32. Povoa AM, Costa F, Rodrigues T, Patricio B, Cardoso F. Prevalence of hypertension during pregnancy in Portugal. *Hypertens Pregnancy*. 2008;27:279-284.

33. Stepan H, Hund M, Andraczek T. Combining biomarkers to predict Pregnancy complications and redefine preeclampsia: the Angiogenic-placental syndrome. *Hypertension*. 2020;75:918-926.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Palma dos Reis CR, Brás S, Meneses T, Cerdeira AS, Vatish M, Martins AT. The sFlt1/PlGF ratio predicts faster fetal deterioration in early fetal growth restriction: A historical cohort study. *Acta Obstet Gynecol Scand*. 2023;00:1-9. doi:10.1111/aogs.14546