OBSTETRICS

The ratio of soluble fms-like tyrosine kinase 1 to placental growth factor predicts time to delivery and mode of birth in patients with suspected preeclampsia: a secondary analysis of the INSPIRE trial

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BACKGROUND: The ratio of soluble fms-like tyrosine kinase 1 to placental growth factor is a useful biomarker for preeclampsia. Since it is a measure of placental dysfunction, it could also be a predictor of clinical deterioration and fetal tolerance to intrapartum stress.

OBJECTIVE: We tested the hypothesis that soluble fms-like tyrosine kinase 1 to placental growth factor ratio predicts time to delivery. Secondary objectives were to examine associations between the soluble fms-like tyrosine kinase 1 to placental growth factor ratio and mode of birth, fetal distress, need for labor induction, and birthweight *z* score.

STUDY DESIGN: Secondary analysis of the INSPIRE trial, a randomized interventional study on prediction of preeclampsia/eclampsia in which women with suspected preeclampsia were recruited and their blood soluble fms-like tyrosine kinase 1 to placental growth factor ratio was assessed. We stratified participants into 3 groups according to the ratio result: category 1 (soluble fms-like tyrosine kinase 1 to placental growth factor $\leq$38); category 2 (soluble fms-like tyrosine kinase 1 to placental growth factor $>$38 and $<$85); and category 3 (soluble fms-like tyrosine kinase 1 to placental growth factor $\geq$85). We modeled time from soluble fms-like tyrosine kinase 1 to placental growth factor determination to delivery using Kaplan-Meier curves and compared the 3 ratio categories adjusting for gestational age at soluble fms-like tyrosine kinase 1 to placental growth factor determination and trial arm with Cox regression. The association between ratio category and mode of delivery, induction of labor, and fetal distress was assessed using a multivariable logistic regression adjusting for gestational age at sampling and trial arm. The association between birthweight *z* score and soluble fms-like tyrosine kinase 1 to placental growth factor ratio was evaluated using multiple linear regression. Subgroup analysis was conducted in women with no preeclampsia and spontaneous onset of labor; women with preeclampsia; and participants in the nonreveal arm.

RESULTS: Higher ratio categories were associated with a shorter latency from soluble fms-like tyrosine kinase 1 to placental growth factor determination to delivery (37 vs 13 vs 10 days for ratios categories 1—3 respectively), hazards ratio for category 3 ratio of 5.64 (95% confidence interval 4.06—7.84, $P<.001$). A soluble fms-like tyrosine kinase 1 to placental growth factor ratio $\geq$85 had specificity of 92.7% (95% confidence interval 89.0%—95.1%) and sensitivity of 54.72% (95% confidence interval, 41.3—69.5) for prediction of preeclampsia indicated delivery within 2 weeks. A ratio category 3 was also associated with decreased odds of spontaneous vaginal delivery (Odds ratio [OR] 0.47, 95% confidence interval 0.25—0.89); an almost 6-fold increased risk of emergency cesarean section (OR 5.89, 95% confidence interval 3.05—11.21); and a 2-fold increased risk for intrapartum fetal distress requiring operative delivery or cesarean section (OR 3.04, 95% confidence interval 1.53—6.05) when compared to patients with ratios $\leq$38. Higher ratio categories were also associated with higher odds of induction of labor when compared to ratios category 1 (category 2, OR 2.20, 95% confidence interval 1.02—4.76; category 3, OR 6.0, 95% confidence interval 2.01—17.93); and lower median birthweight *z* score. Within subgroups of women a) without preeclampsia and with spontaneous onset of labor and b) women with preeclampsia, the log ratio was significantly higher in patients requiring intervention for fetal distress or failure to progress compared to those who delivered vaginaly without intervention. In the subset of women with no preeclampsia and spontaneous onset of labor, those who required intervention for fetal distress or failure to progress had a significantly higher log ratio than those who delivered vaginaly without needing intervention.

CONCLUSION: The soluble fms-like tyrosine kinase 1 to placental growth factor ratio might be helpful in risk stratification of patients who present with suspected preeclampsia regarding clinical deterioration, intrapartum fetal distress, and mode of birth (including the need for intervention in labor).

Key words: intrapartum fetal distress, mode of delivery, neonatal birthweight, sFLT1/PLGF ratio, time to delivery

Introduction

Human placentation requires extensive angiogenesis for the establishment of a suitable vascular network to support fetal development. When placentation is impaired, the crucial balance between proangiogenic factors (such as placental growth factor [PlGF]) and anti-angiogenic factors (such as soluble fms-

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AJOG at a Glance

Why was this study conducted?

To assess if the soluble fms-like tyrosine kinase 1 placental growth factor (sFLT1/PLGF) ratio has a clinically useful role in the prediction of birth outcomes in women with suspected preeclampsia.

Key findings

In a population of women with suspected preeclampsia, an sFLT1/PLGF ratio ≥85 is associated with a 6-fold increased risk for emergency cesarean section and a 3-fold increased risk for intrapartum fetal distress. It is also associated with an increased risk for earlier delivery and lower birthweight *z* score.

What does this add to what is known?

The sFLT1/PLGF ratio might be helpful in risk stratification of women with suspected preeclampsia regarding birth outcomes, namely clinical deterioration (latency to delivery), intrapartum fetal distress, and mode of delivery (increased risk of intervention).

like tyrosine kinase 1 [sFLT1]) is disrupted.[1] Consequently, the ratio between sFLT1 and PLGF has been used in clinical practice as a biomarker that correlates with adverse pregnancy outcomes associated with inadequate placentation such as preeclampsia,[2] fetal growth restriction,[3,4] and preterm delivery.[5,6]

The diagnostic stength of the sFLT1/PLGF ratio is primarily based on its high negative predictive value (NPV): a ratio of ≤38 confers a NPV of 99.3% (95% confidence interval [CI], 97.9%−99.9%) for the occurrence of preeclampsia within 7 days.[7] Its positive predictive value could also be of interest: higher sFLT1/PLGF levels have been shown to correlate with the development of preeclampsia within the next couple of days in patients who present with signs and symptoms of the disease. In patients with an established diagnosis of preeclampsia or gestational hypertension, high sFLT1/PLGF levels are associated with worse pregnancy outcomes.[2,5,7,8] In addition, categorization into high risk (ratio ≥85), intermediate risk (38−85), and low-risk groups (≤38) affords accurate stratification for the occurrence of fetal and maternal adverse outcomes.[8,9]

Since an increased sFLT1/PLGF ratio is correlated with placentatal dysfunction, it has been postulated that it could also have important implications for risk stratification around birth.[10,11] Hypothesized associations between deficient placentation and prematurity are based on data that suggest that up to 30% of placentas from women with spontaneous preterm deliveries have lesions compatible with maternal vascular underperfusion and deficient remodeling of the spiral arteries.[12] Additionally, impaired placentation is thought to be associated with local hypoxia[1] and inadequate fetal oxygenation with lower fetal tolerance to stress, leading to higher rates of intrapartum fetal distress. These adverse changes lead, in turn, to the need for operative delivery or emergency cesarean section.[13] Given the increased maternal and perinatal morbidity associated with these deliveries,[14,15] risk stratification and prediction of such interventions would be desirable for patients and clinicians.[16]

In this study we test the hypothesis of an association between the sFLT1/PLGF ratio and delivery outcomes, namely time from ratio determination to delivery; and the need for operative delivery or emergency cesarean section. A better understanding of this relationship may allow better risk stratification and patient counseling. To test this we performed a secondary analysis of data from the Randomized interventional study in prediction of preeclampsia/eclampsia in women with suspected preeclampsia (INSPIRE) trial, which involved measurement of the sFLT1/PLGF ratio in women with suspected preeclampsia.[17]

Material and methods

This was a secondary analysis of the INSPIRE trial,[17] a randomized interventional study on prediction of developing preeclampsia or eclampsia in women with suspected preeclampsia (ISRCTN87470468). In INSPIRE, women presenting with signs and symptoms of preeclampsia (ie, with suspected preeclampsia) were recruited, and blood samples for analysis of the sFLT1/PLGF ratio collected alongside the bloods requested by the attending physician. They were then randomized into 2 groups: a reveal arm, where clinicians were told the result of the ratio and could take this into account in clinical management; and a nonreveal arm, where the clinicians were blinded to the results. Full details have been described elsewhere.[17] In the present manuscript we analyze data from this trial, specifically we examine the relationship between the sFLT1/PLGF ratio and delivery outcomes. The ratio was defined according to the literature in 3 groups: category 1 (sFLT1/PLGF ≤38); category 2 (sFLT1/PLGF >38 and <85); and category 3 (sFLT1/PLGF ratio ≥85).

Our primary outcome of interest was the time from the blood test (sFLT/PLGF ratio) to delivery. Secondary outcomes included: mode of delivery, classification of cesarean section, fetal distress leading to operative delivery or cesarean section, induction of labor (IOL), birthweight, birthweight *z* score, and small for gestational age (SGA). Preeclampsia-related delivery was any delivery indicated for preeclampsia or related signs and symptoms, adjudicated by 2 obstetricians blinded to the sFLT1/PLGF results. According to the National Institute for Health and Excellence guidelines, cesarean sections were classified as category 1 (immediate threat to maternal or fetal life), category 2 (maternal or fetal compromise, ie, not immediately life-threatening), category 3 (no maternal

or fetal compromise but early birth is necessary), or category 4 (birth scheduled to suit the mother and healthcare provider). For analyses, we broadly classified into emergency (categories 1−3) or planned (category 4) cesarean sections. SGA was defined as a birth weight <10th centile for gestational age adjusted for newborn sex (Viewpoint software, GE Healthcare, United Kingdom).

Ethical approval

This study was performed in accordance with the 1964 Helsinki declaration and its later amendments, and national ethics committee approval (National Research Ethics Committee South Central−Oxford B, number 15/SC/0126). All participating women gave written informed consent.

Statistical analysis

Data is presented for the entire population and analysis is adjusted for trial arm and gestational age at ratio sampling. Mean and standard deviation or median and interquartile range (IQR) were used to report continuous data as appropriate. Categorical data were presented as frequency and percentages. The chi-square test of association was used to compare binary or categorical variables and the Student's *t* test or Wilcoxon rank sum test to compare differences in means of continuous variables as appropriate. Birthweight *z* scores were calculated according to INTERGROWTH-21st newborn standards.[18] Kaplan-Meier survival curves were used to graphically present time elapsed from ratio determination to delivery according to ratio categories, using days from ratio determination to delivery as time-to-event data. A Cox model was performed to assess the influence of ratio category on this time-to-event data (using as reference the lower ratio category, sFLT1/PLGF ≤38) controlling for gestational age at ratio determination and trial arm. A subanalysis of this model was performed in women with no preeclampsia and spontaneous onset of labor. A receiver operating characteristic (ROC) analysis for the prediction of delivery in the 2 following weeks was performed for sFLT1/PLGF ratio, sFLT1 alone and PlGF alone; the areas under the curve for each were compared using a test of equality of ROC areas (roccomp). To test the association of ratio category on the outcomes spontaneous vaginal delivery (SVD), elective (planned) cesarean section, emergency cesarean section, fetal distress, and IOL, a multivariable logistic model was fit controlling for trial arm and gestational age at ratio determination. To test the effect of ratio category on birthweight *z* score, a multiple linear regression model was built, adjusting for trial arm and gestational age at ratio sampling. We also performed subanalyses to assess the correlation between the sFLT1/PLGF ratio and SVD, delivery for fetal distress, and delivery for failure to progress in women with preeclampsia; in women without preeclampsia, who had spontaneous onset of labor; and participants in the nonreveal arm of the trial. For these analyses, a logarithmic transformation of the sFLT1/PLGF ratio (log ratio) was performed, and differences in mean log ratios were compared using *t* test.

Two-sided *P* values of <.05 were considered for statistical significance, and 2-sided CIs of 95% are reported. STATA version 13 (StataCorp, USA) was used for statistical analysis.

Results

Over the study period, 370 women were included. Table 1 shows the baseline characteristics of the study's participants according to the value of sFLT1/PLGF ratio at recruitment. The gestational age at recruitment was higher in patients with category 2 ratios [35.7 (IQR 34.6; 36.7)], compared to those with category 1 [33.6 (IQR 30.6; 35.6)] (*P*<.001), but similar between patients with category 3 [34.9 (IQR 32.7; 35.9) compared to those with category 1. There were no differences in maternal age at recruitment, body mass index, smoking status, and ethnicity. As expected, patients with higher ratios had higher median systolic and diastolic blood pressures and were more frequently nulliparus (known risk factors for preeclampsia[19]) (*P*<.001). Table 2 shows the delivery outcomes of the participants according to their sFLT1/PLGF ratio. The population characteristics and delivery outcomes by trial arm are presented in Supplemental Tables 1 and 2.

Time to delivery

The time from the blood test (sFLT/PLGF ratio) to any delivery was different between the 3 ratio categories: for ratios ≤38, the median time to delivery was 37 (IQR 24; 59) days, whilst for ratios categories 2 and 3 it was 13 (IQR 8; 23.5) and 10 (IQR 6; 20) days, respectively (Table 2). These results are represented graphically in Kaplan-Meier survival curves according to ratio category (Figure 1). A Cox proportional hazards model confirmed these findings, showing that higher ratio categories are significantly associated with an increased risk for earlier birth after controlling for gestational age at ratio sampling and trial arm (for ratio category 2, hazard ratio 1.99 (95% CI 1.47; 2.71, *P*<.001*); and for ratio category 3, hazard ratio 5.64 (95% CI 4.06; 7.84, *P*<.001*) (Table 3). A significant correlation persisted in a subgroup analysis of women without preeclampsia and who experienced spontaneous onset of labor (Supplemental Table 5).

The ratio predicted any delivery within 2 weeks with an area under the curve (AUC) of 0.819 (95% CI, 0.799−0.829)]. A test of equality of ROC areas showed that sFLT1 alone had a significantly superior predictive ability compared to PlGF alone (AUC 0.846 vs AUC 0.754, *P*<.01) and to the sFLT1/PLGF ratio (AUC 0.846 vs AUC 0.819, *P*=.03).

When considering preeclampsia-indicated deliveries, the ratio predicted delivery within 2 weeks with an AUC of 0.89 (95% CI, 0.86−0.94)], Figure 2. sFLT1 alone was superior to PlGF alone (AUC 0.899 vs AUC 0.836, *P*=.01) (Figure 2) and isolated sFLT1 was similar to the sFLT1/PLGF ratio (AUC 0.899 vs AUC 0.896, *P*=.772). A higher category ratio (sFLT1/PLGF ≥85) showed a sensitivity 54.72% (95% CI, 41.3−69.5), specificity 92.74% (95% CI, 89.0−95.1), and AUC=0.73 (95% CI, 0.67−0.81) for prediction of preeclampsia-indicated delivery in the 2

TABLE 1
Characteristics of the study population according to their sFLT1/PLGF ratio category

Population characteristics (n=370)	sFLT1/PLGF ≤38 (n=257)	sFLT1/PLGF 38–85 (n=60)	sFLT1/PLGF ≥85 (n=53)	Statistical significance *P* value
GA at recruitment (wk) Median (IQR)	33.6 (30.6; 35.6)	35.7 (34.6; 36.4)	34.9 (32.7; 35.9)	*P*<.001[a,c]
				P=.06[b]
Maternal age at recruitment (y) Median (IQR)	30.5 (26.7; 34.8)	32.0 (28.8; 37.0)	31.6 (28.2; 35.8)	*P*=.098[a]
				P=.400[b]
BMI Median (IQR)	27.6 (24.1; 32.4)	26.1 (22.6; 31.6)	26.5 (24; 31.3)	*P*=.514[a]
				P=.247[b]
Parity n (%)				*P*<.001[b,c]
Nulliparous	102 (39.7%)	36 (60%)	42 (79.2%)	
Multiparous	155 (60.3%)	24 (40%)	11 (20.8%)	
Smoking status n (%)				*P*=.283
Current smoker	28 (10.9%)	2 (3.3%)	3 (5.7%)	
Never smoker	150 (58.3%)	39 (65%)	36 (67.9%)	
Previous smoker	79 (30.7%)	19 (31.7%)	14 (26.4%)	
Ethnicity n (%)				*P*=.497
Caucasian	231 (89.9%)	55 (91.7%)	46 (86.8%)	
Other	24 (9.3%)	4 (6.7%)	5 (9.4%)	
Highest systolic BP at presentation Median (IQR)	128.5 (118; 140)	142 (130; 157)	145 (131; 160)	*P*<.001[a,c]
				P<.001[b,c]
Highest diastolic BP at presentation Median (IQR)	79 (70; 90)	90 (85; 97)	92 (86; 100)	*P*<.001[a,c]
				P<.001[b,c]

For ethnicity, n=5 values were not recorded.

BMI, body mass index; *BP*, blood pressure; *GA*, gestational age; *IQR*, interquartile range; *PLGF*, placental growth factor; *sFLT1*, soluble fms-like tyrosine kinase 1.

[a] Test between groups 1 and 2; [b] Test between groups 1 and 3; [c] *P*<.001.

following weeks, while a ratio <38 had a sensitivity of 98.4% (95% CI 96.1–99.6), specificity of 42.5% (95% CI 33.2%–52.1%), and AUC 0.70 (0.66–0.75) for the same outcome (Supplemental Table 6).

Compared to patients with ratios ≤38, patients with ratios ≥85 had 35-fold increased risk of needing preeclampsia-indicated delivery within 2 weeks (risk ratio 35.2 [95% CI, 12.9–95.8]).

Mode of delivery

The mode of delivery was significantly different between ratio categories (*P*<.001*, Table 2).

Patients with ratios ≥85 had the lowest rate of SVDs (32.1%), followed by participants with category 2 ratios (43.3%). Participants with ratios ≤38 had the highest rate of SVD (47.9%) (Table 2, Figure 3). This finding was corroborated by logistic regression, with ratios ≥85 conferring an adjusted odds ratio of 0.47 (95% CI 0.25; 0.89) for SVD after controlling for gestational age at ratio test and trial arm. This correlation was still significant after further adjusting for parity (Supplemental Table 7).

There was no difference in the rate of operative vaginal deliveries (Table 2, Figure 3). There were no planned cesarean sections (ie, elective or category 4) in patients with ratios ≥85. Patients with ratios category 2 had the second lowest rate of planned cesarean sections (15%), and this mode of delivery was more frequent in patients with ratios ≤38 (19.8%). In a logistic regression model, a ratio ≥85 was significantly associated with lower odds of elective (planned) cesarean section (odds ratio [OR] 0.08, 95% CI 0.01; 0.59) after adjusting for gestational age at time of ratio test and trial arm.

In contrast, emergency cesarean sections (ie, Cat 1–3) were significantly more frequent in higher ratio groups: their incidence was 15.2% for ratios ≤38; 31.7% for ratios >38 and <85; and 49% for ratios ≥85 (Table 2, Figure 3). The frequency of a category 1 cesarean section (the most emergent of them all) was 3.1 times higher in patients with high ratios (≥85) compared to those with low ratios (≤38) (2.3% vs 7.5%) (Table 2). Compared to patients with ratios ≤38, patients

TABLE 2
Pregnancy outcomes of the participants according to their sFLT1/PLGF ratio category

Pregnancy outcomes	sFLT1/PLGF ≤38 (n=257)	sFLT1/PLGF 38–85 (n=60)	sFLT1/PLGF ≥85 (n=53)	Statistical significance *P* value
GA at delivery (wk) Median (IQR)	39 (37.9; 40)	37.5 (37.1; 38.1)	36.6 (34.3; 37.1)	*P*<.001[a,c]
				P<.001[b,c]
Time to delivery (d) Median (IQR)	37 (24; 59)	13 (8; 23.5)	10 (6; 20)	*P*<.001[a,c]
				P<.001[b,c]
Time to delivery				*P*<.001[c]
<1 wk n (%)	4 (1.6%)	10 (16.7%)	14 (26.4%)	
≥1 wk and<2 wk n (%)	15 (5.8%)	21 (35%)	20 (37.7%)	
≥2 wk n (%)	238 (92.6%)	29 (48.3%)	19 (35.9%)	
Mode of delivery				*P*<.001[c]
SVD n (%)	123 (47.9%)	26 (43.3%)	17 (32.1%)	
OVD n (%)	44 (17.1%)	6 (10.0%)	9 (17.0%)	
EMCS n (%)	39 (15.2%)	19 (31.7%)	27 (50.9%)	
PCS n (%)	51 (19.8%)	9 (15.0%)	0 (0%)	
Induction of labor n (%)	116 (45.1%)	33 (55%)	33 (62.3%)	*P*=.001[c]
Fetal distress leading to instrumental delivery or C-section n (%)	30 (11.76%)	10 (16.7%)	13 (25.5%)	*P*=.034[c]
Type of C-section – % of all C-sections				*P*<.001[c]
Total number	90	28	27	
Cat.1 n (%)	6 (6.7%)	2 (7.1%)	4 (14.8%)	
Cat.2 n (%)	17 (18.9%)	7 (25.0%)	11 (40.7%)	
Cat.3 n (%)	16 (17.8%)	10 (35.7%)	12 (44.4%)	
Cat.4 n (%)	51 (56.6%)	9 (32.1%)	0 (0%)	
Birthweight (g) Median (IQR)	3430 (3055; 3800)	3018 (2683; 3325)	2485 (1900; 2850)	*P*<.001[a,c]
				P<.001[b,c]
Birthweight for gestational age (*z* score) Median (IQR)	0.61 (−0.19; 1.45)	0.19 (−0.79; 0.79)	−0.60 (−1.51; 0.37)	*P*=.013[a,c]
				P<.001[b,c]
Small for gestational age (birthweight <10th centile) n (%)	27 (10.5%)	14 (23.3%)	21 (39.6%)	*P*<.001[c]
Estimated blood loss (mL) Median (IQR)	400 (300; 600)	475 (300; 650)	400 (300; 600)	*P*=.253[a]
				P=.933[b]

Cat, category; *Cat.1 section*, immediate threat to the life of the woman or fetus; *Cat.2 section*, maternal or fetal compromise that is not immediately life-threatening; *Cat.3 section*, no maternal or fetal compromise but needs early delivery; *Cat.4 section*, elective-delivery timed to suit woman or staff; *EMCS*, emergency cesarean section; *GA*, gestational age; *IQR*, interquartile range; *OVD*, operative vaginal delivery; *PCS*, planned cesarean section; *PLGF*, placental growth factor; *sFLT1*, soluble fms–like tyrosine kinase 1; *SVD*, spontaneous vaginal delivery.

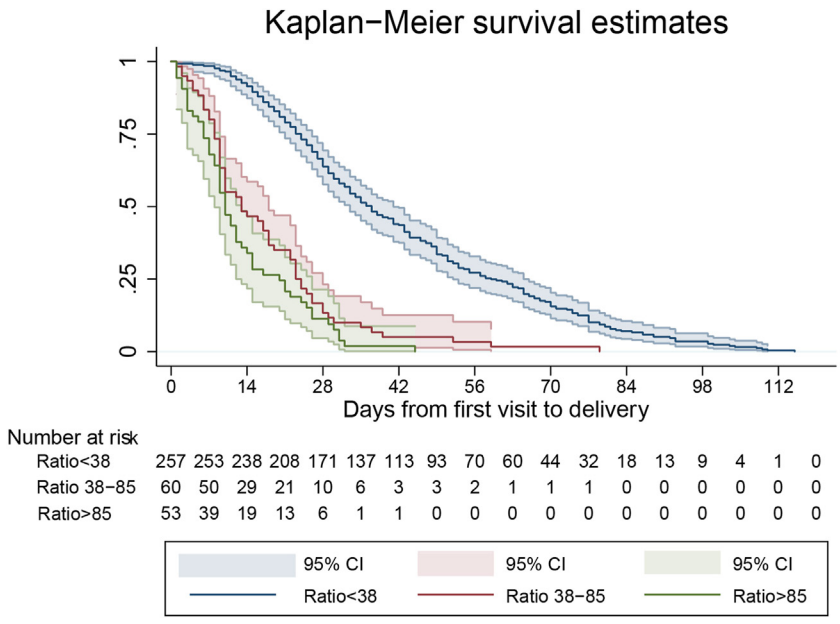
[a] Test between groups 1 and 2; [b] Test between groups 1 and 3; [c] *P*<.05.

with ratios ≥85 have a 5.89-fold increased risk of delivering by emergency cesarean section (adjusted OR 5.89, 95% CI 3.05; 11.21)*; and patients with ratios>38 and <85 have a risk 3 times higher (adjusted OR 3.04, 95% CI 1.53; 6.05) after adjusting for gestational age at time of ratio test and trial arm. This correlation was maintained even after including gestational age at delivery in the model (Supplemental Table 8).

Fetal distress

The incidence of intrapartum fetal distress leading to an operative delivery or cesarean section was significantly more prevalent in higher ratio groups: 11.76% in ratios category 1, 16.7% in

FIGURE 1
Kaplan-Meier survival estimates of time from the first visit to delivery according to ratio categories



Cox proportional hazards model $P<.001$* (adjusting for gestational age at ratio sampling and trial arm).

CI, confidence interval.

ratios category 2 and in more than one-quarter of the participants with ratio category 3 (25.5%). In a logistic regression model adjusting for gestational age at ratio test and trial arm, a ratio ≥85 represents an almost 3-fold risk for this adverse event when compared to ratios ≤38 (OR 2.77, 95% CI 1.30−5.87). Even with the inclusion of gestational age at delivery in the model, the correlation remained significant (Supplemental Table 8).

Induction of labor

IOL was performed in 116 patients (45.1%) with ratios ≤38; 33 patients (55.0%) with ratios >38 and <85; and 33 patients (62.3%) with ratios ≥85 (Table 2). A logistic regression model that tested the effect of ratio category for the outcome IOL, controlling for gestational age at ratio sampling and trial arm showed increased odds for IOL in category 2 when compared with ratios ≤38, (adjusted OR 2.20, 95% CI 1.02; 4.76)*; and for ratios in category 3 these odds were increased 6 fold (adjusted OR 6.0, 95% CI 2.01; 17.93) (Table 4).

TABLE 3
Cox proportional hazards model showing the association between ratio categories (reference: ratio ≤38) and days from ratio sampling to delivery, adjusted for gestational age at ratio sampling and trial arm

Exposure variables	Model hazards ratio (95% CI)
Ratio >38 and <85	1.99 (1.47; 2.71)[a]
Ratio ≥85	5.64 (4.06; 7.84)[a]

Ratio categories are compared to the baseline category (reference: ratio ≤38).

CI, confidence interval.

[a] $P<.001$.

Birthweight and birthweight *z* score

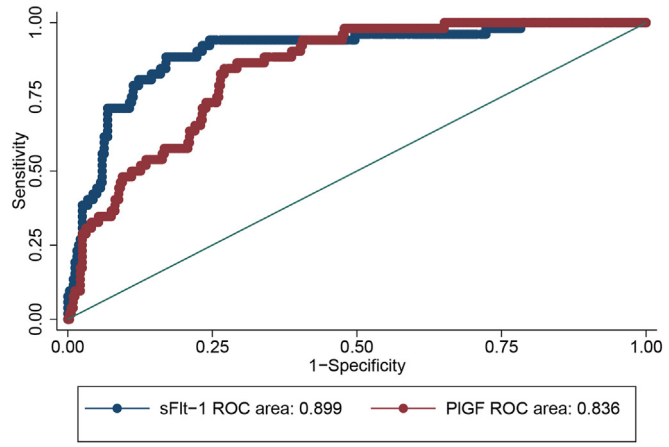
Neonatal birthweight was significantly different between ratio groups, with higher ratios corresponding to lower birthweights. The median birthweight was 3430 g (IQR 3055−3800) for ratios ≤38 vs 3018 g (IQR 2683; 3325) for ratios >38 and <85 ($P<.001$*); and 2485 g (IQR 1900; 2850) for ratios ≥85 ($P<.001$ for the difference with ratios ≤38) (Table 2). The results were similar when normalizing by gestational age by considering birthweight *z* scores, with a median birthweight *z* score of 0.61 (−0.19; 1.45) for ratios ≤38 vs 0.19 (−0.79; 0.79) for ratios >38 and <85 ($P=.013$*); and −0.60 (−1.51; 0.37) for ratios ≥85 ($P<.001$ for the difference with ratios ≤38). In a multiple linear regression model controlling for gestational age at ratio testing and trial arm, higher ratios are still significantly associated with a lower birthweight *z* score using as reference ratios category 1 (for ratio category 2, β coefficient −0.70 with 95% CI −1.09; −0.30; for ratio category 3, β coefficient −1.51 with 95% CI −1.91; −1.11).

As expected, higher ratios are associated with an increased prevalence of SGA infants (newborns with birthweight <10th centile for gestational age and sex): almost 40% of women with ratio in category 3 had newborns <10th centile when compared to 23.3% of the population with ratio category 2, and only 10.5% of women with ratio category 1 ($P<.001$)*.

Subanalyses

In a subanalysis we assessed the relationship between the sFLT/PLGF ratio and mode of delivery in the subset of patients who did not develop preeclampsia and had a spontaneous onset of labor (we exclude IOLs to remove potential confounders of intervention). In this subgroup (patients without preeclampsia and with a spontaneous onset of labor) (n=91), most (68.1%) had a SVD. Around 13.3% required

FIGURE 2
Receiver operating characteristic analysis for prediction of a delivery in the 2 following weeks



The sFLT1/PLGF ratio, isolated sFLT-1 and the inverse of PLGF were compared for the prediction of a delivery in the 2 following weeks.

PLGF, placental growth factor; *ROC*, receiver operating characteristic; *sFLT1*, soluble fms−like tyrosine kinase 1.

intervention (instrumental delivery or cesarean section) for fetal distress, and 11% for failure to progress in labor. The difference in mean log ratio was significantly higher in cases of delivery for fetal distress (1.8±0.15) and failure to progress (1.8±0.15) when compared to SVDs (1.3±0.2) (Supplemental Table 3). A similar relationship was also found for patients who underwent induction of labor.

We also examined the relationship of sFLT/PLGF ratio only in women who developed preeclampsia and found most of these women (n=53, 62%) underwent IOL, so analysis in those without intervention was not meaningful. In women who developed preeclampsia (n=85), 27 (32%) had a SVD, 18 (22%) had an assisted delivery for fetal distress, and 10 (12%) had an assisted delivery for failure to progress in labor. The correlations found between log ratio mean and delivery were similar to the nonpreeclamptic population, with higher mean differences in log ratios in patients who needed expedited delivery for fetal distress (3.7±0.8) or failed progression of labor (3.8±0.17) when compared to those who had SVD (3.6±0.18) (Supplemental Table 3). These data suggest that our findings are independent of the diagnosis of preeclampsia.

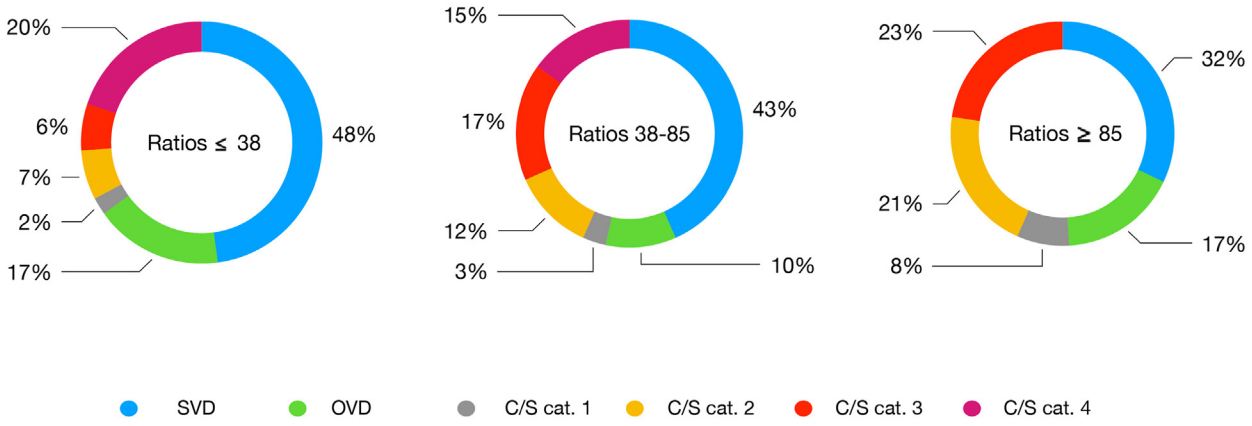
We have also performed a subanalysis of women in the "nonreveal" arm of the trial only (n=184, Supplemental Table 4 and Supplemental Table 9). Seventy-two participants (39%) had a SVD and 50 (27%) had an assisted delivery: 31 (17%) for fetal distress and 19 (10%) for failure to progress. In this subgroup, there was again a higher mean log difference in patients who needed an assisted delivery for fetal distress (2.4±1.2) or failure to progress (2.5±1.2) when compared to women with SVD (2.2±1.2), $P<.001$ (Supplemental Table 9).

Comment

Principal findings

In this study we examined sFLT/PLGF ratio categorization in 3 groups (≤38; 38−85; and ≥85) and show that higher ratios are associated with a shorter latency to delivery; lower odds of SVD; higher odds of emergency cesarean section; and a greater incidence of intrapartum fetal distress leading to instrumental delivery or cesarean section. Higher ratios are also associated with an earlier gestational age at delivery and lower median neonatal

FIGURE 3
Mode of delivery and cesarean section classification by ratio category



C/S, cesarean section; *OVD*, operative vaginal delivery; *SVD*, spontaneous vaginal delivery.

TABLE 4
Logistic regression model showing the association between ratio categories (reference: ratio ≤38) and pregnancy outcomes, adjusted for gestational age at ratio sampling and trial arm

Outcome	Model OR (95% CI) SVD	Model OR (95% CI) ELCS	Model OR (95% CI) EMCS	Model OR (95% CI) Fetal distress	Model OR (95% CI) IOL
Exposure variables					
Ratio >38 and <85	0.71 (0.39; 1.29)	0.74 (0.33; 1.65)	3.04 (1.53; 6.05)[a]	1.75 (0.76; 4.00)	2.20 (1.02; 4.76)[a]
Ratio ≥85	0.47 (0.25; 0.89)[a]	0.08 (0.01; 0.59)[a]	5.89 (3.05; 11.21)[a]	2.77 (1.30; 5.87)[a]	6.00 (2.01; 17.93)[a]

Ratio categories are compared to the baseline category (reference: ratio ≤38).

CI, confidence interval; *ELCS*, elective cesarean section; *EMCS*, emergency cesarean section; *IOL*, induction of labor; *SVD*, spontaneous vaginal delivery.

[a] $P<.05$.

birthweight and birthweight *z* score. This relationship remained significant after adjusting for potential confounders.

Results in the context of what is known

Considering the time from ratio collection to delivery, higher ratio categories were associated with a lower latency to delivery, even after controlling for gestational age at ratio determination. This finding is consistent with previous studies.[20–22] In particular, Thadhani et al[22] showed that in women with hypertensive disorders of pregnancy, an sFLT/PLGF ratio>40 had a hazard ratio for delivery in 2 weeks of 3.1 (95% CI 2.3–4.2) after controlling for maternal age, parity, gestational age at presentation, and systolic blood pressure. This was true even after restricting our analysis to women without preeclampsia and with a spontaneous onset of labor, suggesting that this correlation is independent from disease severity. We hypothesize that higher ratios are associated with greater placental impairment and more rapid clinical deterioration.

In this context, an sFLT1/PLGF ratio significantly predicts preeclampsia indicated delivery in the 2 following weeks (AUC 0.89, [95% CI 0.86–0.94]). This predictive ability of the sFLT1/PLGF ratio appears to be mainly mediated through sFLT1, since the predictive power of sFLT1 alone is similar to the sFLT1/PLGF ratio, and significantly superior to PlGF alone. This finding is corroborated by previous studies.[23] It is important to note that a ratio cut-off of >85 is particularly useful in a clinical setting for its ability to rule in preeclampsia indicated delivery in the 2 following weeks, considering its high specificity at the cost of a lower sensitivity, while a ratio <38 could be useful to rule-out this condition considering its high sensitivity.

Regarding the mode of delivery, a greater incidence of instrumental delivery or cesarean section was observed in higher ratio categories, in keeping with some previous studies.[24–26] In particular, in Valiño et al's[26] paper, median sFLT1 was 1.01 multiples of median (MoM) in women with vaginal deliveries when compared to 3.55 MoM in patients that had an emergent cesarean section before labor onset due to fetal distress. In our study, the increased need for instrumental delivery and cesarean section was also mostly due to intrapartum fetal distress. Apart from the need for cesarean delivery, a higher category of urgency (category 1–3 cesarean) was significantly more frequent in groups with higher sFLT1/PLGF ratios; in particular, emergency cesarean sections were more frequent in higher ratio categories, while planned sections (ie, elective or category 4) were more likely in lower ratios. The increased incidence of cesarean sections in higher ratio categories, particularly emergency and urgent cesarean sections may be related to increased fetal sensitivity to hypoxia and lower tolerance to labor in those with a greater degree of placental insufficiency. Importantly, subanalysis showed that even when the analysis was restricted to women who did not develop preeclampsia, the finding of poorer outcomes with higher ratios remained: the mean log ratio was significantly higher in women requiring assisted delivery for fetal distress when compared to those having a vaginal birth. This was also the case when we considered the sub-group of women with preeclampsia, suggesting that this association is independent of diagnosis; when we analyzed the subgroup of women in the "nonreveal" arm of the trial, indicating that these results are independent of potential clinician bias; and when we further added gestational age at birth to the models, suggesting that higher ratio categories significantly elevate the risk of category 1 cesarean sections and fetal distress, irrespective of gestational age at birth.

The need to induce labor was significantly more frequent in higher ratio categories. Even after controlling gestational age at ratio sampling, which is consistent with the increased prevalence of adverse outcomes and/or preeclampsia in this group and the faster clinical deterioration described previously. Similarly, birthweight and birthweight *z* scores were also significantly lower for higher ratio categories. This is consistent with previously published research[24] and it might again reflect the fetal consequences of a more severe placental impairment in these cases.

Clinical implications

Our results have important clinical implications, showing that in women with suspected preeclampsia the sFLT1/PLGF ratio might be helpful in risk stratification regarding clinical deterioration (latency to delivery), intrapartum fetal distress, and mode of delivery (increased risk of intervention). This finding is independent of the diagnosis of preeclampsia and might help clinicians tailor antepartum and intrapartum care in this population.

Research implications

Future studies should test if the sFLT1/PLGF ratio is predictive of birth outcomes in other populations—namely in the absence of suspected preeclampsia.

Strengths and limitations

Strengths of this study include its considerable sample size when compared to previously published studies and prospective patient recruitment. All analyses were controlled for gestational age at ratio sampling and trial arm. The latter is particularly important, as it could potentially introduce a confounding factor: within the subset of patients assigned to the "reveal" arm of the trial, clinicians were guided to utilize the ratio results to gauge the necessity for hospital admission or increased surveillance, potentially influencing time to delivery. By adjusting our analyses for this factor and by conducting a separate subanalysis of participants within the "nonreveal" arm of the trial, which showed results consistent with the overall population, we have addressed and minimized this potential source of bias.

The main limitation of this study is the difficulty in extrapolating its findings to the general population. All the participants included had suspected preeclampsia at some point in pregnancy, and although a subanalysis of the group where preeclampsia was not confirmed corroborated the findings for the general population, it should be acknowledged that these participants were also not low-risk, as there was a clinical suspicion of preeclampsia at some point during pregnancy. We note the presence of wide CIs in some of our results, therefore, although there is a statistically significant difference, the magnitude of the differences might be difficult to establish precisely. These would be better determined with a larger primary study robustly powered to test these differences from the outset.

Conclusions

In summary, in pregnant patients who presented at least once with suspected preeclampsia, those with higher sFLT1/PLGF ratios have a shorter latency to delivery, increased need for intervention in labor due to fetal distress, and increased risk for emergency cesarean section and IOL. These data suggest that sFLT1/PLGF ratio is related to placentally mediated birth outcomes beyond preeclampsia, and could provide useful patient counseling as well as guidance for planning and monitoring of labor and delivery in these patients. ■

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SUPPLEMENTAL TABLE 1
Characteristics of the study population according to trial arm

Population characteristics	Reveal arm (n=186)	Nonreveal arm (n=184)	Statistical significance *P* value
GA at recruitment (wk) Median (IQR)	34.3 (31.3; 36.0)	34.4 (31.4; 35.7)	*P*=.903
Maternal age at recruitment (y) Median (IQR)	30.9 (27.4; 35.8)	31.1 (26.7; 34.7)	*P*=.473
BMI Median (IQR)	28.3 (24.3; 32.4)	26.7 (23.1; 31.7)	*P*=.045
Parity n (%)			*P*=.351
Nulliparous	86 (46.2%)	94 (51.1%)	
Multiparous	100 (53.8%)	90 (48.2%)	
Smoking status n (%)			*P*=.398
Current smoker	17 (9.1%)	16 (8.7%)	
Never smoker	107 (57.5%)	118 (64.1%)	
Previous smoker	62 (33.3%)	50 (27.2%)	
Ethnicity n (%)			*P*=.794
Caucasian	166 (89.3%)	166 (90.2%)	
Other	15 (8.2%)	18 (9.7%)	
Not recorded	2 (1.1%)	3 (1.6%)	
Highest systolic BP at presentation Median (IQR)	131 (120; 148)	132 (120; 146)	*P*=.826
Highest diastolic BP at presentation Median (IQR)	84 (70; 93)	80 (71; 92)	*P*=.900

For ethnicity, n=5 values were not recorded.

BMI, body mass index; *BP*, blood pressure; *GA*, gestational age; *IQR*, interquartile range.

SUPPLEMENTAL TABLE 2
Pregnancy outcomes of the participants according to trial arm

Pregnancy outcomes	Reveal arm (n=186)	Nonreveal arm (n=184)	Statistical significance *P* value
GA at delivery (wk) Median (IQR)	38.4 (37.3; 39.6)	38.1 (37.1; 39.3)	*P*=.477
Time to delivery (d) Median (IQR)	27.5 (14; 51)	28 (16; 46.5)	*P*=.855
Mode of delivery			*P*=.291
SVD n (%)	94 (50.5%)	72 (39.1%)	
OVD n (%)	27 (14.5%)	32 (17.4%)	
EMCS n (%)	38 (20.5%)	46 (25%)	
PCS n (%)	27 (14.5%)	34 (18.5%)	
Induction of labor n (%)	99 (67.8%)	83 (63.4%)	*P*=.436
Fetal distress leading to instrumental delivery or C-section n (%)	22 (11.9%)	31 (17.1%)	*P*=.155
Type of C-section — % of all C-sections			*P*=.349
Total number	65	80	
Cat.1 n (%)	3 (4.6%)	9 (11.3%)	
Cat.2 n (%)	19 (29.2%)	16 (20%)	
Cat.3 n (%)	16 (24.6%)	22 (27.5%)	
Cat.4 n (%)	27 (41.5%)	33 (41.3%)	
Birthweight (g) Median (IQR)	3235 (2780; 3685)	3268 (2723; 3700)	*P*=.923
Birthweight for gestational age (*z* score) Median (IQR)	0.409 (−0.45; 1.25)	0.353 (−0.43; 1.33)	*P*=.985
Low birth weight (birthweight <2500 g) n (%)	28 (15.1%)	28 (15.2%)	*P*=.965
Estimated blood loss (mL) Median (IQR)	400 (300; 525)	500 (300; 600)	*P*=.027[a]

Cat, category; *Cat.1 section*, immediate threat to the life of the woman or fetus; *Cat.2 section*, maternal or fetal compromise that is not immediately life-threatening; *Cat.3 section*, no maternal or fetal compromise but needs early delivery; *Cat.4 section*, elective-delivery timed to suit woman or staff; *EMCS*, emergency cesarean section; *GA*, gestational age; *IQR*, interquartile range; *OVD*, operative vaginal delivery; *PCS*, planned cesarean section; *SVD*, spontaneous vaginal delivery.

[a] *P*<.05.

SUPPLEMENTAL TABLE 3

Subanalyses of patients with no preeclampsia and spontaneous onset of labor; and patients with preeclampsia

	Patients with no PE, spontaneous onset of labor (n=91)			Patients with PE (n=85)		
Type of delivery	n (%)	Log sFLT1/PLGF difference between means (mean±SD)	Statistical significance for *t* test with log sFLT1/PLGF *P* value	n (%)	Log sFLT1/PLGF difference between means (mean±SD)	Statistical significance for *t* test with log sFLT1/PLGF *P* value
Spontaneous vaginal delivery	62 (68.1%)	1.3±0.2	$P<.001$[a]	27 (31.8%)	3.6±0.18	$P<.001$[a]
Intrapartum fetal distress leading to instrumental delivery or C-section	12 (13.3%)	1.8±0.15	$P<.001$[a]	18 (21.7%)	3.7±0.18	$P<.001$[a]
Failure to progress leading to instrumental delivery or C-section	10 (11%)	1.8±0.15	$P<.001$[a]	10 (11.8%)	3.8±0.17	$P<.001$[a]

C-section, cesarean section; *PE*, preeclampsia; *PLGF*, placental growth factor; *sFLT1*, soluble fms–like tyrosine kinase 1.

[a] $P<.05$.

SUPPLEMENTAL TABLE 4

Pregnancy outcomes of the participants in the nonreveal arm of the trial (n = 184) according to their sFLT1/PLGF ratio category

Pregnancy outcomes	sFLT1/PLGF ≤38 (n=127)	sFLT1/PLGF 38–85 (n=32)	sFLT1/PLGF ≥85 (n=25)	Statistical significance *P* value
GA at delivery (wk) Median (IQR)	38.7 (37.7; 39.9)	37.6 (37.1; 38.3)	36.7 (35; 37.1)	*P*=.001[a,c]
				P<.001[b,c]
Time to delivery (d) Median (IQR)	35 (22; 55)	15 (9; 26)	12 (8; 24)	*P*<.001[a,c]
				P<.001[b,c]
Time to delivery				*P*<.001[c]
<1 wk n (%)	2 (1.6%)	2 (6.3%)	5 (20%)	
≥1 wk and <2 wk n (%)	8 (6.3%)	13 (40.6%)	8 (32%)	
≥2 wk n (%)	117 (92.1%)	17 (53.1%)	12 (48%)	
Mode of delivery				*P*=.016[c]
SVD n (%)	52 (40.9%)	13 (40.6%)	7 (28.0%)	
OVD n (%)	25 (19.7%)	2 (6.3%)	5 (20.0%)	
EMCS n (%)	22 (17.3%)	12 (37.5%)	12 (48.0%)	
PCS n (%)	28 (22.1%)	5 (15.6%)	1 (4%)	
Induction of labor n (%)	54 (42.5%)	13 (40.6%)	16 (64%)	*P*=.019[c]
Fetal distress leading to instrumental delivery or C-section n (%)	20 (15.7%)	3 (9.4%)	8 (33.3%)	*P*=.052
Type of C-section – % of all C-sections				*P*=.006[c]
Total number	50	17	13	
Cat.1 n (%)	5 (10%)	1 (5.9%)	3 (23.1%)	
Cat.2 n (%)	8 (16%)	3 (17.7%)	5 (38.5%)	
Cat.3 n (%)	9 (18%)	8 (47.1%)	5 (38.5%)	
Cat.4 n (%)	28 (56%)	5 (29.4%)	0 (0%)	
Birthweight (g) Median (IQR)	3420 (3030; 3790)	3067.5 (2685; 3527.5)	2485 (1990; 2815)	*P*=.019[a,c]
				P<.001[b,c]
Birthweight for gestational age (*z* score) Median (IQR)	0.56 (−0.22; 1.43)	0.30 (−0.52; 0.15)	−0.65 (−1.43; −0.04)	*P*=.321[a]
				P<.001[b,c]
Small for gestational age (birthweight <10th centile) n (%)	13 (10.2%)	6 (18.8%)	12 (48.0%)	*P*<.001[c]
Estimated blood loss (mL) Median (IQR)	400 (300; 500)	400 (275; 575)	400 (250; 600)	*P*=.799[a]
				P=.587[b]

Cat, category; *Cat.1 section*, immediate threat to the life of the woman or fetus; *Cat.2 section*, maternal or fetal compromise that is not immediately life-threatening; *Cat.3 section*, no maternal or fetal compromise but needs early delivery; *Cat.4 section*, elective-delivery timed to suit woman or staff; *EMCS*, emergency cesarean section; *GA*, gestational age; *IQR*, interquartile range; *OVD*, operative vaginal delivery; *PCS*, planned cesarean section; *PLGF*, placental growth factor; *sFLT1*, soluble fms-like tyrosine kinase 1; *SVD*, spontaneous vaginal delivery.

[a] Test between groups 1 and 2; [b] Test between groups 1 and 3; [c] *P*<.05.

SUPPLEMENTAL TABLE 5

Cox proportional hazards model showing the association between ratio categories (reference: ratio ≤38) and d from ratio sampling to delivery, adjusted for gestational age at ratio sampling and trial arm, in patients with no preeclampsia and no induction of labor (model 1); and in patients with preeclampsia (model 2)

Exposure variables	Model 1 (no preeclampsia, no IOL) Hazards ratio (95% CI)	Model 2 (preeclamptic patients) Hazards ratio (95% CI)
Ratio >38 and <85	1.56 (0.76; 3.21)	2.67 (1.24; 5.76)[a]
Ratio ≥85	4.83 (1.56; 15.01)[a]	7.07 (3.52; 14.18)[a]

Ratio categories are compared to the baseline category (reference: ratio ≤38).

CI, confidence interval; *IOL*, induction of labor.

[a] $P<.001$.

SUPPLEMENTAL TABLE 6

Performance of an sFIT1-PLGF ratio<38 in the prediction of preeclampsia indicated delivery in the 2 following weeks

Sensitivity (%, 95% confidence interval)	98.4% (96.1—99.6)
Specificity (%, 95% confidence interval)	42.5% (33.2—52.1)
Area under the curve (AUC, 95% confidence interval)	0.70 (0.66—0.75)

PLGF, placental growth factor; *sFLT1*, soluble fms-like tyrosine kinase 1.

SUPPLEMENTAL TABLE 7

Logistic regression model showing the association between ratio categories (reference: ratio ≤38) and spontaneous vaginal delivery in women who underwent a trial of vaginal delivery, adjusted for gestational age at ratio sampling, trial arm, and parity

Outcome	Model OR (95% CI) SVD
Exposure variables	
Ratio >38 and <85	0.70 (0.35; 1.37)
Ratio ≥85	0.40 (0.2; 0.81)[a]
Parity	3.01 (1.86; 4.97)[a]

Ratio categories are compared to the baseline category (reference: ratio ≤38).

CI, confidence interval; *SVD*, spontaneous vaginal deliveries.

[a] $P<.05$.

SUPPLEMENTAL TABLE 8

Logistic regression model showing the association between ratio categories (reference: ratio ≤38) and pregnancy outcomes, adjusted for gestational age at ratio sampling, trial arm, and gestational age at delivery

Outcome	Model OR (95% CI) CS1	Model OR (95% CI) Fetal distress
Exposure variables		
Ratio >38 and <85	1.00 (0.16; 6.11)	1.70 (0.71; 4.05)
Ratio ≥85	8.20 (1.38; 48.79)[a]	2.60 (1.00; 6.72)[a]
Gestational age at delivery	1.36 (0.95; 1.97)	0.94 (0.84; 1.15)

Ratio categories are compared to the baseline category (reference: ratio ≤38).

CI, confidence interval; *CS1*, section category 1.

[a] $P<.05$.

SUPPLEMENTAL TABLE 9
Subanalysis for trial arm "nonreveal"

	Patients in trial arm "nonreveal" (n=184)		
Type of delivery	n (%)	Log sFLT1/PLGF difference between means (mean±SD)	Statistical significance for t-test with log sFLT1/PLGF *P* value
Spontaneous vaginal delivery	72 (39%)	2.2±0.12	$P<.001$[a]
Intrapartum fetal distress leading to instrumental delivery or C-section	31 (17%)	2.4±0.12	$P<.001$[a]
Failure to progress leading to instrumental delivery or C-section	19 (10%)	2.5±0.12	$P<.001$[a]

C-section, cesarean section; *PLGF*, placental growth factor; *sFLT1*, soluble fms-like tyrosine kinase 1.

[a] $P<.05$.