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sFlt-1/PlGF ratio and timing of delivery in early-onset fetal growth restriction with antegrade umbilical artery flow

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KEYWORDS: early-onset; fetal growth restriction; placental growth factor; soluble fms-like tyrosine kinase-1; umbilical artery Doppler

CONTRIBUTION

What are the novel findings of this work?
In pregnancies with early-onset fetal growth restriction and antegrade umbilical artery flow, soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio at diagnosis is associated with the time interval to delivery.

What are the clinical implications of this work?
Determination of sFlt-1/PlGF ratio in pregnancies with early-onset fetal growth restriction and antegrade umbilical artery flow may be helpful in planning surveillance, corticosteroid administration and outpatient *vs* inpatient management.

ABSTRACT

Objective *To analyze the value of the soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio in predicting the time to delivery in early-onset fetal growth restriction (FGR) with preserved antegrade umbilical artery (UA) flow at diagnosis.*

Methods *This was a prospective observational single-center cohort study of pregnancies with early-onset (< 32 + 0 weeks) FGR and antegrade UA flow, in which maternal serum sFlt-1/PlGF ratio was determined at diagnosis. FGR was defined as estimated fetal weight < 3rd centile or < 10th centile with UA pulsatility index > 95th centile, fetal middle cerebral artery pulsatility index < 5th centile or cerebroplacental ratio < 5th centile. The previously described sFlt-1/PlGF ratio cut-off value of 85 for facilitating the diagnosis of pre-eclampsia was assessed in the prediction of the need to deliver in < 1 week and ≥ 4 weeks.*

Results *In total, 120 cases were included. There were 116 (96.7%) liveborn neonates and 108 (90.0%) perinatal survivors. Median (interquartile range (IQR)) gestational age at diagnosis of early-onset FGR was 27.1 (25.7–29.4) weeks. Median (IQR) sFlt-1/PlGF ratio at diagnosis was 196 (84–474). Ninety (75.0%) cases had a sFlt-1/PlGF ratio ≥ 85. Among pregnancies with a liveborn neonate, median (IQR) interval to delivery in the groups with sFlt-1/PlGF ratio < 85 and ≥ 85 was 41 (22–54) days and 11 (4–20) days, respectively (*$P < 0.01$*). The probability of having to deliver within 1 week after diagnosis was 0% and 35.6% in those with sFlt-1/PlGF ratio < 85 and ≥ 85, respectively (*$P = 0.03$*), and the probability of delaying delivery for ≥ 4 weeks was 72.4% and 19.5%, respectively (*$P < 0.01$*).*

Conclusion *sFlt-1/PlGF ratio < 85 at diagnosis of early-onset FGR with antegrade UA flow identifies a group of pregnancies in which the need to deliver within 1 week is very low and the interval to delivery is expected to be prolonged for ≥ 4 weeks in > 70% of cases.*

INTRODUCTION

Early-onset fetal growth restriction (FGR) in the absence of congenital anomalies is defined as a distinct phenotype of FGR that arises before 32 weeks. This concept has emerged as a pragmatic attempt to dichotomize a continuous biological phenomenon in which the degree of placental dysfunction is related negatively to the gestational age at presentation with FGR and positively to the risk of pre-eclampsia, adverse perinatal outcome and long-term sequelae[1,2].

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The main challenge in the antenatal surveillance of early-onset FGR is thus to achieve the optimal balance between the fetal risks of continuing the pregnancy and the neonatal risks of preterm delivery. Therefore, precise adjustment of monitoring intervals based on disease progression is essential[3,4] and, to guide them, Doppler evaluation of the umbilical arteries (UA) has been a cornerstone test since its use is associated with improved outcome[5]. The loss of end-diastolic UA flow reflects end-stage placental dysfunction and chronic fetal hypoxia, which precedes the need to deliver, as determined by abnormal computerized cardiotocography, by 1 week on average[6], so intensive surveillance should be implemented. However, when antegrade UA flow is still present, the chronology of fetal deterioration is particularly difficult to predict. The interval to delivery usually varies widely from 1 to 5 weeks[7], and an optimal surveillance regimen is lacking. One in three cases shows non-progressive UA patterns allowing near-term delivery, while critical circumstances related to severely impaired placental function (i.e. extremely early gestational ages or associated pre-eclampsia) can trigger an accelerated deterioration[7,8]. Thus, we hypothesized that the soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio may be helpful in planning fetal surveillance in early-onset FGR since it is related to the placental dysfunction underlying pre-eclampsia and FGR[9,10] and is associated with a shortened time until delivery when it exceeds the cut-off value of 85[11,12].

The aim of this study was to evaluate the sFlt-1/PlGF ratio cut-off of 85 for the prediction of the need to deliver in < 1 week and ≥ 4 weeks in pregnancies with early-onset FGR and antegrade UA flow. Secondarily, we explored its performance in the subgroup of cases with normal fetal Doppler at diagnosis.

METHODS

Study design and population

This was an observational prospective cohort study conducted in a single tertiary care referral hospital. We selected all consecutive singleton pregnancies that attended from February 2014 to October 2018, fulfilling the criteria for early-onset FGR before $32 + 0$ weeks of gestation[2] and with antegrade UA end-diastolic flow at diagnosis. Those recruited before August 2016 took part in a previous study[9]. sFlt-1/PlGF ratio was measured at diagnosis since early-onset FGR has been proposed as a criterion for suspicion of pre-eclampsia, in which the angiogenic-related biomarkers can be used to rule out or rule in the disease[13,14]. Those fetuses with an origin of growth restriction other than placental dysfunction (major malformation, congenital infection or chromosomal anomaly) were excluded, as well as those without sFlt-1/PlGF ratio determination or incomplete perinatal outcome. Written informed consent was obtained before participation and the local Research Ethics Committee approved the study (PI13/02405).

The original study protocol for the identification and intensive monitoring of pregnancies complicated by early-onset FGR or pre-eclampsia has been described elsewhere in detail[15]. In brief, we implemented a contingent strategy consisting of selection of women at high risk for FGR or pre-eclampsia based on data from maternal history and second-trimester uterine artery Doppler. Intensive monitoring was carried out, including measurement of the sFlt-1/PlGF ratio at 24–28 weeks or when suspicion of pre-eclampsia arose. Serial follow-up examinations were tailored, taking into account the results of the sFlt-1/PlGF ratio (every 2 weeks if sFlt-1/PlGF ratio was > 38 and two or three times a week if the value of 85 was exceeded). This strategy allowed us to detect most cases of early-onset FGR at an initial stage in which antegrade UA flow was still conserved. Nonetheless, we also included patients referred from other centers with an established diagnosis of early-onset FGR if they met the study criteria.

Data collection and outcome measures

At the first ultrasound examination, we recorded maternal characteristics including age, height, weight, smoking status, race, method of conception, low-dose aspirin intake, heparin prophylaxis and risk factors for pre-eclampsia and other placental dysfunction-related disorders according to the National Institute for Health and Care Excellence (NICE) guidelines[16].

Gestational age was estimated according to the American College of Obstetricians and Gynecologists (last menstrual period was corrected by the crown–rump length before $14 + 0$ weeks or biparietal diameter from $14 + 0$ weeks to $21 + 6$ weeks, when a significant discrepancy of more than 7 days or more than 10 days was found, respectively)[17].

The diagnosis of early-onset FGR, fetal surveillance and timing and mode of delivery essentially followed the stage-based protocol proposed by Figueras and Gratacós[18]. Thereby, early-onset FGR was diagnosed whenever estimated fetal weight (EFW)[19] was $< 3^{rd}$ centile, or when EFW was $< 10^{th}$ centile combined with (1) UA pulsatility index (PI) $> 95^{th}$ centile, (2) fetal middle cerebral artery (MCA) PI $< 5^{th}$ centile or (3) cerebroplacental ratio (CPR) $< 5^{th}$ centile, before $32 + 0$ weeks of gestation. EFW centiles were customized using the GROW software, validated for use in the Spanish population[20], and PI centiles were calculated using the online software available at http://medicinafetalbarcelona.org/calc/. After diagnosis, weekly monitoring (UA, MCA, CPR and ductus venosus Doppler plus conventional cardiotocography) was planned and labor induction was indicated after 37 weeks. If absent end-diastolic UA flow was detected, subsequent follow-up examinations were performed every 48–72 h and elective Cesarean section was recommended at 34 weeks. When reversed end-diastolic UA flow or ductus venosus PI $> 95^{th}$ centile was found, hospitalization and daily monitoring were indicated until elective Cesarean section at 30 weeks. Whenever reversed a-wave flow in the ductus venosus or spontaneous decelerations

on cardiotocography were noted, elective Cesarean section was indicated, provided that the gestational age was $\geq 26+0$ weeks and EFW was ≥ 500 g (if any of these thresholds was not reached, the decision to deliver was agreed with the parents after detailed neonatal counseling). After confirming the diagnosis of FGR, corticosteroids for fetal maturity (betamethasone 12 mg/day for 2 days) were administered at or beyond $25+0$ weeks. A second cycle of corticosteroids and magnesium sulfate for fetal neuroprotection was indicated if there was a risk for imminent delivery at $31+6$ weeks or less.

The presence of pre-eclampsia was evaluated at each visit by measuring blood pressure and determining proteinuria. Pre-eclampsia was defined according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy[21]. In cases in which pre-eclampsia was confirmed, maternal indications for delivery followed current protocols, as described previously[15]. During expectant management, maternal complications were assessed, including eclampsia, pulmonary edema, refractory hypertension, HELLP syndrome (complete or incomplete hemolysis, elevated liver enzymes and low platelet count), oliguria <500 mL/24 h and placental abruption. If any of these complications was identified, immediate delivery was indicated. Delivery was also recommended in the presence of severe features of pre-eclampsia after $34+0$ weeks and in any cases with pre-eclampsia after $37+0$ weeks.

Maternal serum samples were collected at the time of diagnosis (± 3 days) of FGR, and the sFlt-1/PlGF ratio was measured. sFlt-1 and PlGF concentrations (pg/mL) were determined using an automated assay system (Cobas® 6000 e701 module, Roche Diagnostics, Penzberg, Germany). The sFlt-1/PlGF ratio was expressed in absolute values. The previously described cut-off value of 85 for aiding in the diagnosis of PE[11] was used for interpretation of the results, since it has also been validated as a surrogate marker of placental dysfunction that conditions a shortening of the time from presentation to delivery[11,12]. The results of the sFlt-1/PlGF ratio were known by the clinicians, but they were advised to keep the decision to deliver adjusted to current protocols.

Perinatal data were recorded, including gestational age at delivery, mode of delivery, birth weight, Apgar score, arterial cord pH, neonatal intensive care unit admission, severe morbidity at discharge (bronchopulmonary dysplasia, hypoxic ischemic encephalopathy, intraventricular hemorrhage Grade ≥ 3, cystic periventricular leukomalacia Grade ≥ 2, necrotizing enterocolitis, sepsis and retinopathy of prematurity) and mortality. Postnatal follow-up for at least 6 months was available for all survivors.

Sample size was estimated for a 5% significance level and 90% power and assuming that the risk for delivery in <1 week in early-onset FGR with antegrade UA flow is about 20%[7], being three times more frequent when sFlt-1/PlGF ratio is ≥ 85 at diagnosis[9]. Thus, we calculated that 112 early-onset FGR cases were required to identify a difference of 30% in the need to deliver within 1 week. We additionally attempted a preliminary (unpowered) subgroup analysis in those cases with a FGR diagnosis based only on EFW $<3^{rd}$ centile, with normal fetal Doppler at the time of diagnosis. The rationale was that, in these cases, the diagnosis and management of early-onset FGR is particularly challenging and, if the information provided by the sFlt-1/PlGF ratio in this particular subgroup is sufficiently predictive of the interval to delivery, it may be developed further to aid in diagnosis and reduce the need for such close monitoring in favorable situations.

Statistical analysis

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was followed for reporting the results[22]. Continuous variables were expressed as mean (SD) or as median (interquartile range (IQR)) when non-normally distributed. Categorical variables were expressed as *n* (%). Univariate comparisons between cases with sFlt-1/PlGF ratio <85 *vs* ≥ 85 at diagnosis of early-onset FGR were performed using Student's *t*-test or the Mann–Whitney *U*-test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Kaplan–Meier survival curves were generated for the analysis of time to delivery after the diagnosis of early-onset FGR. Due to insufficient sample size for comparison, subgroup analysis of time to delivery in cases with normal UA Doppler was limited to assessing the distributions using box-and-whiskers plots. Two-sided $P<0.05$ was considered statistically significant. Data were entered carefully and analyzed after data cleansing, using the statistical package Stata, version 14.1 (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 229 fetuses were diagnosed with early-onset FGR during the study period. In total, 120 singleton pregnancies fulfilled the inclusion criteria and were included in the analysis (Figure 1). Of those, 70 (58.3%) were referred from other centers, and the remaining 50 were identified by following our protocol for early recognition of pregnancies complicated by placental dysfunction. The initial diagnosis of FGR was based on EFW $<3^{rd}$ centile with normal fetal Doppler in 27 (22.5%) cases, EFW $<10^{th}$ centile with CPR or MCA-PI $<5^{th}$ centile in 48 (40.0%) cases and EFW $<10^{th}$ centile with UA-PI $>95^{th}$ centile in 45 (37.5%) cases. The overall median (IQR) sFlt-1/PlGF ratio at diagnosis of early-onset FGR was 196 (84–474). In 90 (75.0%) cases, the sFlt-1/PlGF ratio was ≥ 85. Maternal characteristics of the study groups are presented in Table 1. There was a higher percentage of Hispanic women in the group with sFlt-1/PlGF ratio ≥ 85 than in those with sFlt-1/PlGF ratio <85 (28.9% *vs* 10.0%, $P=0.02$). No other significant differences were observed. Sonographic characteristics at FGR diagnosis are described in Table 2. The overall median (IQR) gestational age at initial diagnosis of FGR was 27.1 (25.7–29.4) weeks, and no significant difference

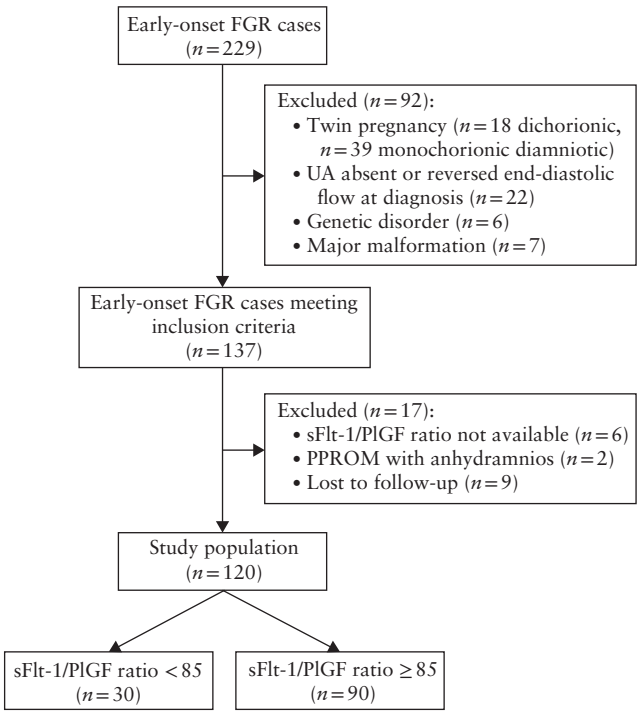

Figure 1 Flowchart summarizing inclusion of study population of pregnancies with early-onset fetal growth restriction (FGR) and antegrade umbilical artery (UA) flow. PlGF, placental growth factor; PPROM, preterm prelabor rupture of membranes; sFlt-1, soluble fms-like tyrosine kinase-1.

was observed between the sFlt-1/PlGF ratio ≥ 85 and < 85 groups. Signs of fetal brain sparing were present more often in the group with sFlt-1/PlGF ratio ≥ 85. In 25 (20.8%) cases, we observed progression towards abnormal ductus venosus PI (> 95th centile), of which 23 had sFlt-1/PlGF ratio ≥ 85.

Maternal and perinatal outcomes are shown in Table 3. Pre-eclampsia was present at diagnosis in 21 (17.5%) cases, and another 42 (35.0%) cases developed pre-eclampsia after diagnosis. All the latter cases belonged to the sFlt-1/PlGF ratio ≥ 85 group. There was a significant difference in composite neonatal morbidity, with a higher rate in the sFlt-1/PlGF ratio ≥ 85 group when compared with the sFlt-1/PlGF ratio < 85 group (53.7% *vs* 28.6%; $P = 0.04$). One case opted for termination of pregnancy, three cases (one with sFlt-1/PlGF ratio < 85) resulted in stillbirth (in all cases, neonatal comfort care was agreed with the parents after detailed neonatal counseling due to EFW < 500 g or gestational age < 26 weeks) and there were eight neonatal deaths (one with sFlt-1/PlGF ratio < 85). Therefore, the overall perinatal survival rate was 108/120 (90.0%). There were four deaths after the perinatal period, giving an overall survival rate of 86.7%.

Time-to-delivery analysis

Only the 116 cases resulting in delivery of a liveborn neonate were considered for the analysis of time to delivery. Median (IQR) interval to delivery in the study population was 16 (7–36) days. An overall shorter latency time was observed in the sFlt-1/PlGF ratio ≥ 85 group compared with in the sFlt-1/PlGF ratio < 85 group (11 (4–20) *vs* 41 (22–54) days; $P < 0.01$). Figure 2 shows the distribution of the interval to delivery, according to sFlt-1/PlGF ratio ≥ 85 or < 85 and whether fetal Doppler findings were normal or pathological at diagnosis. In those with normal Doppler, median (IQR) time until delivery

Table 1 Baseline characteristics of study population of 120 pregnancies with early-onset fetal growth restriction and antegrade umbilical artery flow, according to soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio < 85 or ≥ 85 at diagnosis

Characteristic	*sFlt-1/PlGF ratio ≥ 85* (n = *90*)	*sFlt-1/PlGF ratio < 85* (n = *30*)	P
Age (years)	33.0 ± 5.7	33.6 ± 5.6	NS
Height (cm)	161.3 ± 6.4	162.5 ± 6.9	NS
Prepregnancy weight (kg)	66.6 ± 11.5	64.0 ± 14.6	NS
BMI (kg/m^2)	25.5 ± 4.8	24.2 ± 5.3	NS
Smoking status			
Current smoker	14 (15.6)	8 (26.7)	NS
Cigarettes per day	7 (2–22)	9 (3–20)	NS
Race or ethnicity			0.02†
White or Caucasian	59 (65.6)	26 (86.7)	
Hispanic	26 (28.9)	3 (10.0)	
Asian	1 (1.1)	1 (3.3)	
Black or African-American	3 (3.3)	0 (0)	
Other	1 (1.1)	0 (0)	
Risk factors for placental dysfunction			
High			
Previous PE	11 (12.2)	1 (3.3)	NS
Chronic hypertension	8 (8.9)	1 (3.3)	NS
Prepregnancy diabetes	2 (2.2)	0 (0)	NS
Chronic kidney disease	0 (0)	1 (3.3)	NS
Thrombophilia	2 (2.2)	2 (6.7)	NS
SLE	0 (0)	0 (0)	NS
Moderate			
Nulliparous	63 (70.0)	19 (63.3)	NS
Age ≥ 40 years	7 (7.8)	5 (16.7)	NS
BMI ≥ 35 kg/m^2	5 (5.6)	3 (10.0)	NS
Family history of PE*	6 (6.7)	2 (6.7)	NS
≥ 1 high-risk or ≥ 2 moderate-risk factors	30 (33.3)	8 (26.7)	NS
Mode of conception			NS
Spontaneous	80 (88.9)	27 (90.0)	
In-vitro fertilization	8 (8.9)	1 (3.3)	
Oocyte donation	2 (2.2)	2 (6.7)	
Low-dose (100 mg/day) aspirin			NS
No	75 (83.3)	23 (76.7)	
Starting ≤ 16 weeks	11 (12.2)	4 (13.3)	
Starting > 16 weeks	4 (4.4)	3 (10.0)	
Low-dose heparin prophylaxis			NS
No	87 (96.7)	27 (90.0)	
Starting ≤ 16 weeks	1 (1.1)	3 (10.0)	
Starting > 16 weeks	2 (2.2)	0 (0)	

Data are given as mean ± SD, *n* (%) or median (range). *First-degree relative (mother or sister) with history of pre-eclampsia (PE). †Significant difference after Bonferroni adjustment in proportion of Caucasian and Hispanic women. BMI, prepregnancy body mass index; NS, not significant; SLE, systemic lupus erythematosus.

Table 2 Sonographic characteristics at diagnosis in study population of 120 pregnancies with early-onset fetal growth restriction (FGR) and antegrade umbilical artery flow, according to soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio < 85 or ≥ 85 at diagnosis

Characteristic	*sFlt-1/PlGF ratio ≥ 85* (n = *90*)	*sFlt-1/PlGF ratio < 85* (n = *30*)	P
Gestational age at diagnosis of FGR (weeks)	27.1 (25.9–29.4)	26.6 (23.1–29.6)	NS
Estimated fetal weight (g)	769 ± 286	740 ± 306	NS
Customized centile	2 (1–4)	2 (1–3)	NS
< 3rd centile	78 (86.7)	27 (90.0)	NS
Deepest amniotic fluid pocket diameter (cm)	4.2 ± 1.2	5.0 ± 1.3	NS
Umbilical artery pulsatility index	1.6 ± 0.4	1.4 ± 0.3	NS
Centile	92 (82–99)	82 (66–94)	0.02
> 95th centile	38 (42.2)	7 (23.3)	NS
Middle cerebral artery pulsatility index	1.6 ± 0.4	1.8 ± 0.3	0.03
Centile	9 (2–34)	14 (8–50)	0.03
< 5th centile	32 (35.6)	3 (10.0)	< 0.01
Cerebroplacental ratio	1.0 ± 0.3	1.3 ± 0.5	< 0.01
Centile	2 (1–4)	3 (1–29)	< 0.01
< 5th centile	73 (81.1)	16 (53.3)	< 0.01

Data are given as median (interquartile range), mean ± SD or *n* (%). NS, not significant.

Table 3 Maternal and perinatal outcomes of study population of 120 pregnancies with early-onset fetal growth restriction (FGR) and antegrade umbilical artery flow, according to soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio < 85 or ≥ 85 at diagnosis

Outcome	*sFlt-1/PlGF ratio ≥ 85* (n = *90*)	*sFlt-1/PlGF ratio < 85* (n = *30*)	P
Corticosteroids for fetal maturation*	77/77 (100)	17/17 (100)	NS
Magnesium sulfate for fetal neuroprotection†	60/63 (95.2)	11/13 (84.6)	NS
Delivery indication			
Fetal condition	59 (65.6)	28 (93.3)	< 0.01
Maternal condition	31 (34.4)	2 (6.7)	
Gestational age at delivery (weeks)	29.4 (27.1–31.0)	31.9 (29.6–35.0)	< 0.01
Diagnosis-to-delivery interval (days)	11 (4–20)	41 (22–54)	< 0.01
Birth weight (g)‡	940 ± 331	1306 ± 482	< 0.01
Female fetal gender‡	40/87 (46.0)	18/29 (62.1)	NS
5-min Apgar score < 7‡	14/87 (16.1)	3/29 (10.3)	NS
Arterial cord pH ≤ 7.00‡	0/87 (0)	0/29 (0)	NS
Cesarean section‡	83/87 (95.4)	23/29 (79.3)	< 0.01
Perinatal mortality	10 (11.1)	2 (6.7)	NS
Pre-eclampsia			
At diagnosis of FGR	17 (18.9)	4 (13.3)	NS
After diagnosis of FGR	42 (46.7)	0 (0)	< 0.01
Maternal morbidity			
HELLP syndrome	12 (13.3)	1 (3.3)	NS
Refractory hypertension	4 (4.4)	2 (6.7)	NS
Pulmonary edema	1 (1.1)	0 (0)	NS
Oliguria	5 (5.5)	0 (0)	NS
Placental abruption	11 (12.2)	1 (3.3)	NS
Eclampsia	0 (0)	0 (0)	NS
Any maternal morbidity§	26 (28.9)	4 (13.3)	NS
Neonatal morbidity among perinatal survivors			
BPD	8/80 (10.0)	1/28 (3.6)	NS
Hypoxic ischemic encephalopathy	0/80 (0)	0/28 (0)	NS
IVH Grade 3 or 4	1/80 (1.2)	0/28 (0)	NS
PVL Grade 2 or 3	2/80 (2.5)	0/28 (0)	NS
Necrotizing enterocolitis	8/80 (10.0)	1/28 (3.6)	NS
Retinopathy of prematurity	15/80 (18.8)	0/28 (0)	0.01
Sepsis	34/80 (42.5)	7/28 (25.0)	NS
Any neonatal morbidity§	43/80 (53.8)	8/28 (28.6)	0.04
Admitted to NICU	78/80 (97.5)	19/28 (67.9)	< 0.01
Days in NICU	27 (14–48)	12 (0–36)	< 0.01

Data are given as *n*/*N* (%), *n* (%), median (interquartile range) or mean ± SD. *In live births ≤ 34 + 6 weeks. †In live births ≤ 31 + 6 weeks. ‡In live births. §More than one condition observed in some cases. BPD, bronchopulmonary dysplasia (defined as oxygen need at 36 weeks); HELLP, hemolysis, elevated liver enzymes and low platelet count; IVH, intraventricular hemorrhage (Grade 3, with dilation of lateral ventricles; Grade 4, intraparenchymal hemorrhage); NICU, neonatal intensive care unit; NS, not significant; PVL, cystic periventricular leukomalacia (Grade 2, small localized periventricular cysts; Grade 3, extensive periventricular cysts in frontoparietal and occipital regions).

was 20 (10–34) days *vs* 50 (41–57) days in the groups with sFlt-1/PlGF ≥ 85 and < 85, respectively ($P < 0.01$).

Survival analysis is presented in Figure 3. Table 4 shows the probabilities of delivering in < 1, < 2, < 3 and < 4 weeks after the diagnosis of early-onset FGR with antegrade UA flow, according to sFlt-1/PlGF ratio. In 31 (26.7%) cases, delivery was indicated in < 1 week, all of which had sFlt-1/PlGF ratio ≥ 85 at diagnosis. On the other hand, in 38 (32.8%) cases, the pregnancy continued ≥ 4 weeks. The probability of reaching a prolongation of pregnancy of ≥ 4 weeks increased significantly to 72.4% (21/29) when sFlt-1/PlGF ratio was < 85 at diagnosis.

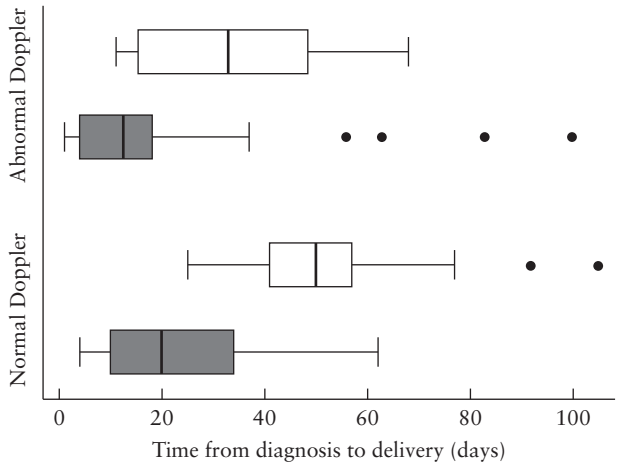

Figure 2 Box-and-whiskers plot showing distribution of time to delivery in 116 pregnancies (those ending in live birth) with early-onset fetal growth restriction and antegrade umbilical artery flow, according to soluble fms-like tyrosine kinase-1/placental growth factor ratio < 85 (□) or ≥ 85 (■) and fetal Doppler status (normal or abnormal) at diagnosis. Boxes are median and interquartile range (IQR). Whiskers are range excluding outliers more than 1.5 × IQR from upper or lower quartile. Circles are outliers.

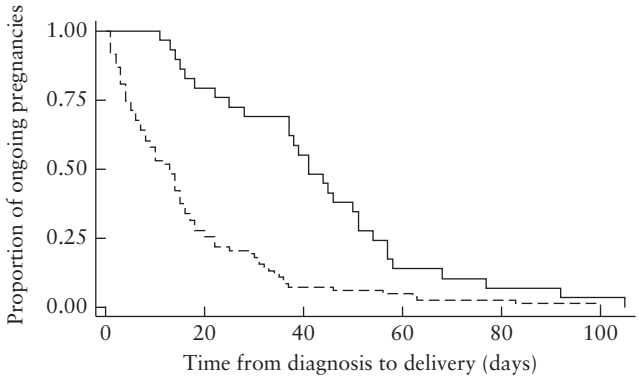

Figure 3 Kaplan–Meier graph showing time from diagnosis to delivery in pregnancies with early-onset fetal growth restriction and antegrade umbilical artery flow, according to soluble fms-like tyrosine kinase-1/placental growth factor ratio < 85 (——) or ≥ 85 (– – –) at diagnosis.

DISCUSSION

In early-onset FGR with antegrade end-diastolic flow in the UA, the time for which the pregnancy can be prolonged safely is uncertain. The interval from diagnosis to delivery varies widely, with a median (IQR) of 16 (7–36) days in our series, which is in agreement with the published literature[6,7]. Our study provides new evidence on the usefulness of the sFlt-1/PlGF ratio in the prediction of the remaining time until delivery in this challenging scenario. The cut-off of 85[11] was exceeded in 75% of cases at diagnosis, of which 36% required delivery within 1 week, compared with 0% in the group with sFlt-1/PlGF ratio < 85. This shorter interval is likely to be responsible for the higher rate of perinatal morbidity observed in this group. On the other hand, 72.4% of women in the group with sFlt-1/PlGF ratio < 85 had their pregnancy prolonged for ≥ 4 weeks, compared with 19.5% in the group with sFlt-1/PlGF ratio ≥ 85. Particularly in the subgroup of cases with normal fetal Doppler at diagnosis, a result of < 85 indicates a mild progressive pattern with a long time to delivery of 50 (41–57) days.

The management of early-onset FGR is limited to the observation of fetal status to identify the optimal benefit–risk balance of prolonging the pregnancy. Maternal surveillance should also be ensured since pre-eclampsia is frequently associated (52.5% of cases in our study). Despite the intrauterine fetal risks, waiting until late hemodynamic changes occur may benefit long-term outcome[23]. The sequence of fetal deterioration is well described, and all critical decisions (frequency of monitoring, hospitalization, administration of steroids/magnesium sulfate, and mode and indication for delivery) are based on this knowledge. However, there is considerable variability in the Doppler changes between fetuses[7]. Earlier gestational age at diagnosis and the concurrence of pre-eclampsia are the main triggers

Table 4 Survival and relative risk (RR) of delivery in 116 pregnancies with early-onset fetal growth restriction and antegrade umbilical artery flow that delivered a liveborn neonate, according to soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio < 85 or ≥ 85 at diagnosis

	sFlt-1/PlGF ratio ≥ 85 (n = 87)		*sFlt-1/PlGF ratio < 85* (n = 29)			
Time until delivery	*Cumulative incidence of delivery* (n (%))	*Survival without delivery (% (95% CI))*	*Cumulative incidence of delivery* (n (%))	*Survival without delivery (% (95% CI))*	*RR of delivery* (95% CI)*	P
< 1 week	31 (35.6)	64.4 (53.4–73.4)	0 (0)	100 (67.0–100)	—	0.03
< 2 weeks	47 (54.0)	46.0 (35.3–56.0)	2 (6.9)	93.1 (75.1–98.2)	7.8 (2.0–30.3)	< 0.01
< 3 weeks	66 (75.9)	24.1 (15.8–33.5)	6 (20.7)	79.3 (59.6–90.1)	3.7 (1.8–7.6)	< 0.01
< 4 weeks	70 (80.5)	19.5 (12.0–28.4)	8 (27.6)	72.4 (52.3–85.1)	2.9 (1.6–5.3)	< 0.01

*In pregnancies with sFlt-1/PlGF ratio ≥ 85 *vs* < 85.

contributing to an accelerated and more unpredictable need for delivery. This is not surprising since both FGR and pre-eclampsia are associated with poorer placental function. Nonetheless, the widespread stage-based protocols for managing early-onset FGR do not consider these factors in the determination of follow-up intervals. When antegrade UA flow is present, weekly outpatient follow-up has been recommended, without considering other factors[18,24,25]. Moreover, FGR has been removed as a criterion of severe pre-eclampsia since it is managed similarly in women with and those without pre-eclampsia[26].

The sFlt-1/PlGF ratio has been studied extensively in the context of pre-eclampsia, but it is not altered exclusively in this disorder. We[9] and others[27] have described that the ratio is also increased in FGR, and elevations are greater in cases of earlier onset, with the highest values being observed in those with both FGR and pre-eclampsia. Furthermore, we have detailed the longitudinal changes in the sFlt-1/PlGF ratio in the last weeks before delivery in early-onset FGR. It is elevated from at least 4 weeks before delivery, and the increase is more pronounced in cases with associated pre-eclampsia and as the time of delivery approaches[10]. Therefore, the sFlt-1/PlGF ratio is a very good candidate to be used as an objective surrogate of the degree of placental dysfunction. This property has been used in early-onset pre-eclampsia to identify which cases are more likely to have complications in the short term and which others can be safely managed expectantly, without precipitating an iatrogenic decision to deliver. Thus, among women with early-onset signs or symptoms of pre-eclampsia, delivery occurred within 2 weeks in 86% of cases when sFlt-1/PlGF ratio was ≥ 85, compared with 16% in those with sFlt-1/PlGF ratio < 85[12]. Importantly, knowledge of the information offered by the biomarkers is associated with a lower incidence of adverse outcome in pre-eclampsia, attributable to more appropriate antenatal surveillance and more timely delivery[28].

In this study, we showed that the ability of the sFlt-1/PlGF ratio to stratify the risk for short-term delivery is also applicable at initial phases of early-onset FGR, providing useful information for individual tailoring of surveillance. In fact, while pre-eclampsia and CPR have not proved to be useful in guiding the management of these pregnancies[1], a sFlt-1/PlGF ratio cut-off of 85 seems to be promising in the prediction of the time-to-delivery interval. Weekly monitoring may be insufficient above this cut-off since one in three cases with sFlt-1/PlGF ratio ≥ 85 requires delivery within 1 week, and both women and clinicians should be aware of recognizing the features of pre-eclampsia. Moreover, hospitalization and corticosteroid administration should be considered. On the contrary, if sFlt-1/PlGF ratio is < 85, the need to deliver in < 1 week and the presence of associated pre-eclampsia are highly unlikely (0% in our series), irrespective of the result of the Doppler study at diagnosis. Therefore, these cases do not require such intensive monitoring, and delaying the follow-up examination in a referral center by more than 1 week could be considered when there are difficulties in transfer. Most pregnancies with sFlt-1/PlGF ratio < 85 continue for ≥ 4 weeks, which can be reassuring when the diagnosis is established near viability, especially if fetal Doppler is still normal.

Our study has some limitations. First, the clinicians were not blinded to sFlt-1/PlGF ratio values, and this could have biased the results, particularly with regards to the subjective interpretation of the signs and symptoms associated with complicated pre-eclampsia, leading to iatrogenic delivery. Nevertheless, a recent clinical trial showed that knowledge of the biomarker values did not shorten the time until delivery[28]. Second, the widely used sFlt-1/PlGF ratio cut-off of 85 has been inferred from that described for pre-eclampsia[11,12] since there are no specific thresholds for FGR. Third, although we observed higher values of the sFlt-1/PlGF ratio in Hispanic women, in correlation with their higher risk for pre-eclampsia[29], we did not make adjustments since the impact of confounding factors such as ethnicity, BMI or parity on the ratio is insufficient to require correction[30]. Finally, the sample size was underpowered for further subgroup analyses of clinical interest such as cases diagnosed before viability, those with concurrent hypertensive disorders or those with normal fetal Doppler. In the latter, we performed an exploratory analysis with suggestive results, but the findings are too limited to draw conclusions on whether this represents a differentiated group. Further clinical trials are needed to clarify the impact of the sFlt-1/PlGF ratio on perinatal outcome in early-onset FGR.

In conclusion, the sFlt-1/PlGF ratio might be a useful tool in early-onset FGR with antegrade UA flow to stratify the short-term risk of delivery and to guide timely management.

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