Ultrasound Obstet Gynecol 2023; **61**: 181–190
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.26116.

Prediction of perinatal survival in early-onset fetal growth restriction: role of placental growth factor

J. RODRÍGUEZ-CALVO[1,2,3], C. VILLALAÍN[1,2,3], P. I. GÓMEZ-ARRIAGA[1,2,3], M. S. QUEZADA[1,2,3], I. HERRAIZ[1,2,3#] and A. GALINDO[1,2,3#]

[1]*Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Hospital Universitario 12 de Octubre, Instituto de Investigación Hospital 12 de Octubre (imas12), Madrid, Spain;* [2]*Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin (RICORS network), Instituto de Salud Carlos III, Madrid, Spain;* [3]*Universidad Complutense de Madrid, Madrid, Spain*

KEYWORDS: early-onset; fetal growth restriction; FGR; perinatal survival; PlGF

CONTRIBUTION

What are the novel findings of this work?
In early-onset fetal growth restriction (eoFGR), a model combining estimated fetal weight and placental growth factor (PlGF) at the time of diagnosis provides the best prediction of perinatal survival. Prenatal prediction of severe neonatal morbidity in eoFGR is modest regardless of the model used.

What are the clinical implications of this work?
Determination of PlGF at diagnosis of eoFGR should help the clinician to assess the chances of perinatal survival.

ABSTRACT

Objective *To analyze the ability to predict perinatal survival and severe neonatal morbidity of cases with early-onset fetal growth restriction (eoFGR) using maternal variables, ultrasound parameters and angiogenic markers at the time of diagnosis.*

Methods *This was a prospective observational study in a cohort of singleton pregnancies with a diagnosis of eoFGR (< 32 weeks of gestation). At diagnosis of eoFGR, complete assessment was performed, including ultrasound examination (anatomy, biometry and Doppler assessment) and maternal serum measurement of the angiogenic biomarkers, soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF). Logistic regression models for the prediction of perinatal survival (in cases diagnosed at < 28 weeks) and severe neonatal morbidity (in all liveborn cases) were calculated.*

Results *In total, 210 eoFGR cases were included, of which 185 (88.1%) survived perinatally. The median gestational age at diagnosis was 27 + 0 weeks. All cases diagnosed at ≥ 28 weeks survived. In cases diagnosed < 28 weeks, survivors (*vs *non-survivors) had a higher gestational age (26.1* vs *24.4 weeks), estimated fetal weight (EFW; 626* vs *384 g), cerebroplacental ratio (1.1* vs *0.9), PlGF (41* vs *18 pg/mL) and PlGF multiples of the median (MoM; 0.10* vs *0.06) and lower sFlt-1/PlGF ratio (129* vs *479) at the time of diagnosis (all* P < *0.001). The best combination of two variables for predicting perinatal survival was provided by EFW and PlGF MoM (area under the receiver-operating-characteristics curve (AUC), 0.84 (95% CI, 0.75–0.92)). These were also the best variables for predicting severe neonatal morbidity (AUC, 0.73 (95% CI, 0.66–0.80)).*

Conclusions *A model combining EFW and maternal serum PlGF predicts accurately perinatal survival in eoFGR cases diagnosed before 28 weeks of gestation. Prenatal prediction of severe neonatal morbidity in eoFGR cases is modest regardless of the model used.*

INTRODUCTION

Early-onset fetal growth restriction (eoFGR) without demonstrable congenital anomaly is defined by a Delphi consensus as a fetus that does not reach its growth potential diagnosed before 32 weeks of gestation[1]. It

Correspondence to: Dr C. Villalaín, Department of Obstetrics and Gynaecology, Hospital Universitario 12 de Octubre, Avda de Córdoba s/n, Madrid 28041, Spain (e-mail: cecilia.villalain@salud.madrid.org)
#I.H. and A.G. contributed equally to this study.

Accepted: 18 October 2022

belongs to the spectrum of manifestations related to severe placental dysfunction and affects approximately one in 300 pregnancies. The estimated annual incidence in Europe is 3.3 per 10 000 population, meeting the criteria for a rare disease[2]. Efficient therapeutic interventions have not been developed and eoFGR remains a leading cause of iatrogenic prematurity, perinatal death and long-term morbidity[3].

The recognition of eoFGR is usually straightforward with correct antenatal surveillance, as this condition leads to a series of pronounced clinical and sonographic manifestations, such as decreased fundal height, pre-eclampsia (PE), small measurements on fetal biometry and increased resistance in the uterine and umbilical arteries. However, obstetric management of eoFGR remains a major challenge in terms of establishing adequate follow-up to prevent stillbirth and to achieve timely delivery to avoid postnatal death from prematurity[4]. Because of the lack of effective treatments and difficulties in predicting the intrauterine behavior of eoFGR, parental counseling at the time of diagnosis has an element of uncertainty. Current assessment is based on updated neonatal survival charts for preterm infants adjusted by gestational age (GA) at delivery, birth weight and gender[5]. Between-hospital variation in outcome should also be considered, especially in extremely preterm infants[6]. Additionally, fetal Doppler status may have a prognostic role[7,8]. The main issue is that the time-to-delivery interval after diagnosis is highly variable depending on the rate of progression of the fetoplacental deterioration, and none of these parameters estimates it accurately[9]. Angiogenic factors (soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF)) are surrogate markers of placental dysfunction and are related to the time-to-delivery interval in the setting of placental-dysfunction-related disorders[10,11]. Nevertheless, only recently have they been proposed as useful tools for monitoring and prognostic assessment in eoFGR[12–14].

This study aimed to predict perinatal survival and, secondarily, severe neonatal morbidity using maternal variables, ultrasound parameters and angiogenic markers at the time of diagnosis of eoFGR.

METHODS

Study population

This was an observational prospective cohort study carried out in a tertiary hospital. All consecutive singleton pregnancies that were diagnosed with eoFGR of placental origin, i.e. in the absence of congenital anomalies[1], between February 2014 and September 2020 (those recruited before October 2018 were also included in a previous paper[12]) were included. In our center, we followed a previously described screening protocol for the identification of early forms of PE/FGR[15] based on the use of uterine artery Doppler and sFlt-1/PlGF ratio in selected women, but cases of eoFGR referred from other centers were also included.

Complete assessment was performed at the initial diagnosis, including ultrasound examination, measurement of serum levels of sFlt-1 and PlGF, and calculation of the sFlt-1/PlGF ratio. Perinatal counseling involving an expert neonatologist and psychological support when needed was undertaken. We also measured maternal blood pressure and screened for proteinuria (spot urine protein–creatinine ratio) to determine the co-occurrence of PE and to tailor management[16]. The PE status was not a cause for exclusion. Cases with a prenatal or postnatal diagnosis of congenital anomaly, lack of sFlt-1/PlGF measurement or incomplete follow-up were excluded. Written informed consent was obtained prior to participation. The study was approved by the local research ethics committee (PI13/02405). The items of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies were checked[17].

Data collection and outcomes

We recorded all maternal and ultrasound scan data in our reporting system (ViewPoint 5; GE Healthcare, Chicago, IL, USA). They included maternal age, weight, height, smoking habit, race/ethnicity, mode of conception, low-dose aspirin prophylaxis, low-molecular-weight heparin prophylaxis and risk factors for PE (that are shared with eoFGR) described by the guidelines of the National Institute for Health and Care Excellence[18].

GA was estimated based on the last menstrual period, which was corrected by the crown–rump length (between 9 + 0 and 14 + 0 weeks' gestation) if a discrepancy of > 7 days was present or by the biparietal diameter (between 14 + 0 and 21 + 6 weeks) if there was a > 10-day discrepancy[19]. From 14 weeks of gestation onwards, biparietal diameter, head circumference, abdominal circumference (AC) and femoral length were measured systematically on all routine scans and estimated fetal weight (EFW) was calculated using Hadlock's formula[20]. Customization was used to calculate the EFW centiles by applying the GROW software for the Spanish population[21]. Whenever FGR was suspected before 32 weeks (EFW/AC or fundal height below the 10th centile, decline in growth centile, reduced fetal movements, low amniotic fluid volume or non-reassuring fetal heart rate pattern), the case was referred to our fetal medicine unit, in which, once the diagnosis was confirmed and a detailed fetal examination was carried out, TORCH screen of maternal serum was ordered and a cytogenetic analysis via amniocentesis was offered. Ultrasound examinations were performed by one of the authors (J.R.-C., C.V., P.I.G.-A., M.S.Q. or I.H., all maternal–fetal medicine specialists) using high-quality equipment (Aplio 500; Canon Medical Systems, Otawara, Japan). Fetoplacental Doppler evaluation included umbilical artery (UA)-pulsatility index (PI), uterine artery-PI, middle cerebral artery (MCA)-PI, cerebroplacental ratio (CPR) and ductus venosus (DV)-PI. DV-PI was measured whenever UA-PI was > 95th centile, MCA-PI < 5th centile or CPR < 5th centile. PI centiles were obtained using a free online calculator (http://

medicinafetalbarcelona.org/calc/) based on the Doppler charts of Arduini and Rizzo[22], Hecher *et al.*[23] and Baschat and Gembruch[24]. For the predictive purposes of this study, altered Doppler was defined as absent/reversed UA flow and impaired MCA-PI ($< 5^{th}$ centile) since this combination of parameters has recently shown the best association with perinatal complications in eoFGR, greater than that of uterine artery-PI and DV-PI[8].

The diagnosis of eoFGR was established, according to the Delphi consensus-based definition[1], when an ultrasound examination performed before 32 weeks of gestation revealed (1) absent end-diastolic flow in the UA, (2) EFW or fetal AC below the 3^{rd} centile or (3) EFW/AC below the 10^{th} centile combined with UA-PI or uterine artery-PI above the 95^{th} centile. Although this consensus was released after the start of this study, we have reviewed carefully all cases and have established the moment of eoFGR diagnosis coinciding with the scan in which Delphi criteria were met for the first time. Prenatal surveillance and decision to deliver followed the stage-based protocol of Figueras and Gratacós[4] for FGR management. In brief, Stage I (antegrade UA end-diastolic flow) was monitored weekly using ultrasound plus conventional cardiotocography, and labor induction was planned around 37 weeks' gestation. Stage II (absent end-diastolic UA flow) was monitored every 48–72 h, and delivery was planned around 34 weeks by elective Cesarean section. Stage-III cases (reversed end-diastolic UA flow or DV-PI above the 95^{th} centile) underwent daily in-hospital monitoring until elective Cesarean section around 30 weeks. In Stage-IV cases (reversed DV a-wave or spontaneous decelerations on cardiotocography), elective Cesarean section within 12 h was indicated. This was applied systematically whenever 26 + 0 weeks of gestation had been reached and EFW was greater than 500 g, since these are the criteria that are considered to establish the reasonable limit of viability in eoFGR[7,25]. In all these cases, an initial course of antenatal corticosteroid therapy for fetal maturation consisting of two 12-mg intramuscular doses of betamethasone was administered shortly after confirming the eoFGR diagnosis. A repeat course of corticosteroids was indicated if delivery was expected within 7 days and before 34 weeks of gestation, provided that the prior course had been administered more than 14 days before. Furthermore, magnesium sulfate was used for fetal neuroprotection with a 6-g bolus followed by a constant infusion of 2 g per h[26] when imminent delivery was expected before 32 + 0 weeks. In highly selected cases and after extensive counseling, the same management pathway could be offered at parental request even if the prior viability criteria were not met. However, we did not face this scenario in our sample.

The existence of PE was ruled out systematically. At each visit, blood pressure and urine protein were measured. A high degree of suspicion for PE was always maintained, and whenever hypertension or an sFlt-1/PlGF ratio > 85 (cut-off for the diagnosis of PE[27]) was found, the frequency of visits was doubled, even in the absence of proteinuria or other criteria of organ damage. Nevertheless, for research purposes, PE was defined by the demonstration of both hypertension and proteinuria[28]. If there was coexisting PE, expectant management was intended until term, unless signs or symptoms of imminent complications were present, or any severity criteria were demonstrated after 34 + 0 weeks[29].

Measurement of sFlt-1 and PlGF in maternal serum was carried out at diagnosis of eoFGR (± 3 days). The concentrations in pg/mL of sFlt-1 and PlGF were analyzed using an automated assay (Cobas® 6000 e701 module; Roche Diagnostics, Penzberg, Germany). Absolute values were transformed into multiples of the median (MoM) adjusted by GA[30]. Attending clinicians had full access to these results, but the decision to deliver was made according to previously described protocols[15,28]. Nevertheless, the indirect influence of angiogenic biomarkers when interpreting clinical, ultrasound and biochemical data that could lead to a decision to deliver could not be avoided.

Perinatal data were collected from hospital records and included the date and route of delivery, birth weight, sex, 5-min Apgar score, umbilical cord arterial pH, admission to the neonatal intensive care unit (NICU) and days in NICU. Perinatal survival was defined as a child surviving the first 28 days postpartum. Composite severe neonatal morbidity in perinatal survivors was defined as the presence of at least one of these complications at discharge: bronchopulmonary dysplasia (need for oxygen therapy or positive airway pressure, mechanical ventilator support in babies born at or beyond 36 weeks of GA), necrotizing enterocolitis requiring surgery, periventricular leukomalacia ≥ Grade 2, intraventricular hemorrhage ≥ Grade 3, sepsis (clinical or confirmed sepsis by bacterial hemoculture isolation), retinopathy of prematurity ≥ Grade 3, patent ductus arteriosus requiring surgical treatment and need for vasopressor therapy. Postnatal follow-up was available for at least 12 months.

Statistical analysis

Sample size calculation was 85% powered for a 5% alpha level, assuming that perinatal survival in eoFGR is about 85%, and that the best predictive model for perinatal survival prediction could differentiate between a group with > 95% of survival and another with < 75% of survival. With these assumptions, a minimum of 112 eoFGR cases were required to have sufficient statistical power.

The main dependent variables were perinatal survival (primary outcome) and composite severe neonatal morbidity (secondary outcome). The independent variables were selected in accordance with the previous literature on the main determinants of perinatal morbidity and mortality in eoFGR[7,8,14,31], and included baseline maternal characteristics, GA at diagnosis of eoFGR, ultrasound (EFW, altered Doppler) and biochemical (sFlt-1, PlGF) data at diagnosis of eoFGR.

A descriptive analysis of the independent variables was performed. Furthermore, a comparison between perinatal survivors and non-survivors was performed for

the subgroup of eoFGR cases diagnosed before 28 weeks' gestation since no mortality was observed after this GA. A descriptive analysis of the perinatal outcomes was also presented. Fewer than 5% of data for variables obtained at diagnosis, follow-up and delivery were missing, and they were treated as missing completely at random (Table S1). Continuous variables are presented as mean ± SD or median (interquartile range) when normally or non-normally distributed, respectively. Categorical variables are presented as *n* (%). Univariate comparisons between independent variables and the primary and secondary outcomes were performed using the appropriate tests (Student's *t*-test or Mann–Whitney *U*-test for continuous and chi-square or Fisher's exact test for categorical variables). Variables with a *P*-value < 0.10 on the univariate analysis were included in a logistic regression model for the prediction of perinatal survival and neonatal severe morbidity. Due to the limited number of cases developing the event in the study, only combinations of two variables were included in these logistic regression models. Diagnostic accuracy of each model was assessed through sensitivity, specificity, predictive values, receiver-operating-characteristics (ROC) curves and area under the ROC curve (AUC) with 95% CI obtained by bootstrapping (1000 replicates). Optimal cut-off values were identified by Youden's method (maximizing the sum of the sensitivity and specificity). Paired ROC curves were compared by the DeLong method. Two-sided *P*-values of < 0.05 were considered significant. Statistical analysis was performed using statistical package STATA, version 14.1 (StataCorp. LLC, College Station, TX, USA).

RESULTS

Of 230 fetuses with eoFGR, 210 were included in the analysis (Figure S1). The median GA at diagnosis of eoFGR was 27 + 0 weeks. The majority (197/210, 93.8%) of cases met the viability criteria. The remaining 13 (6.2%) cases did not because the GA was < 26 + 0 weeks or EFW was < 500 g at the last ultrasound examination. Cases of intrauterine death, as well as those of neonatal death in which delivery was indicated for maternal reasons and fetuses did not reach viability criteria, are shown in Table S2. Perinatal survival rate was 88.1% (185/210), with 13 intrauterine and 12 neonatal deaths.

Main baseline characteristics according to perinatal outcome are presented in Table 1. As stated in the Methods section, given that all perinatal deaths occurred in cases diagnosed before 28 weeks of gestation, comparisons were made between perinatal survivors and non-survivors with a diagnosis < 28 weeks. There were no differences in baseline characteristics between the two groups.

The main perinatal outcomes of liveborn cases are shown in Table 2. The median GA at delivery was 30 + 6 weeks and 32/197 (16.2%) cases had a term delivery. In 4/32 (12.5%) term newborns, birth weight between the 10th and 20th centiles was confirmed. All four cases had normal PlGF at eoFGR diagnosis (between 295 and 732 pg/mL). Antenatal corticosteroids and magnesium sulfate were administered in 99.3% and 88.7% of cases with perinatal survival, respectively. The main indication for delivery among liveborn cases was related to eoFGR (68.5%), but up to 20.3% (40/197) of cases required delivery due to maternal complications associated with PE (HELLP syndrome in 4.6%, renal failure in 2.0%, refractory hypertension in 1.5%, placental abruption in the context of PE in 1.5%, a combination of these in 7.2%) or PE with or without severe features reaching 34 or 37 weeks of gestation, respectively (2.5% and 1.0%). Additionally, in 6.6% of liveborn cases, placental abruption without PE warranted prompt delivery. Severe neonatal morbidity occurred in 42.7% of cases with perinatal survival. The most frequent complication was neonatal sepsis, which occurred in 27.0% of cases, followed by need for vasopressor therapy in 17.8% of neonates.

Prediction of perinatal survival in eoFGR diagnosed before 28 weeks

The most relevant sonographic parameters and angiogenic biomarkers evaluated at diagnosis of eoFGR are presented in Table S3. Among cases diagnosed before 28 weeks of gestation, those achieving perinatal survival had a significantly higher GA at diagnosis (26.1 *vs* 24.4 weeks; *P* < 0.001), EFW (626 *vs* 384 g) and cerebroplacental ratio (1.1 *vs* 0.9), and a less altered angiogenic profile, with lower sFlt-1/PlGF ratio (129 *vs* 479) and a particular difference seen in the PlGF levels, both in absolute (41 *vs* 18 pg/mL) and MoM values (0.10 *vs* 0.06).

Single- and two-variable models of statistically significant variables on univariate analysis were tested and the most relevant are presented in Table 3. The mean AUCs after bootstrapping for all evaluated models are presented in Figure 1a. Models including PlGF (or PlGF MoM) performed significantly better than other models, and the best performance was achieved by the combination of EFW and PlGF (or PlGF MoM) at diagnosis, which was significantly better than the combination of EFW and GA at diagnosis (*P* = 0.04). The cut-off for PlGF that yielded the best sensitivity/specificity balance was 37 pg/mL (0.07 for PlGF MoM). Cases with PlGF < 37 pg/mL at diagnosis had lower survival rates (64% *vs* 95%; *P* < 0.001), shorter time to delivery (14 *vs* 43 days; *P* < 0.001) and lower estimated weight gain from diagnosis to delivery (302 *vs* 674 g; *P* < 0.001). The perinatal survival rate with PlGF < 37 pg/mL and PlGF ≥ 37 pg/mL was 58.1% *vs* 92.3% (*P* = 0.001), respectively, in normotensive pregnancies and 71.0% *vs* 100% (*P* = 0.006), respectively, in PE cases.

Figure 2 illustrates the survival rates, time to delivery and estimated weight gain from diagnosis to delivery when stratified by EFW and PlGF at diagnosis.

Prediction of severe neonatal morbidity in eoFGR

The main Doppler characteristics and angiogenic biomarker results stratified by composite severe neonatal morbidity are presented in Table S4. Those with

Table 1 Baseline characteristics of pregnancies with early-onset fetal growth restriction (eoFGR) achieving perinatal survival and those diagnosed before 28 weeks according to pregnancy outcome

		eoFGR diagnosed < 28 weeks (n = *123*)		
Characteristic	*All eoFGR with perinatal survival* (n = *185*)	*Perinatal survival* (n = *98*)	*Perinatal death* (n = *25*)	P
Referred from another center	95 (51.4)	51 (52.0)	14 (56.0)	0.72
Maternal age (years)	32.2 ± 5.9	32.3 ± 5.7	34.2 ± 4.7	0.15
Height (cm)	162 ± 7	163 ± 7	164 ± 6	0.80
Prepregnancy weight (kg)	66.6 ± 11.5	66.7 ± 12.6	64.0 ± 14.6	0.32
Prepregnancy BMI (kg/m^2)	24.8 ± 4.9	24.8 ± 4.9	25.1 ± 4.7	0.51
Current smoker	22 (11.9)	11 (11.2)	2 (8.0)	0.63
Cigarettes per day	7 (2–22)	6 (1–23)	9 (3–20)	0.61
Race or ethnicity				0.54†
White or Caucasian	124 (67.0)	65 (66.3)	20 (80.0)	
Hispanic	31 (16.8)	16 (16.3)	1 (4.0)	
Asian	6 (3.2)	4 (4.1)	1 (4.0)	
Black or African American	16 (8.6)	7 (7.1)	1 (4.0)	
Other	8 (4.3)	6 (6.1)	2 (8.0)	
Risk factors for placental dysfunction				
High				
Previous PE	24 (13.0)	12 (12.2)	2 (8.0)	0.55
Chronic hypertension	17 (9.2)	9 (9.2)	3 (12.0)	0.68
Prepregnancy diabetes	3 (1.6)	1 (1.0)	0 (0)	0.61
Chronic kidney disease	1 (0.5)	1 (1.0)	0 (0)	0.61
Thrombophilia	3 (1.6)	1 (1.0)	0 (0)	0.61
Systemic lupus erythematosus	1 (0.5)	0 (0)	0 (0)	NA
Moderate				
Nulliparous	116 (62.7)	61 (62.2)	19 (76.0)	0.20
Age ≥ 40 years	17 (9.2)	11 (11.2)	3 (12.0)	0.91
Prepregnancy BMI ≥ 35 kg/m^2	7 (3.8)	4 (4.1)	1 (4.0)	0.99
Family history of PE*	9 (4.9)	3 (3.1)	2 (8.0)	0.31
More than one high-risk or two moderate-risk factors	58 (31.4)	29 (29.6)	8 (32.0)	0.82
Mode of conception				0.62
Spontaneous	165 (89.2)	86 (87.8)	21 (84.0)	
In-vitro fertilization	20 (10.8)	12 (12.2)	4 (16.0)	
Low-dose aspirin intake (100 mg/day)				0.05
No	139 (75.1)	69 (70.4)	22 (88.0)	
Starting at or before 16 weeks	39 (21.1)	25 (25.5)	1 (4.0)	
Starting after 16 weeks	7 (3.8)	4 (4.1)	2 (8.0)	
Low-dose heparin prophylaxis				0.31
No	176 (95.1)	92 (93.9)	24 (96.0)	
Starting at or before 16 weeks	8 (4.3)	5 (5.1)	0 (0)	
Starting after 16 weeks	1 (0.5)	1 (1.0)	1 (4.0)	

Data are given as *n* (%), mean ± SD or median (interquartile range). All cases diagnosed ≥ 28 weeks survived, so comparisons according to perinatal outcome were made among cases diagnosed < 28 weeks. *First-degree relative (mother or sister) with a history of pre-eclampsia (PE). †Significant differences between Caucasian and Hispanic women after Bonferroni adjustment. BMI, body mass index; NA, not applicable.

any severe morbidity had lower EFW (702 *vs* 854 g; $P < 0.001$) and poorer Doppler status, although it did not imply a more advanced FGR stage. Finally, neonates with morbidity had a higher angiogenic imbalance, especially in terms of lower PlGF values (32 *vs* 71 pg/mL; $P < 0.001$).

A prediction of composite severe neonatal morbidity was attempted using the same models developed for the prediction for perinatal mortality (Table 4). The performance of all models was low, with the AUC ranging from 0.503 to 0.731. The best AUC was obtained by PlGF MoM in two-variable combinations with EFW, GA or altered Doppler (0.731 *vs* 0.722 *vs* 0.725), which were all significantly better than other models. The mean AUCs after bootstrapping for all evaluated models are presented in Figure 1b.

The performance of the main predictive models for perinatal survival and severe neonatal morbidity at fixed false-positive rates is presented in Table S5.

DISCUSSION

Main findings

This study showed that, at the time of eoFGR diagnosis, perinatal survival is best predicted by combining EFW and PlGF. Whenever EFW is > 500 g or PlGF is ≥ 37 pg/mL, the scenario is relatively optimistic since perinatal survival is at least 80% and increases to more than 95% if both conditions are met. With EFW of ≤ 500 g, PlGF < 37 pg/mL carries an ominous prognosis, and more than

Table 2 Perinatal outcomes of liveborn cases with early-onset fetal growth restriction (FGR) according to survival

Outcome	*Perinatal survival* (n = *185*)	*Neonatal death* (n = *12*)	P
GA at delivery (weeks)	31.0 (29.0–34.6)	26.6 (26.0–27.5)	< 0.001
Time from diagnosis to delivery (days)	19 (9–46)	7 (3–15)	0.01
Corticosteroids for fetal maturation*	140/141 (99.3)	11/11 (100)	0.78
Magnesium sulfate for fetal neuroprotection†	94/106 (88.7)	10/11 (90.9)	0.02
PE	92 (49.7)	8 (66.7)	0.26
FGR stage at delivery			0.04
Stage I	92 (49.7)	2 (16.7)	
Stage II	18 (9.7)	2 (16.7)	
Stage III	53 (28.6)	3 (25.0)	
Stage IV	22 (11.9)	5 (41.7)	
Onset of delivery			0.89
Spontaneous	4 (2.2)	0 (0)	
PPROM	3 (1.6)	0 (0)	
Maternal indication, related to PE	36 (19.5)	4 (33.3)	
Fetal indication, related to FGR	127 (68.6)	8 (66.7)	
Placental abruption without PE	13 (7.0)	0 (0)	
Other indication	2 (1.1)	0 (0)	
Birth weight (g)	1100 (800–1485)	540 (465–640)	< 0.001
Female gender	83 (44.9)	2 (16.7)	0.05
5-min Apgar score < 7	15 (8.1)	6 (50.0)	< 0.001
Arterial pH ≤ 7.00	1 (0.5)	0 (0)	NA
Cesarean section	151 (81.6)	12 (100)	0.26
Neonatal morbidity among perinatal survivors‡			
Composite	79 (42.7)	12 (100)	< 0.001
BPD	25 (13.5)	1 (8.3)	0.66
IVH Grade III or IV	2 (1.1)	1 (8.3)	0.05
Necrotizing enterocolitis	14 (7.6)	0 (0)	0.66
Sepsis	50 (27.0)	9 (75.0)	< 0.001
Retinopathy of prematurity Grade III or IV	4 (2.2)	0 (0)	NA
Periventricular leukomalacia ≥ Grade II	4 (2.2)	0 (0)	NA
Patent ductus arteriosus	18 (9.7)	2 (16.7)	0.46
Need for vasopressor therapy	33 (17.8)	10 (83.3)	< 0.001
NICU admission	148 (80.0)	11 (91.7)	0.32
Days in NICU	24 (12–47)	10 (4–13)	< 0.001

Data are given as median (interquartile range), *n*/*N* (%) or *n* (%). *Including those liveborn between 24 + 0 and 34 + 6 weeks. †Including those liveborn at or before 31 + 6 weeks. ‡More than one condition observed in some cases. BPD, bronchopulmonary dysplasia (defined as need for supplementary oxygen at 36 weeks); GA, gestational age; IVH, intraventricular hemorrhage (Grade III, dilation of lateral ventricles; Grade IV, intraparenchymal hemorrhage); NA, not applicable; NICU, neonatal intensive care unit; PE, pre-eclampsia; PPROM, preterm prelabor rupture of membranes.

Table 3 Performance of different models for prediction of perinatal survival in fetuses with a diagnosis of early-onset growth restriction < 28 weeks

Model	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*	*PPV (95% CI) (%)*	*NPV (95% CI) (%)*	*AUC (95% CI)*
EFW*	74.5 (64.7–82.8)	64.0 (42.5–82.0)	89.0 (80.2–94.9)	39.0 (24.2–55.5)	0.692 (0.587–0.798)
GA at diagnosis*	98.0 (92.8–99.8)	56.0 (34.9–75.6)	86.4 (77.0–93.0)	33.3 (19.6–49.5)	0.637 (0.528–0.746)
PlGF*	59.2 (48.8–69.0)	88.0 (68.8–97.5)	95.1 (86.3–99.0)	35.5 (23.7–48.7)	0.736 (0.655–0.817)
PlGF MoM*	68.4 (58.2–77.4)	72.0 (50.6–87.9)	90.5 (81.5–96.1)	36.7 (23.4–51.7)	0.702 (0.601–0.803)
Altered Doppler†	98.0 (92.8–99.8)	4.0 (0.1–20.4)	80.0 (78.6–81.3)	33.3 (19.6–49.5)	0.510 (0.468–0.551)
EFW + GA at diagnosis	95.9 (89.9–98.9)	20.0 (6.8–40.7)	82.5 (74.2–88.9)	55.6 (21.2–86.3)	0.765 (0.655–0.876)
EFW + PlGF‡	98.0 (92.8–99.8)	36.0 (18.0–57.5)	85.7 (77.8–91.6)	81.8 (48.2–97.7)	0.831 (0.737–0.924)
EFW + PlGF MoM	95.9 (89.9–99.4)	44.0 (24.4–65.1)	87.0 (79.2–92.7)	73.3 (44.9–92.2)	0.835 (0.747–0.923)
EFW + altered Doppler	95.9 (89.9–99.4)	20.0 (6.8–40.7)	82.5 (74.2–88.9)	55.6 (21.2–86.3)	0.766 (0.643–0.876)
GA at diagnosis + altered Doppler	98.0 (92.8–99.8)	28.0 (12.1–49.4)	84.2 (80.7–87.2)	77.8 (43.6–94.1)	0.751 (0.651–0.852)
GA at diagnosis + PlGF	98.3 (95.2–99.7)	26.1 (10.2–48.4)	91.2 (89.1–93.0)	66.7 (34.9–88.1)	0.794 (0.690–0.817)
PlGF + altered Doppler	90.0 (55.5–99.7)	0 (0–13.7)	26.5 (12.9–44.4)	0 (0–97.5)	0.809 (0.706–0.913)
PlGF MoM + altered Doppler	98.9 (94.4–100)	0 (0–13.7)	79.5 (71.3–86.3)	0 (0–97.5)	0.724 (0.627–0.821)

*Evaluated at cut-offs obtained by Youden's index (estimated fetal weight (EFW) < 501 g, gestational age (GA) at diagnosis < 25 + 0 weeks, placental growth factor (PlGF) < 37 pg/mL, PlGF multiples of the median (MoM) < 0.07). †Defined as absent or reversed umbilical artery flow and impaired middle cerebral artery flow. ‡Statistically significant differences ($P < 0.05$) when compared to all univariate models and bivariate models without PlGF. AUC, area under the receiver-operating-characteristics curve; NPV, negative predictive value; PPV, positive predictive value.

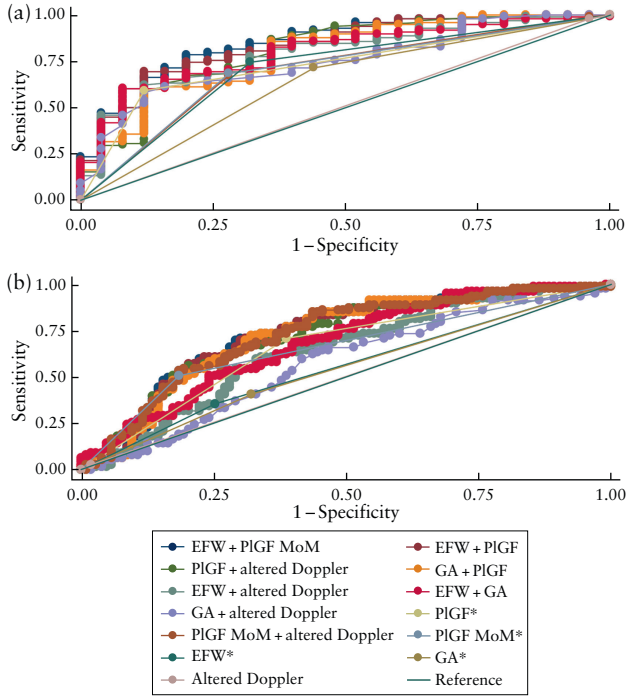

Figure 1 Mean area under the receiver-operating-characteristics curve of different proposed models for prediction of perinatal survival (a) and severe neonatal morbidity (b) after bootstrapping (1000 replications) in cases with early-onset fetal growth restriction. Altered Doppler was defined as absent or reversed umbilical artery flow and impaired middle cerebral artery flow. *Evaluated at cut-offs obtained by Youden's index (for perinatal survival: estimated fetal weight (EFW) < 501 g, gestational age at diagnosis (GA) < 25 + 0 weeks, placental growth factor (PlGF) < 37 pg/mL, PlGF multiples of the median (MoM) < 0.07; for neonatal morbidity: EFW < 650 g, GA < 26 + 4 weeks, PlGF < 46 pg/mL, PlGF MoM < 0.07).

half of such cases will not survive. However, we did not find adequate prenatal predictors of neonatal morbidity.

Interpretation of results

Accurate parental counseling in the context of eoFGR remains challenging, especially when the diagnosis is made around viability. It is known that, controlling for GA, extremely preterm infants with eoFGR have a 3-fold higher risk of mortality and a 2-week lag in survival compared with normally grown fetuses; and their viability is compromised when delivery occurs before 25–26 weeks of gestation[32]. However, at the time of diagnosing eoFGR, it is difficult to establish when delivery will be indicated, especially at the earliest stages of fetal deterioration. In the study of Story *et al.*[33], including 20 eoFGR cases diagnosed before 24 weeks' gestation, four babies were delivered at term and did not require neonatal admission. This also occurred in 15% of our cases of eoFGR. Similarly, there is a wide variability in the progression of Doppler abnormalities from diagnosis to delivery in eoFGR[34]. Therefore, our current ability to predict survival in eoFGR is limited. This study supplies new evidence regarding the utility of PlGF to better predict survival in eoFGR diagnosed before 28 weeks. At

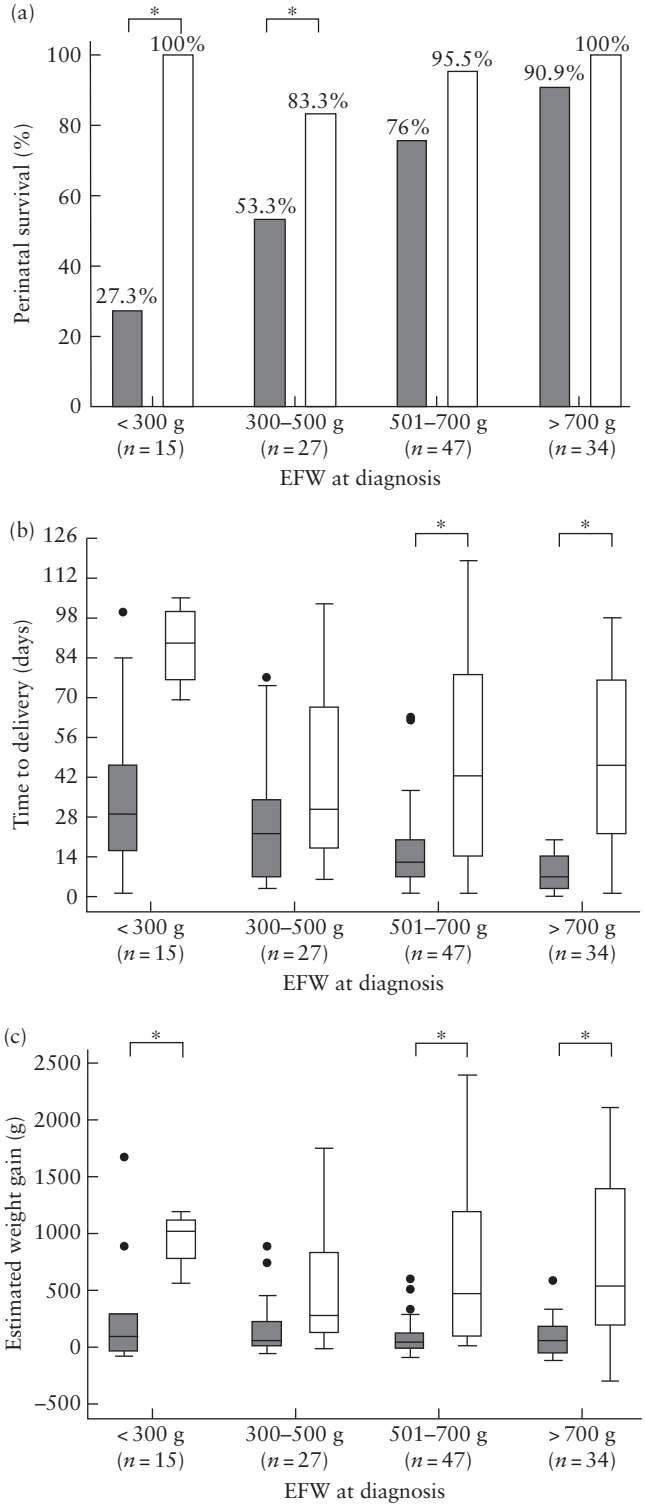

Figure 2 Perinatal survival rates (a), time from diagnosis to delivery (b) and estimated weight gain from diagnosis to delivery (c) in cases with early-onset fetal growth restriction, according to estimated fetal weight (EFW) and placental growth factor at diagnosis (PlGF) (■, PlGF < 37 pg/mL; □, PlGF ≥ 37 pg/mL). In boxplots, boxes with internal lines are median and interquartile range, whiskers are values 1.5-times the interquartile range and individual datapoints are outliers. *$P < 0.05$.

diagnosis, the combination of EFW and PlGF provides more accurate information than does GA or Doppler status. This does not contradict that the GA at birth

Table 4 Performance of different models for prediction of neonatal morbidity in surviving neonates with a prenatal diagnosis of early-onset fetal growth restriction

Model	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*	*PPV (95% CI) (%)*	*NPV (95% CI) (%)*	*AUC (95% CI)*
EFW*	75.5 (66.2–83.3)	35.4 (25.0–47.0)	61.1 (52.2–69.5)	51.9 (37.8–64.7)	0.555 (0.487–0.621)
GA at diagnosis*	66.0 (56.2–75.0)	44.3 (33.1–55.9)	61.4 (51.8–70.4)	49.3 (37.2–61.4)	0.552 (0.480–0.623)
PlGF*	62.3 (52.3–71.5)	70.9 (59.6–80.6)	74.2 (63.8–82.9)	58.3 (47.8–68.3)	0.661 (0.597–0.734)
PlGF MoM*	49.4 (37.9–60.9)	17.9 (11.2–26.6)	31.0 (23.3–39.8)	32.2 (20.6–45.6)	0.661 (0.593–0.730)
Altered Doppler†	98.1 (93.4–99.8)	2.5 (0.3–8.9)	57.4 (49.9–64.8)	50.0 (6.8–93.2)	0.503 (0.481–0.525)
EFW + GA at diagnosis	76.4 (67.2–84.1)	50.6 (39.1–62.1)	67.5 (58.3–75.8)	61.5 (48.6–73.3)	0.682 (0.605–0.758)
EFW + PlGF‡	76.7 (67.3–84.5)	60.8 (49.1–71.6)	71.8 (62.4–80.0)	66.7 (54.6–77.3)	0.726 (0.651–0.801)
EFW + PlGF MoM	59.5 (47.9–70.4)	72.8 (63.2–81.1)	62.7 (50.7–73.6)	70.1 (60.5–78.6)	0.731 (0.656–0.804)
EFW + altered Doppler	78.3 (69.2–85.7)	32.9 (22.7–44.4)	61.0 (52.3–69.3)	53.1 (38.3–67.5)	0.640 (0.560–0.721)
GA at diagnosis + altered Doppler	78.3 (69.2–85.7)	32.9 (22.7–44.4)	61.0 (52.3–69.3)	53.1 (38.3–67.5)	0.574 (0.490–0.658)
GA at diagnosis + PlGF	80.6 (71.6–87.7)	49.4 (37.9–60.9)	67.5 (58.4–75.6)	66.1 (52.6–77.9)	0.722 (0.644–0.798)
PlGF + altered Doppler	82.5 (73.8–89.3)	45.6 (34.3–57.2)	66.4 (57.5–74.5)	66.7 (54.5–77.9)	0.722 (0.648–0.797)
PlGF MoM + altered Doppler	53.2 (41.6–64.5)	80.6 (71.6–87.7)	67.7 (54.7–79.1)	69.2 (60.1–77.3)	0.725 (0.651–0.780)

*Evaluated at cut-offs obtained by Youden's index (estimated fetal weight (EFW) < 650 g, gestational age (GA) at diagnosis < 26 + 4 weeks, placental growth factor (PlGF) < 46 pg/mL, PlGF multiples of the median (MoM) < 0.07). †Defined as absent or reversed umbilical artery flow and impaired middle cerebral artery flow. ‡Statistically significant difference ($P < 0.05$) when compared to models without PlGF. AUC, area under the receiver-operating-characteristics curve; NPV, negative predictive value; PPV, positive predictive value.

continues to be the main determinant of survival, nor does it undermine the importance of prolonging the pregnancy as long as possible in eoFGR[35]. PlGF, which is a known surrogate for placental function, correlates well with the expected time-to-delivery in PE[10,36], and the sFlt-1/PlGF ratio has also been shown to be predictive of the time-to-delivery interval in eoFGR[12,13]. We have now observed that eoFGR cases with PlGF values < 37 pg/mL, which is the 1st centile at 20–32 weeks[27], have a 3-times shorter time-to-delivery interval (14 *vs* 43 days), and they achieve less than half of the estimated weight gain between diagnosis and delivery (median, 59 *vs* 373 g). In short, very low PlGF at eoFGR diagnosis increases the risk of rapid maternal–fetal deterioration and lower fetal weight gain. This translates to lower perinatal survival irrespective of the presence of PE. In periviable cases, this information could be used for guiding parental counseling and decision-making options.

Our findings are in line with a secondary analysis of the STRIDER UK study[14] that recruited eoFGR singletons between 22 + 0 and 29 + 6 weeks of gestation. Multivariate regression analysis identified EFW and angiogenic biomarkers as the independent predictors of overall survival, with AUC of 0.88 (*vs* 0.83 in this study). This further supports our choice of EFW as the parameter associated with PlGF in the survival model, although there were no differences among the different models with PlGF in terms of their AUC. In addition, the model with PlGF and EFW demonstrated a better fit to the data, with more balanced sensitivity and specificity. In contrast to the STRIDER UK study[14], in which the sFlt-1/PlGF ratio was used, we did not find that sFlt-1 improved the prediction. However, we still encourage its measurement at diagnosis of eoFGR, as sFlt-1 is associated strongly with the development of PE in the setting of eoFGR[12].

Regarding neonatal morbidity in eoFGR cases, it remains difficult to predict prenatally. Recently, Meler *et al.*[8] reported that, in periviable small-for-gestational-age fetuses diagnosed at 22 + 0 to 25 + 6 weeks of gestation, the combination of absent/reversed end-diastolic UA flow and abnormal MCA Doppler had a sensitivity of 87%, a false-positive rate of 14% and AUC of 0.89 (95% CI, 0.81–0.96) for the prediction of severe morbidity. We used the same criteria to define our altered Doppler outcome, but we were unable to replicate such results (our AUC, 0.50 (95% CI, 0.48–0.53)). A possible explanation is that we did not include fetuses with EFW < 10th centile that did not meet the Delphi criteria for eoFGR. A good prognosis in these cases is probably easier to predict when Doppler alterations are absent. The addition of PlGF also improved our predictive models for severe neonatal morbidity, but the results were modest. We speculate that severe neonatal morbidity in eoFGR depends largely on intercurrent factors that appear or manifest after birth, such as sepsis (the main contributor to severe morbidity in our series), which are unlikely to be predicted prenatally.

Strengths and limitations

We acknowledge some limitations. First, this is a single-center study, and our perinatal results may not be extrapolated to other centers. However, our survival rate (88%) is comparable with that observed in a recent systematic review[3] (81%). Second, we included eoFGR cases only if they fulfilled the Delphi criteria, which do not account for brain-sparing features (MCA-PI or CPR < 5th centile), unlike the Figueras and Gratacós[4] criteria that we have followed in clinical practice. However, this implied a diagnostic delay in only 20 cases. Third, although some measures have been included to reduce the risk of overfitting, such as bootstrapping, our results need both internal and external validation of the proposed cut-offs.

Fourth, we used the Elecsys® (Roche Diagnostics, Basel, Switzerland) platform for the measurement of PlGF, which yields slightly different results compared with others[37], and we recommend the transformation of the proposed cut-offs to the available platform[38]. Finally, clinicians were not blinded to angiogenic marker data, and this could have biased the decision to deliver, although it has been reported that the knowledge of the biomarkers did not shorten the time until delivery[39].

Conclusion

This study indicates that PlGF shows great potential to improve capability to predict the chances of survival when eoFGR is diagnosed.

ACKNOWLEDGMENTS

This work was funded by project PI13/02405, from the Instituto de Salud Carlos III (Spanish Ministry of Economy, Industry and Competitiveness) and cofunded by the European Regional Development Fund.

Disclosure

C.V., I.H. and A.G. have received lecture fees and consultancy payments from Roche Diagnostics.

REFERENCES

1. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol* 2016; **48**: 333–339.
2. Spencer R, Rossi C, Lees M, Peebles D, Brocklehurst P, Martin J, Hansson SR, Hecher K, Marsal K, Figueras F, Gratacós E, David AL; EVERREST Consortium. Achieving orphan designation for placental insufficiency: annual incidence estimations in Europe. *BJOG* 2019; **126**: 1157–1167.
3. Pels A, Beune IM, van Wassenaer-Leemhuis AG, Limpens J, Ganzevoort W. Early-onset fetal growth restriction: A systematic review on mortality and morbidity. *Acta Obstet Gynecol Scand* 2020; **99**: 153–166.
4. 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.
5. Manktelow BN, Seaton SE, Field DJ, Draper ES. Population-based estimates of in-unit survival for very preterm infants. *Pediatrics* 2013; **131**: e425–432.
6. Rysavy MA, Li L, Bell EF, Das A, Hintz SR, Stoll BJ, Vohr BR, Carlo WA, Shankaran S, Walsh MC, Tyson JE, I CM, Smith PB, Murray JC, Colaizy TT, Brumbaugh JE, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Between-hospital variation in treatment and outcomes in extremely preterm infants. *N Engl J Med* 2015; **372**:1801–1811.
7. Baschat AA, Cosmi E, Bilardo CM, Wolf H, Berg C, Rigano S, Germer U, Moyano D, Turan S, Hartung J, Bhide A, Müller T, Bower S, Nicolaides KH, Thilaganathan B, Gembruch U, Ferrazzi E, Hecher K, Galan HL, Harman CR. Predictors of neonatal outcome in early-onset placental dysfunction. *Obstet Gynecol* 2007; **109**: 253–261.
8. Meler E, Mazarico E, Peguero A, Gonzalez A, Martinez J, Boada D, Vellvé K, Arca G, Gómez-Roig MD, Gratacós E, Figueras F. Death and severe morbidity in isolated periviable small-for-gestational-age fetuses. *BJOG* 2022. DOI: 10.1111/1471-0528.17181.
9. Turan OM, Turan S, Gungor S, Berg C, Moyano D, Gembruch U, Nicolaides KH, Harman CR, Baschat AA. Progression of Doppler abnormalities in intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2008; **32**: 160–167.
10. Verlohren S, Herraiz I, Lapaire O, Schlembach D, Moertl M, Zeisler H, Calda P, Holzgreve W, Galindo A, Engels T, Denk B, Stepan H. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. *Am J Obstet Gynecol* 2012; **206**: 58.e1–8.
11. 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.
12. 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.
13. Mendoza M, Hurtado I, Bonacina E, Garcia-Manau P, Serrano B, Tur H, Rodo C, Maiz N, Carreras E. Individual risk assessment for prenatal counseling in early-onset growth-restricted and small-for-gestational-age fetuses. *Acta Obstet Gynecol Scand* 2021; **100**: 504–512.
14. Sharp A, Jackson R, Cornforth C, Harrold J, Turner MA, Kenny L, Baker PN, Johnstone ED, Khalil A, von Dadelszen P, Papageorghiou AT, Alfirevic Z. 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.
15. Herraiz I, Simón E, Gómez-Arriaga PI, Quezada MS, García-Burguillo A, López-Jiménez EA, Galindo A. Clinical implementation of the sFlt-1/PlGF ratio to identify preeclampsia and fetal growth restriction: A prospective cohort study. *Pregnancy Hypertens* 2018; **13**: 279–285.
16. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, Olovsson M, Brennecke SP, Stepan H, Allegranza D, Dilba P, Schoedl M, Hund M, Verlohren S. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. *N Engl J Med* 2016; **374**: 13–22.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–1457.
18. The National Institute for Health and Care Excellence (NICE). *Hypertension in pregnancy: diagnosis and management*. NICE Guideline (NG133). https://www.nice.org.uk/guidance/ng133.
19. Committee opinion no 611: method for estimating due date. *Obstet Gynecol* 2014; **124**: 863–866.
20. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements: A prospective study. *Am J Obstet Gynecol* 1985; **151**: 333–337.
21. Gardosi J, Francis A. Customized Weight Centile Calculator. GROW version 8.0.1, 2018. Gestation Network, www.gestation.net.
22. Arduini D, Rizzo G. Normal values of Pulsatility Index from fetal vessels: a cross-sectional study on 1556 healthy fetuses. *J Perinat Med* 1990; **18**: 165–172.
23. Hecher K, Campbell S, Snijders R, Nicolaides K. Reference ranges for fetal venous and atrioventricular blood flow parameters. *Ultrasound Obstet Gynecol* 1994; **4**: 381–390.
24. Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. *Ultrasound Obstet Gynecol* 2003; **21**: 124–127.
25. Lees CC, Stampalija T, Baschat AA, da Silva Costa F, Ferrazzi E, Figueras F, Hecher K, Kingdom J, Poon LC, Salomon LJ, Unterscheider J. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol* 2020; **56**: 298–312.
26. Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, Iams JD, Wapner RJ, Sorokin Y, Alexander JM, Harper M, Thorp JM Jr, Ramin SM, Malone FD, Carpenter M, Miodovnik M, Moawa' A, O'Sullivan MJ, Peaceman AM, Hankins GD, Langer O, Caritis SN, Roberts JM; Eunice Kennedy Shriver NICHD Maternal–Fetal Medicine Units Network. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med* 2008; **359**: 895–905.
27. Verlohren S, Galindo A, Schlembach D, Zeisler H, Herraiz I, Moertl MG, Manfred G, Pape J, Dudenhausen JW, Denk B, Stepan H. An automated method for the determination of the sFlt-1/PlGF ratio in the assessment of preeclampsia. *Am J Obstet Gynecol* 2010; **202**: 161.e1–11.
28. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. *Am J Obstet Gynecol* 2000; **183**: S1–22.
29. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G, Ishaku S; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension* 2018; **72**:24–43.
30. Verlohren S, Herraiz I, Lapaire O, Schlembach D, Zeisler H, Calda P, Sabria J, Markfeld-Erol F, Galindo A, Schoofs K, Denk B, Stepan H. 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.
31. Nawathe A, Lees C. Early onset fetal growth restriction. *Best Pract Res Clin Obstet Gynaecol* 2017; **38**: 24–37.
32. Visser GH, Bilardo CM, Lees C. Fetal growth restriction at the limits of viability. *Fetal Diagn Ther* 2014; **36**: 162–165.
33. Story L, Sankaran S, Mullins E, Tan S, Russell G, Kumar S, Kyle P. Survival of pregnancies with small for gestational age detected before 24 weeks gestation. *Eur J Obstet Gynecol Reprod Biol* 2015; **188**: 100–103.
34. Turan OM, Turan S, Gungor S, Berg C, Moyano D, Gembruch U, Nicolaides KH, Harman CR, Baschat AA. Progression of Doppler abnormalities in intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2008; **32**: 160–167.
35. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, Calvert S, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, Valcamonico A, Visser GH, Wolf H; TRUFFLE study group. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomized trial. *Lancet* 2015; **385**: 2162–2172.
36. Duhig KE, Myers JE, Gale C, Girling JC, Harding K, Sharp A, Simpson NAB, Tuffnell D, Seed PT, Shennan AH, Chappell LC. Placental growth factor

measurements in the assessment of women with suspected Preeclampsia: A stratified analysis of the PARROT trial. *Pregnancy Hypertens* 2021; **23**: 41–47.
37. Simón E, Herraiz I, Villalaín C, Gómez-Arriaga PI, Quezada MS, López-Jiménez EA, Galindo A. Correlation of Kryptor and Elecsys® immunoassay sFlt-1/PlGF ratio on early diagnosis of preeclampsia and fetal growth restriction: A case–control study. *Pregnancy Hypertens* 2020; **20**: 44–49.
38. Burke Ó, Benton S, Szafranski P, von Dadelszen P, Buhimschi SC, Cetin I, Chappell L, Figueras F, Galindo A, Herraiz I, Holzman C, Hubel C, Knudsen U, Kronborg C, Laivuori H, Lapaire O, McElrath T, Moertl M, Myers J, Ness RB, Oliveira L, Olson G, Poston L, Ris-Stalpers C, Roberts JM, Schalekamp-Timmermans S, Schlembach D, Steegers E, Stepan H, Tsatsaris V, van der Post JA, Verlohren S, Villa PM, Williams D, Zeisler H, Redman CW, Staff AC; Global Pregnancy Collaboration. Extending the scope of pooled analyses of individual patient biomarker data from heterogeneous laboratory platforms and cohorts using merging algorithms. *Pregnancy Hypertens* 2016; **6**: 53–59.
39. Klein E, Schlembach D, Ramoni A, Langer E, Bahlmann F, Grill S, Schaffenrath H, van der Does R, Messinger D, Verhagen-Kamerbeek WD, Reim M, Hund M, Stepan H. Influence of the sFlt-1/PlGF Ratio on Clinical Decision-Making in Women with Suspected Preeclampsia. *PLoS One* 2016; **11**: e0156013.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Missing data of evaluated variables

Table S2 Cases of intrauterine death and neonatal death that did not reach 26 + 0 weeks of gestation or birth weight of at least 500 g

Table S3 and S4 Characteristics of study population at diagnosis of early-onset fetal growth restriction according to perinatal survival and gestational age at diagnosis (Table S3) or presence or absence of neonatal morbidity (Table S4)

Table S5 Performance of four best predictive models for perinatal survival and severe neonatal morbidity at 5% and 10% fixed false-positive rates (FPR)

Figure S1 Flowchart of study population.