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**SHORT TITLE:** perinatal survival of early-onset FGR and PlGF

# Perinatal survival counselling of early-onset fetal growth restriction with placental growth factor

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**KEY WORDS**

PlGF; fetal growth restriction; early-onset; perinatal survival

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## CONTRIBUTION

What does this work add to what is already known?

In early-onset FGR, the combination of estimated fetal weight and PlGF at diagnosis provides the best prediction of perinatal survival.

What are the clinical implications of this work?

Determination of PlGF at diagnosis of early-onset FGR helps the clinician to assess the chances of perinatal survival.

## ABSTRACT

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

**Methods**: prospective observational study in a cohort of singleton pregnancies with a diagnosis of eoFGR (< 32+0 weeks). At diagnosis of eoFGR, complete assessment was performed, including ultrasound examination (anatomy, biometry and Doppler study) and maternal serum measurement of the angiogenic biomarkers sFlt-1 and PlGF. Logistic regression models for the prediction of perinatal survival (in cases diagnosed < 28+0 weeks) and severe neonatal morbidity (in all cases) were calculated.

**Results**: we included 210 eoFGR cases, with 185 (88%) perinatal survivors. Median gestational age at diagnosis was 27+0 weeks. All cases diagnosed at ≥ 28+0 weeks survived. In cases diagnosed < 28+0 weeks, survivors (vs. non-survivors) showed at diagnosis: higher gestational age (26.1 vs. 24.4 weeks), estimated fetal weight (626 vs. 384 g), cerebroplacental ratio (1.1 vs. 0.9) and PlGF (41 vs. 18 pg/ml), and lower sFlt-1/PlGF ratio (129 vs. 479), all $p < 0.001$. The best combination of two variables for predicting perinatal survival was provided by EFW and PlGF (AUC 0.83; 95% CI, 0.74 - 0.92). These were also the best variables for predicting severe neonatal morbidity (AUC 0.73; 95% CI, 0.65 – 0.80).

**Conclusion**: EFW and maternal serum determination of PlGF accurately predict perinatal survival in eoFGR cases diagnosed before 28 weeks. Prenatal prediction of severe neonatal morbidity in eoFGR performs modestly.

## INTRODUCTION

Early-onset fetal growth restriction (eoFGR) without demonstrated congenital anomalies is defined by Delphi consensus as a particular entity that is diagnosed before 32 weeks[1]. It belongs to the spectrum of manifestations related to severe placental dysfunction and affects to 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 therapeutics 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 it leads to a series of pronounced clinical and ultrasonographical manifestations such as decreased fundal height, preeclampsia (PE), small fetal biometry, and increased resistances in the uterine and umbilical arteries. However, obstetrical management of eoFGR remains a major challenge in terms of establishing adequate follow-up to prevent stillbirth and timely delivery to avoid postnatal death from prematurity[4]. Because of the lack of effective treatments and the difficulties to predict the intrauterine behaviour of eoFGR, parental counselling at the time of diagnosis leaves a trace of uncertainty. Current assessment is based on updated neonatal survival charts for preterm infants adjusted by gestational age (GA) at delivery, birthweight and gender[5]. Between-hospital variations in outcomes should also be considered, especially in extremely preterm infants[6]. Additionally, fetal Doppler status could have a prognostic role[7,8]. The main problem is that the time-to-delivery interval after diagnosis is highly variable depending on the rate of progression of the feto-placental deterioration, and none of these parameters estimates it accurately[9]. Angiogenic factors (soluble fms-like tyrosine kinase-1, sFlt1; placental growth factor, PlGF) are surrogate markers of placental dysfunction and have the property of being 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[12,13,14].

Our study aims to predict perinatal survival and, secondarily, severe neonatal morbidity using maternal variables, ultrasound parameters and angiogenic markers at diagnosis of eoFGR.

## METHODS

Study population

This is an observational prospective cohort study carried out in a tertiary hospital. We included all consecutive singleton pregnancies that were diagnosed with eoFGR of placental origin, i.e absent congenital anomalies[1], between February 2014 and September 2020 (those recruited before October 2018 were also included in a previous paper[12]). In our centre, we followed a previously described protocol for the identification of early forms of PE/FGR[15] based on the use of the uterine artery (UtA) 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 initial diagnosis, including ultrasound examination, perinatal counselling together with an expert neonatologist and psychological support when needed. We also measured maternal blood pressure, proteinuria (spot urine protein:creatinine ratio) and serum levels of the sFlt-1/PlGF ratio to rule-out PE[16]. Cases with a prenatal or postnatal diagnosis of congenital anomalies, lack of sFlt-1/PlGF measurement or incomplete follow-up were excluded. Written informed consent was obtained before 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). 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 of PE (that are common with those of eoFGR) described by the guidelines of the National Institute for Health and Care Excellence[18].

GA was estimated using the last menstrual period, which was corrected by the crown-rump length (between 9 + 0 and 14 + 0 weeks) 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 days discrepancy[19]. From 14 weeks onwards, biparietal diameter, head circumference, abdominal circumference (AC), and femoral length were systematically measured at all routine scans and estimated fetal weight (EFW) was calculated using Hadlock's formula[20]. We used customization to calculate the EFW centiles applying the GROW software for the Spanish population[21]. Whenever FGR was suspected before 32 weeks (EFW/AC or fundal height below 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, where once the diagnosis was confirmed and a detailed fetal examination was carried out, TORCH screen in maternal serum was ordered, and a cytogenetic study through amniocentesis was offered. Ultrasound examinations were performed by one of the authors (all fetal-maternal medicine specialists) with high-quality equipment (Aplio 500, Canon Medical Systems, Otawara, Japan). Feto-placental Doppler evaluation included UtA-pulsatility index (PI), umbilical artery (UA)-PI, middle cerebral artery (MCA)-PI, cerebroplacental ratio (CPR) and ductus venosus (DV)-PI. PI centiles were obtained with a free online calculator available at http://medicinafetalbarcelona.org/calc/. For the predictive purposes of this study, altered Doppler was defined as absent/reversed UA flow and impaired MCA-PI, since this combination of parameters has recently shown the best association with perinatal complications in eoFGR[8].

The diagnosis of eoFGR was established, according to the Delphi consensus-based definition[1], when in an ultrasound examination performed before 32 weeks, (1) absent end-diastolic flow in UA was demonstrated, or (2) the estimated fetal weight (EFW) or the fetal abdominal circumference (AC) was below 3rd centile, or (3) the EFW/AC was below 10th centile combined with UA-pulsatility index (PI) or UtA-PI above 95th centile. Although this consensus was released after the start of our study, we have carefully reviewed 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 & Gratacós[4]. In brief, stage I (antegrade UA end-diastolic flow) was monitored weekly with ultrasound plus conventional cardiotocography, and labor induction was planned around 37 weeks. Stage II (absent end-diastolic UA flow) was monitored every 48-72 hours and delivery was planned around 34 weeks by elective cesarean section. Stage III (reverse end-diastolic UA flow or DV-PI above 95$^{th}$ centile) underwent daily in-hospital monitoring until elective cesarean section around 30 weeks. In stage IV (reverse DV a-wave or spontaneous decelerations in the cardiotocography), elective cesarean section within 12 hours was indicated. This was systematically applied whenever the 26+0 weeks of gestation had been reached and the EFW was greater than 500g since these are the criteria that are considered to establish the reasonable limit of viability in eoFGR[7,22]. In all these cases, a first course of antenatal corticosteroid therapy for fetal maturation consisting of two 12-mg intramuscular dosis 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 was administered more than 14 days before. Furhermore, magnesium sulfate was used for fetal neuroprotection when imminent delivery was expected before 32 + 0 weeks. In highly selected cases and after extensive counselling, the same management pathway could be offered at parental's request even if the prior criteria of viability were not met. However, we did not face this scenario in our sample.

The existence of PE was sistematically ruled out. At each control, blood pressure and proteinuria were measured. A high index of suspicion for PE was always maintained, and whenever hypertension or an sFlt-1/PlGF ratio > 85 (defined cut-off for aid in diagnosis of PE[23]) 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[24]. 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[25].

The measurement of sFlt-1 and PlGF in the maternal serum was carried out at diagnosis of eoFGR (+/- 3 days). The concentrations in pg/ml of sFlt-1 and PlGF were analyzed with an automated assay (Cobas® 6000 e701 module, Roche Diagnostics, Penzberg, Germany). Attending clinicians had full access to these results, but the decision to deliver was taken according to the previously described protocols. Nevertheless, the indirect influence of the angiogenic biomarkers when interpreting clinical, ultrasound or analytical data that could lead to such decision could not be avoided.

Perinatal data were collected from hospital records and included the date and route of delivery, birthweight, sex, 5-min Apgar score, umbilical cord arterial pH, admission to the neonatal intensive care unit (NICU) and days at NICU. Perinatal survival was defined as a live child after the first 28 days of life. 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 or mechanical ventilator support in babies born at or beyond 36 weeks of GA), necrotizing enterocolitis requiring surgery, hypoxic-ischemic encephalopathy, 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 or the need for vasopressor therapy. Postnatal follow-up was available for at least 12 months.

Sample size calculation was 85% powered for a 5% alpha error, 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.



Statistical analysis

The main dependent variables were perinatal survival (primary outcome) and composite severe neonatal morbidity (secondary outcome). The independent variables were selected in accordance with previous literature on the main determinants of perinatal morbidity and mortality in eoFGR[7,8,14,26], and included the basal maternal characteristics, GA at diagnosis of eoFGR, ultrasound (EFW, altered Doppler) and analytical data (sFlt-1, PlGF) at diagnosis of eoFGR.

A descriptive analysis of the independent variables was made. Furthermore, a comparison between perinatal survivors and non-survivors was performed for the subgroup of eoFGR cases diagnosed before 28 weeks, since no mortality was observed after this GA. A descriptive analysis of the perinatal outcomes was also depicted. We had < 5% missing values in variables obtained at diagnosis, follow-up and delivery and they were treated as missing completely at random (Supplemental Table 1). Continuous variables were presented as mean (SD) or median (interquartile range) when non-normally distributed. Categorical variables were 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). Those variables showing a p value < 0.10 on the univariate analyses 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 at 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, the receiver-operating characteristic (ROC) curves, and the area under the ROC curve (AUC-ROC) with 95% confidence interval (95% CI) obtained by bootstrapping (1000 replicates). Optimal cut-off values were identified by Youden's method (maximising the sum of the sensitivity and the specificity). Paired ROC curves were compared by the De Long method. Two-sided p values of <0.05 were considered significant. Statistical analysis was performed using statistical package STATA, version 14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX, USA: StataCorp LP).



**RESULTS**

There were 230 fetuses with eoFGR of which 210 were finally included for analysis (Supplemental Figure 1). The median GA at diagnosis of eoFGR was 27 + 0 weeks. The majority (197/210, 94%) reached viability criteria. The remaining 13 cases (6%) did not either because the GA was < 26+0 weeks or EFW was < 500g at last ultrasound examination. Their main characteristics are summarized in Supplemental Table 2. Perinatal survival was of 185/210 (88%), with 13 intrauterine and 12 neonatal deaths.

A description of the main basal characteristics is depicted in Table 1, where results are stratified by perinatal survival. As stated in the methods section, given that all perinatal deaths occurred in cases diagnosed before 28 weeks, comparisons were made between perinatal survivors and non-survivors with a diagnosis <28 weeks. There were no differences in basal characteristics between these 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 (15.2%) cases had a term delivery. Antenatal corticosteroids were administered in 99.3% and magnesium sulfate in 88.7% of eligible cases. The main reason for indicating delivery was associated to eoFGR (66.2%) but up to 19% required delivery due to maternal complications associated to PE, which affected 48% of pregnancies. Also of note, in 7%, placental abruption conditioned prompt delivery. Severe neonatal morbidity occurred in 42.7% of the survivors. The most frequent complication was neonatal sepsis, in 27% of cases, followed by need for vasopressor therapy in 17% of neonates.

<u>Prediction of perinatal survival in eoFGR diagnosed before 28 weeks</u>

The most relevant sonographic parameters and angiogenesis biomarkers evaluated at diagnosis of eoFGR are depicted in Supplemental Table 3. Among cases diagnosed before 28 weeks, those achieving perinatal survival had a significantly higher GA at diagnosis (26.1 vs 24.4 weeks, p<0.001), EFW (626 vs 384g, p<0.001), better Doppler status and a less altered angiogenesis profile, especially so at the expense of a higher PlGF (41 vs 18 pg/mL, p<0.001).

Single and two-variable models were tested, and their results are presented in Table 3. The mean AUC after bootsrapping for all evaluated models is graphed in Figure 1A. Models including PlGF performed significantly better than the others and the best performance was achieved by the combination of EFW and PlGF at diagnosis, which was significantly better than the combination of EFW and GA at diagnosis (AUC 0.823 vs 0.765, p=0.04). The cutoff for PlGF that yielded the best sensitivity/specificity balance was 37 pg/mL. Cases with PlGF <37 pg/dL 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 (302g *vs* 674g, p<0.001). Figure 2 illustrates the survival rates, time until delivery and estimated weight gain from diagnosis to delivery when stratified by EFW and PlGF at diagnosis.

<u>Prediction of severe neonatal morbidity in eoFGR</u>

The main Doppler characteristics and angiogenesis biomarkers results stratified by composite severe neonatal morbidity are presented in Supplemental Table 4. Those with any severe morbidity had a lower EFW (702 vs 854g, 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 at the expense of lower PlGF values (32 vs 71 pg/mL, p<0.001).

A prediction of a composite of severe neonatal morbidity was attempted using the same models developed for the prediction for perinatal mortality. The performance of all models was low, ranging the AUC from 0.503 to 0.726, with the best obtained by PlGF in two-variable combinations with EFW, GA or composite altered Doppler (0.726 vs 0.722 vs 0.722) which were all significantly better than the rest. The performance of all models for the prediction of composite adverse outcome is presented in Table 4. The mean AUC after bootsrapping for all evaluated models is graphed in Figure 1B.

**DISCUSSION**

Main findings

Our study showed that, at diagnosis of eoFGR, perinatal survival is better assessed by combining EFW and PlGF. Whenever EFW is > 500g or PlGF is ≥ 37 pg/ml, the scenario is relatively optimistic since perinatal survival is at least 80% and increases to more than 90% if both conditions are present. With EFW of ≤ 500g, a PlGF < 37 pg/ml carries an ominous prognosis, and more than half of these cases will not survive. However, we did not find adequate prenatal predictors of neonatal morbidity.

Interpretation of results

Accurate parental assessment after the identification of eoFGR remains a clinical challenge, especially when the diagnosis is made around viability. It is known that, controlling for GA, extremely preterm infants exposed to eoFGR have a 3-fold higher risk of mortality and a 2-week lag in survival compared with normally grown fetuses, so that their viability is highly compromised when delivery occurs before 25-26 weeks[27]. However, at the time of diagnosing eoFGR, it is difficult to establish when delivery will have to be indicated: in the study of Story et al. which included 20 eoFGR diagnosed before 24 weeks, four babies delivered at term and not required 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[28]. Therefore, our current ability to predict survival in eoFGR is limited. This study supplies new evidence about the utility of PlGF to better predict the survival chances in eoFGR diagnosed before 28 weeks. The combination of EFW plus PlGF at diagnosis provides more accurate information than the GA or Doppler status at this same moment. This does not contradict the fact that the GA achieved at birth continues as the main determinant of survival, nor does it oppose the importance of prolonging the pregnancy as long as possible in eoFGR[29]. PlGF, which is a known surrogate for placental function, correlates well with the expected time to delivery in previous studies on PE[10,30]. Similarly, we observed that eoFGR with extremely low values of PlGF (< 37 pg/mL), which is the first centile at 20-32 weeks[31], have 3-times shorter time-to-delivery intervals (14 *vs* 43 days) with a narrow confidence interval. Furthermore, they reach less than half the weight gain until delivery (302g *vs* 674g). In short, a low PlGF value at eoFGR diagnosis indicates that rapid fetal deterioration and low weight gain are expected. In periviable cases, this information could be used to guide parental counselling and decision-making.

Our findings are in line with a secondary analysis of the STRIDER UK study that recruited eoFGR singletons between 22+0 and 29+6 weeks. Multivariate regression analysis identified EFW and angiogenic biomarkers as the independent predictors of overall survival, with AUC of 0.88[14] (vs. 0.83 in our study). This further support our choice of EFW as the parameter associated with PlGF in the survival model, although there were no differences between models with PlGF in terms of their AUC. In addition, the model with PlGF and EFW portrayed a better fit to the data, with more compensated sensitivity and specificity. As a difference with the abovementioned study, where the sFlt-1/PlGF ratio was used, we did not find that the addition of sFlt-1 improved the prediction. However, we still encourage to also measure sFlt-1 at diagnosis of eoFGR, as we demonstrated that sFlt-1 was strongly associated with the short-term delevopment of PE in the setting of eoFGR[12].

Regarding neonatal morbidity of eoFGR, it remains difficult to predict prenatally. Recently, Meler *et al.*[8] reported that, in periviable small-for-gestational-age fetuses diagnosed at 22 + 0 – 25 + 6 weeks, the combination of absent or reversed end-diastolic UA flow and abnormal MCA Doppler had a sensitivity of 87%, a false-positive value 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 "altered Doppler", but we were unable to replicate such results, being our AUC of 0.50 (95% CI, 0.48 – 0.53). A possible explanation is that we did not include fetuses with EFW < 10$^{th}$ centile that did not meet the Delphi criteria for eoFGR. A good prognosis in these cases is probably easier to be predicted when Doppler alterations are absent. The addition of PlGF also improved our predictive models for severe neonatal morbidity, but the results were still modest. We speculate that severe neonatal morbidity in eoFGR largely depends 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 individually predicted in the prenatal period.

<u>Strengths and limitations</u>

We acknowledge some limitations. First, this is a single centre study, and our perinatal results may not be extrapolated to other centres. However, our survival rate (88%) is comparable with that observed in a recent systematic review (81%)[3]. Second, our results need both internal and external validation for the proposed cut-offs. Although some measures have been included to reduce the risk of overfitting such as bootstrapping, the single center design and the relatively low number of perinatal deaths used for the development of the models require external validation. Furthermore, we have used the Elecsys® platform for the measurement of PlGF, which yields slightly different results than others[32], and we recommend the transformation of the proposed cut-offs to the available platform[33]. Third, although EFW plus PlGF provided the best AUC for prediction of perinatal survival, there were not differences between this AUC and that of other bivariate models containing PlGF. Finally, clinicians were not blinded to angiogenic markers, and this could have biased the decision to deliver, although it was reported that the knowledge of the biomarkers did not shorten the time until delivery[Error! Bookmark not defined.].

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

**Table 1.** Baseline characteristics of the study population according to perinatal survival, for all early-onset fetal growth restriction cases and for those diagnosed before 28 weeks.

| Characteristic | All eoFGR with perinatal survival (n=185) | eoFGR diagnosed <28 weeks (n=114) | | p |
|---|---|---|---|---|
| | | Perinatal survival (n=89) | Perinatal death (n=25) | |
| Referred | 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 |
| Pre-pregnancy weight (kg) | 66.6 ± 11.5 | 66.7 ± 12.6 | 64.0 ± 14.6 | 0.32 |
| Pre-pregnancy BMI (kg/m$^2$) | 24.8 ± 4.9 | 24.8 ± 4.9 | 25.1 ± 4.7 | 0.51 |
| Smoking status | | | | |
| Current | 22 (12.1) | 11 (11.3) | 2 (8.0) | 0.63 |
| Cigarettes per day (median, range) | 7 (2 - 22) | 6 (1 - 23) | 9 (3 - 20) | 0.61 |
| Race or ethnic group | | | | 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 (8.7) | 7 (7.1) | 1 (4.0) | |
| Other | 8 (4.3) | 6 (6.1) | 2 (8.0) | |
| Risk factors for placental dysfunction | | | | |
| High | | | | |
| Previous preeclampsia | 24 (13.1) | 12 (12.2) | 2 (8.0) | 0.55 |
| Chronic hypertension | 17 (9.2) | 9 (9.3) | 3 (12.0) | 0.68 |
| Pre-pregnancy 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 (0.6) | 0 (0) | 0 (0) | NA |
| Moderate | | | | |
| Nulliparity | 116 (62.7) | 61 (62.2) | 19 (76.0) | 0.20 |
| Age ≥ 40 y | 17 (9.2) | 11 (11.2) | 3 (12.0) | 0.91 |
| Pre-pregnancy BMI ≥ 35 kg/m$^2$ | 7 (3.8) | 4 (4.1) | 1 (4.0) | 0.99 |
| Family history of preeclampsia* | 9 (4.9) | 3 (2.2) | 2 (8.0) | 0.31 |
| ≥ 1 high-risk or 2 moderate-risk factors | 58 (31.4) | 29 (29.6) | 8 (32.0) | 0.82 |
| Mode of conception | | | | |

| | | | | |
|---|---|---|---|---|
| Spontaneous | 165 (89.1) | 86 (87.8) | 21 (84.0) | |
| In vitro fertilization | 20 (10.9) | 12 (12.2) | 4 (16.0) | 0.62 |
| Low-dose aspirin intake (100 mg/day) | | | | |
| No | 139 (75.1) | 69 (79.4) | 22 (88.0) | 0.05 |
| 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 | | | | |
| No | 176 (95.1) | 92 (93.9) | 24 (96.0) | 0.31 |
| 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) | |

All cases diagnosed $\geq$ 28 weeks survived. Comparisons are made among cases diagnosed <28 weeks
Data are mean ± standard deviation or n (%), unless otherwise stated.
* First-degree relative (mother or sister) with a history of PE
† Significant differences between Caucasian and Hispanic women after Bonferroni adjustment.

BMI, body mass index; NS, not significant.

**Table 2.** Perinatal outcomes among liveborn cases of early-onset fetal growth restriction.

| **Outcome** | **Perinatal survival (n=185)** | **Neonatal death (n=12)** | **p** |
|---|---|---|---|
| Gestational age at delivery (weeks), median (IQR) | 31.0 (29.0 – 34.6) | 26.6 (26.0 – 27.5) | <0.001 |
| Time from diagnosis to delivery (days), median (IQR) | 19 (9 - 46) | 7 (3 -15) | 0.01 |
| Corticosteroids for fetal maturation* | 140 (99.3) | 11 (100) | 0.78 |
| Magnesium sulfate for fetal neuroprotection† | 94 (88.7) | 10 (90.9) | 0.02 |
| Preeclampsia | 92 (49.7) | 8 (66.7) | 0.26 |
| Fetal growth restriction stage at delivery | | | |
| Stage I | 92 (49.7) | 2 (16.7) | |
| Stage II | 18 (9.7) | 2 (16.7) | 0.04 |
| Stage III | 53 (28.7) | 3 (25.0) | |
| Stage IV | 22 (11.9) | 5 (41.7) | |
| Onset of delivery | | | |
| Spontaneous | 4 (2.2) | 0 (0) | |
| PPROM | 3 (1.6) | 0 (0) | |
| Maternal indication, related to preeclampsia | 36 (19.5) | 4 (33.3) | 0.89 |
| Fetal indication, related to fetal growth | 127 (68.7) | 8 (66.7) | |
| Placental abruption | 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 (45.1) | 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 (13.7) | 1 (9.1) | 0.66 |
| IVH grade III or IV | 2 (1.1) | 1 (9.1) | 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 |
| Patent ductus arteriosus | 18 (9.7) | 2 (16.7) | 0.46 |

| | | | |
|---|---|---|---|
| Need for vasopressor therapy | 33 (17.8) | 10 (83.3) | <0.001 |
| Days at NICU, median (IQR) | 24 (12 - 47) | 10 (4-13) | <0.001 |

Data are mean ± standard deviation or n (%), unless otherwise stated.
*Including liveborn between 24 + 0 and 34 + 6 weeks.
† Including liveborn at or before 31 + 6 weeks.
‡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; IQR, interquartile range; IVH, intraventricular hemorrhage (Grade III: with dilation of the lateral ventricles; Grade IV: intraparenchymal hemorrhage); NA, not applicable; NICU, neonatal intensive care unit; PPROM, preterm premature rupture of membranes.

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

| | Sensitivity (CI 95%) | Specificity (CI 95%) | PPV (CI 95%) | NPV (CI 95%) | AUC (CI 95%) |
|---|---|---|---|---|---|
| **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) |
| **Altered Doppler†** | 98.0 (92.8 – 99.8) | 4 (0.1 – 20.4) | 80.0 (78.6 – 81.3) | 33.3 (4.5 – 84.1) | 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 + Altered Doppler** | 95.9 (89.9 – 98.9) | 20.0 (6.8 – 40.7) | 82.5 (74.2 – 88.9) | 55.6 (21.2 – 86.3) | 0.766 (0.643 – 0.876) |
| **EFW + PlGF at diagnosis‡** | 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) |
| **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) |

* Evaluated at cutoffs obtained by Youden´s index (EFW < 501g, GA at diagnosis < 25+0 weeks, PlGF < 37pg/mL).
† 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 curve; CI, confidence interval; EFW, estimated fetal weight; GA, gestational age; PlGF, placental growth factor; PPV, positive predictive value; NPV, negative predictive value.

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

| | **Sensitivity (CI 95%)** | **Specificity (CI 95%)** | **PPV (CI 95%)** | **NPV (CI 95%)** | **AUC (CI 95%)** |
|---|---|---|---|---|---|
| **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) |
| **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 + 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) |
| **EFW + PlGF at diagnosis‡** | 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) |
| **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 (52.5 - 78.9) | 0.722 (0.648 – 0.797) |

* Evaluated at cutoffs obtained by Youden´s index (EFW < 650g, GA at diagnosis < 26+4 weeks, PlGF < 46pg/mL).
† Defined as absent or reversed umbilical artery flow and impaired middle cerebral artery flow.
‡Statistically significant differences (p < 0.05) when compared to models without PlGF.
AUC, area under the curve; CI, confidence interval; EFW, estimated fetal weight; GA, gestational age; PlGF, placental growth factor; PPV, positive predictive value; NPV, negative predictive value.

## LEGENDS FOR ILLUSTRATIONS

**Figure 1**. Area under the curve for the mean of the different proposed models for (A) perinatal survival and (B) severe neonatal morbidity prediction after bootstrapping (1000 replications).

Altered Doppler is defined as absent or reversed umbilical artery flow and impaired middle cerebral artery flow.

AUC, area under the curve; EFW, estimated fetal weight; GA, gestational age; PlGF, placental growth factor.

**Figure 2**. Perinatal survival rates (A) are represented by histograms. Time until delivery (B) and estimated weight gain from diagnosis until delivery (C) are represented by box-plots showing median values (horizontal lines within the boxes), interquartile ranges (boxes), highest and lowest values within the box +/- 1.5 interquartile ranges (whiskers) and outliers that fall outside the whiskers (individual points). A, B and C are stratified by estimated fetal weight and PlGF at diagnosis.

*$p<0.05$.

PlGF, placental growth factor.

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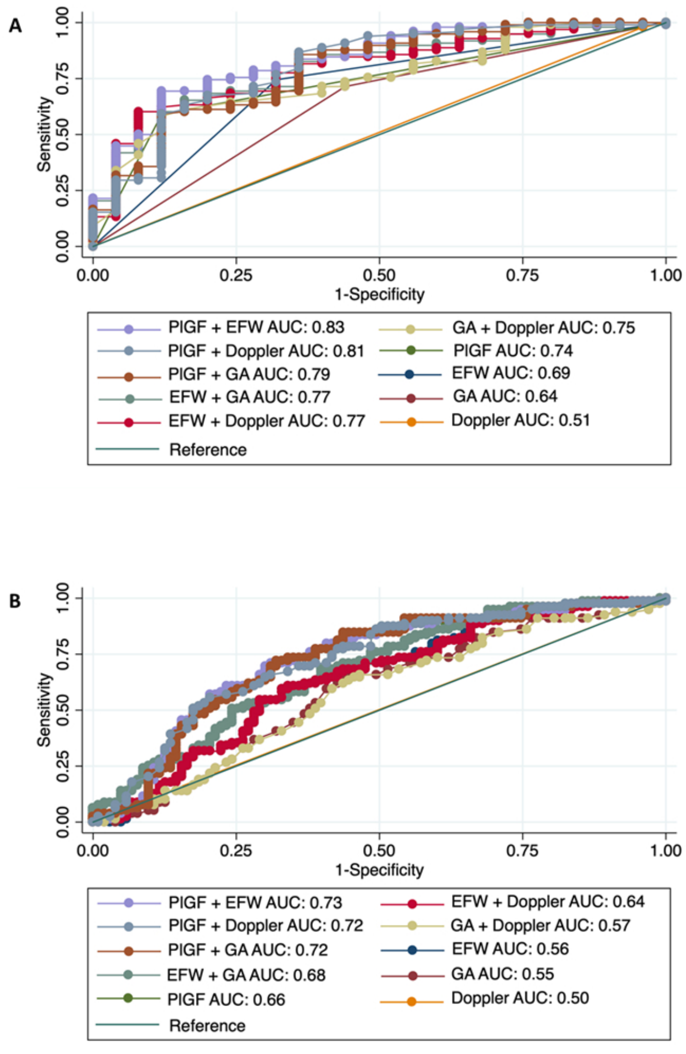



Figure 1. Area under the curve for the mean of the different proposed models for (A) perinatal survival and (B) severe neonatal morbidity prediction after bootstrapping (1000 replications).
Altered Doppler is defined as absent or reversed umbilical artery flow and impaired middle cerebral artery flow.
AUC, area under the curve; EFW, estimated fetal weight; GA, gestational age; PlGF, placental growth factor.

220x300mm (96 x 96 DPI)

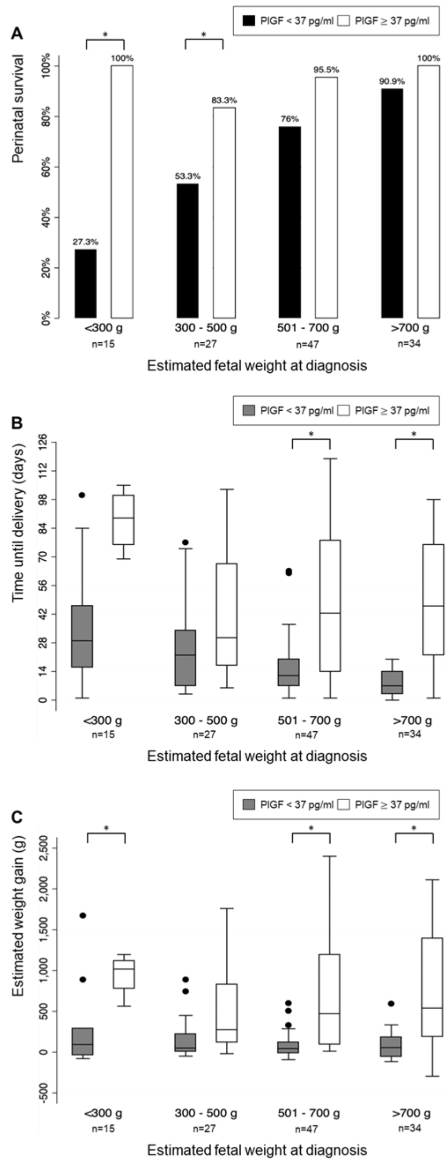



Figure 2. Perinatal survival rates (A) are represented by histograms. Time until delivery (B) and estimated weight gain from diagnosis until delivery (C) are represented by box-plots showing median values (horizontal lines within the boxes), interquartile ranges (boxes), highest and lowest values within the box +/- 1.5 interquartile ranges (whiskers) and outliers that fall outside the whiskers (individual points). A, B and C are stratified by estimated fetal weight and PlGF at diagnosis.
*p<0.05.
PlGF, placental growth factor.

200x360mm (96 x 96 DPI)

**Supplemental Table 1.** Missing values

| Variables at diagnosis | | | | | |
|---|---|---|---|---|---|
| Gestational age at diagnosis | Estimated fetal weight | Umbilical artery PI | Middle cerebral artery PI | Uterine artery PI | Fetal growth restriction stage |
| 0 (0) | 0 (0) | 5 (2.4) | 9 (4.3) | 7 (3.3) | 0 (0) |
| sFlt-1 | PlGF | sFlt-1/PlGF | | | |
| 4 (1.9) | 0 (0) | 4 (1.9) | | | |
| Follow-up variables | | | | | |
| Preeclampsia | Gestational age at preeclampsia diagnosis | Corticosteroids for fetal maturation | Magnesium sulfate administration | Legal termination of pregnancy | |
| 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | |
| Outcome variables | | | | | |
| Gestational age at delivery | Mode of delivery | Reason for indicating delivery | Intrauterine death | Neonatal death | Newborn sex |
| 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (1.0) |
| Birthweight | Apgar at 5 min | Arterial pH | NICU admission | Respiratory distress* | Bronchopulmonary dysplasia* |
| 3 (1.4) | 0 (0) | 42 (20.0) | 0 (0) | 3 (2.0) | 1 (0.7) |
| Neonatal sepsis* | Intraventricular hemorrhage* | Retinopathy > grade II* | Periventricular leukomalacia* | Nectrotizing enterocolitis* | Need for vasopresors* |
| 2 (1.4) | 1 (0.7) | 0 (0) | 0 (0) | 0 (0) | 1 (0.7) |

*Among survivors admitted to NICU.

NICU, neonatal intensive care unit; PI, pulsatility index; PlGF, placental growth factor; sFlt-1, soluble Fms-like tyrosine kinase-1.

**Supplemental Table 2.** Individual description of periviable cases that did not reach 26+0 weeks of gestation or a birthweight of at least 500g.

| Case ID | Data at diagnosis of eoFGR | | | | Data at delivery | | | Outcome |
|---|---|---|---|---|---|---|---|---|
| | GA (w+d) | EFW | FGR Stage | PlGF (pg/mL) | GA (w+d) | Birthweight (g) | FGR stage (max) | |
| 20 | 20+2 | 178 | I | 4 | 21+2 | 150 | III | IUD, vaginal delivery |
| 24 | 20+2 | 218 | I | 7 | 24+3 | 290 | III | IUD, vaginal delivery |
| 38 | 24+6 | 384 | III | 73 | 25+5 | 520 | III | IUD, vaginal delivery. Suspected extensive cerebral hemorrhage on last ultrasound |
| 41 | 22+4 | 429 | I | 17 | 23+0 | 380 | I | Emergent CS for HELLP syndrome. Neonatal death |
| 47 | 24+1 | 358 | III | 13 | 25+1 | 350 | III | IUD |
| 49 | 20+0 | 186 | I | 12 | 24+1 | 280 | III | IUD, non-severe PE |
| 72 | 25+1 | 638 | I | 13 | 25+2 | 720 | I | Emergent CS for complicated PE (persistent oliguria). Neonatal death |
| 89 | 20+1 | 183 | IV | 8 | 20+2 | 123 | IV | IUD |
| 96 | 19+4 | 201 | II | 15 | 25+4 | 260 | IV | IUD |
| 106 | 23+3 | 285 | I | 13 | 25+5 | 380 | III | Emergent CS for HELLP syndrome. Neonatal death |
| 138 | 23+2 | 364 | III | 15 | 24+2 | 370 | III | IUD |
| 157 | 21+0 | 273 | I | 27 | 23+4 | 235 | III | IUD. Single umbilical artery |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 207 | 24+3 | 531 | II | 15 | 25+3 | 520 | II | IUD. Severe PE |

CS, cesarean section; EFW, estimated fetal weight; FGR, fetal growth restriction; GA, gestational age; ID, identification number in the database; HELLP, hemolysis, elevated liver enzymes and low platelet count; IUD, intrauterine death; PE, preeclampsia; PlGF, placental growth factor; w+d, weeks + days of gestation.

**Supplemental Table 3**. Characteristics of the study population at diagnosis of early-onset fetal growth restriction according to perinatal survival and gestational age at diagnosis.

| Characteristic | Perinatal survival (n=185) | Gestational age at diagnosis <28 weeks | | p |
|---|---|---|---|---|
| | | Perinatal survival (n=98) | Perinatal death (n=25) | |
| Gestational age (weeks) | 27.3 (26.0 - 29.4) | 26.1 (24.4 – 26.7) | 24.4 (19.6 – 25.6) | <0.001 |
| Estimated fetal weight | 764 (619 – 1029) | 626 (491 – 720) | 384 (273 – 531) | <0.001 |
| Customized centile | 3 (1 - 6) | 2 (1 - 6) | 0 (0 - 2) | 0.02 |
| <3rd centile | 90 (48.7) | 90 (48.7) | 19 (76.0) | 0.01 |
| Mean uterine artery pulsatility index | 1.6 ± 0.6 | 1.7 ± 0.5 | 2.0 ± 0.7 | 0.04 |
| Centile | 95 (90 - 98) | 96 (92 - 98) | 98 (96 - 99) | 0.02 |
| >95th centile | 90 (48.7) | 90 (48.7) | 20 (80.0) | 0.003 |
| Umbilical artery pulsatility index | 1.6 ± 0.6 | 1.6 ± 0.6 | 2.3 ± 0.9 | 0.003 |
| Centile | 90 (62 - 99) | 88 (54 - 98) | 96 (85 - 99) | 0.04 |
| >95th centile | 72 (38.9) | 72 (38.9) | 13 (52.0) | 0.21 |
| AREDF | 22 (11.9) | 10 (10.2) | 9 (36.0) | 0.001 |
| Middle cerebral artery pulsatility index | 1.7 ± 0.7 | 1.8 ± 0.4 | 1.6 ± 0.4 | 0.009 |
| Centile | 17 (4 - 50) | 26 (7 - 55) | 11 (4 - 32) | 0.13 |
| <5th centile | 44 (23.8) | 44 (23.8) | 7 (28.0) | 0.64 |
| Cerebroplacental ratio | 1.1 ± 0.3 | 1.1 ± 0.3 | 0.9 ± 0.4 | <0.001 |
| Centile | 3 (1 - 11) | 4 (1 - 16) | 1 (0 - 6) | 0.04 |
| <5th centile | 107 (57.9) | 107 (57.9) | 17 (68.0) | 0.33 |
| Fetal growth restriction stage | | | | |
| Stage I | 169 (91.4) | 92 (93.9) | 15 (60.0) | |
| Stage II | 9 (4.9) | 2 (2.9) | 2 (8.0) | <0.001 |
| Stage III | 5 (2.7) | 3 (3.1) | 6 (24.0) | |
| Stage IV | 2 (1.1) | 1 (1.0) | 2 (8.0) | |
| sFlt-1/PlGF | 144 (33 - 423) | 129 (33 - 321) | 479 (199 - 703) | <0.001 |
| sFlt-1 (pg/mL) | 6139 (2686 - 11921) | 4893 (2159 - 9569) | 7044 (6057 - 10450) | 0.03 |
| PlGF (pg/mL) | 42 (26 - 88) | 41 (26 - 80) | 18 (13 - 32) | <0.001 |

Data are meadian (IQR) or n (%), unless otherwise stated. Comparisons were between groups diagnosed <28 weeks

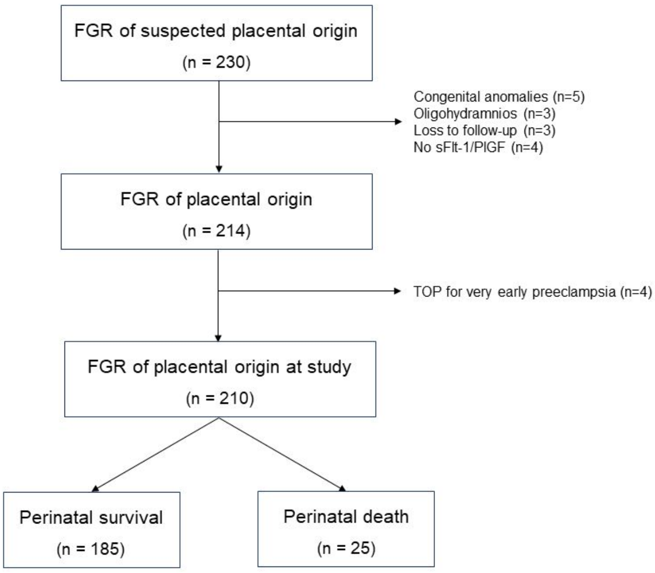
AREDF, absent or reversed end diastolic flow; IQR, interquartile range; PlGF, placental growth factor; sFlt-1, soluble Fms-like tyrosine kinase-1.

**Supplemental Table 4.** Characteristics of the study population at diagnosis of early-onset fetal growth restriction according to the presence or absence of neonatal morbidity.

| Characteristic | All perinatal survival (n=185) | Severe morbidity | | p |
|---|---|---|---|---|
| | | None (n=106) | Any (n=79) | |
| Gestational age (weeks) | 27.3 (26.0 - 29.4) | 24.4 (19.6 – 25.6) | 26.1 (24.4 – 26.7) | 0.04 |
| Estimated fetal weight | 764 (619 – 1029) | 854 (650 – 1132) | 702 (568 – 885) | <0.001 |
| Customized centile | 3 (1 - 6) | 3 (1 - 7) | 2 (0 - 5) | 0.07 |
| <3rd centile | 90 (48.7) | 48 (45.3) | 42 (53.2) | 0.01 |
| Mean Uterine artery pulstatility index | 1.6 ± 0.6 | 1.5 ± 0.6 | 1.8 ± 0.6 | 0.001 |
| Centile | 95 (90 - 98) | 94 (90 - 97) | 97 (93 - 99) | 0.002 |
| >95th centile | 90 (48.7) | 43 (40.6) | 47 (59.5) | 0.01 |
| Umbilical artery pulsatility index | 1.6 ± 0.6 | 1.5 ± 0.5 | 1.7 ± 0.7 | 0.002 |
| Centile | 90 (62 - 99) | 87 (54 - 97) | 95 (80 - 99) | 0.006 |
| >95th centile | 72 (38.9) | 39 (49.4) | 33 (31.1) | 0.01 |
| AREDF | 22 (11.9) | 9 (8.5) | 13 (16.4) | 0.10 |
| Middle cerebral artery pulsatility index | 1.7 ± 0.7 | 1.7 ± 0.6 | 1.6 ± 0.4 | 0.009 |
| Centile | 17 (4 - 50) | 23 (7 - 55) | 10 (3 - 37) | 0.02 |
| <5th centile | 44 (23.8) | 20 (18.9) | 24 (30.4) | 0.07 |
| Cerebroplacental ratio | 1.1 ± 0.3 | 1.2 ± 0.6 | 1.0 ± 0.4 | <0.001 |
| Centile | 3 (1 - 11) | 4 (0 - 19) | 1 (1 - 6) | <0.001 |
| <5th centile | 107 (57.9) | 53 (50.0) | 54 (69.6) | 0.01 |
| Fetal growth restriction stage | | | | |
| Stage I | 169 (91.4) | 101 (95.2) | 68 (86.1) | |
| Stage II | 9 (4.9) | 3 (2.8) | 6 (7.6) | 0.14 |
| Stage III | 5 (2.7) | 1 (0.9) | 4 (5.1) | |
| Stage IV | 2 (1.1) | 1 (0.9) | 1 (1.3) | |
| sFlt-1/PlGF | 144 (33 - 423) | 72 (19 - 326) | 260 (133 - 478) | <0.001 |
| sFlt-1 (pg/mL) | 6139 (2686 - 11921) | 4177 (2018 - 10409) | 8405 (4912 - 12801) | <0.001 |
| PlGF (pg/mL) | 42 (26 - 88) | 71 (36 - 166) | 32 (20 - 51) | <0.001 |

Data are mean ± standard deviation or n (%), unless otherwise stated.
AREDF, absent or reversed end diastolic flow, IQR, interquartile range; PlGF, placental growth factor; sFlt-1, soluble Fms-like tyrosine kinase-1.

**Supplemental Figure 1.** Flow-chart of study population.




FGR, fetal growth restriction; PPROM, preterm premature rupture of membranes; TOP, termination of pregnancy; PlGF, placental growth factor; sFlt-1, soluble Fms-like tyrosine kinase-1.