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Prediction of adverse neonatal outcome at admission for early-onset preeclampsia with severe features

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Abstract:	Background: Preeclampsia remains the leading cause of maternal morbidity and mortality. Consequently, research has focused on validating tools to predict maternal outcomes regarding clinical and biochemical features from the maternal compartment. However, preeclampsia also leads to neonatal complications due to placental insufficiency and prematurity, being the early-onset type associated with the poorest outcome. Hence, it is imperative to study whether these existing tools can predict adverse neonatal outcome. Objective: To assess the predictive value for adverse neonatal outcome of Doppler ultrasound, angiogenic factors and multi-parametric risk-score models in women with early-onset severe preeclampsia. Study design: This is a prospective cohort study of consecutive singleton pregnancies complicated by early-onset severe preeclampsia. Results: Of 63 women with early-onset severe preeclampsia, 18 (28.6%) presented an adverse neonatal outcome. PlGF showed the best discrimination between neonatal outcomes among angiogenic factors. Good predictive values for the prediction of neonatal complications were found with the combination of PREP-L score with advanced Doppler (AUC ROC 0.9 95% CI 0.82-0.98]) and with PlGF levels (AUC ROC 0.91 [95% CI 0.84-0.98]). Conclusions: The combination of maternal risk scoring (PREP-L score) with angiogenic factors or fetal Doppler ultrasound at the time of diagnosis of early-onset preeclampsia with severe features performs well in predicting adverse neonatal outcome.
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The Editors

Pregnancy Hypertension

Dear Editor in Chief,

Please find enclosed the manuscript entitled ***"Prediction of adverse neonatal outcome at admission for early-onset preeclampsia with severe features"*** to be considered for possible publication in your journal as an original research article.

In this paper, we show that in patients with early-onset preeclampsia with severe features the combination of maternal risk multiparametric score (PREP-L score) with angiogenic factors or fetal Doppler ultrasound at the diagnosis performs well in predicting adverse neonatal outcome.

We believe that this manuscript is appropriate for publication by your journal because it provides information on improving maternal care and women's heatlh.

Each author participated in conducting analyses, drafting the manuscript, editing, and approving the submitted version. The authors declare that the article is original and unpublished and not being considered for publication elsewhere. All authors fulfill all conditions required for authorship. There is no direct or indirect commercial or financial incentive associated with publishing this article.

Thank you for your consideration.

Yours sincerely,

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HIGHLIGHTS

- Early-onset PE with severe features is associated with neonatal complications.
- Risk-score models and fetal Doppler did not accurately predict neonatal outcomes.
- Combination of risk-score and doppler and/or PlGF for better prediction of neonatal outcomes.

Prediction of adverse neonatal outcome at admission for early-onset preeclampsia with severe features.

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ABSTRACT

Background: Preeclampsia remains the leading cause of maternal morbidity and mortality. Consequently, research has focused on validating tools to predict maternal outcomes regarding clinical and biochemical features from the maternal compartment. However, preeclampsia also leads to neonatal complications due to placental insufficiency and prematurity, being the early-onset type associated with the poorest outcome. Hence, it is imperative to study whether these existing tools can predict adverse neonatal outcome.

Objective: To assess the predictive value for adverse neonatal outcome of Doppler ultrasound, angiogenic factors and multi-parametric risk-score models in women with early-onset severe preeclampsia.

Study design: This is a prospective cohort study of consecutive singleton pregnancies complicated by early-onset (developed before 34 week's gestation) severe preeclampsia.

Results: Of 63 women with early-onset severe preeclampsia, 18 (28.6%) presented an adverse neonatal outcome. Placental growth factor (PlGF) showed the best discrimination between neonatal outcomes among angiogenic factors. PREP-L score is a multi-parametric risk-score for the prediction of complications in early-onset preeclampsia which includes maternal characteristics and clinical and analytical data obtained at admission. Good predictive values for the prediction of neonatal complications were found with the combination of PREP-L score with advanced Doppler (AUC ROC 0.9 95% CI 0.82-0.98]) and with PlGF levels (AUC ROC 0.91 [95% CI 0.84-0.98]).

Conclusions: The combination of maternal risk scoring (PREP-L score) with angiogenic factors or fetal Doppler ultrasound at the time of diagnosis of early-onset preeclampsia with severe features performs well in predicting adverse neonatal outcome.

KEYWORDS:

Angiogenic factors; Early-onset severe preeclampsia; Neonatal adverse outcome; Doppler ultrasound; Placental growth factor; Soluble fms-like tyrosine kinase 1.

INTRODUCTION

Preeclampsia (PE) is a pregnancy-related syndrome characterized by hypertension and end-organ dysfunction that affects about 2-8% of pregnancies (1). It is worldwide a leading cause of maternal morbidity and mortality (2), and, accordingly, prediction and prevention of these maternal complications have been the main research focus. In addition, PE is also linked to neonatal complications mainly due to the associated placental insufficiency and prematurity, being responsible for 10% of stillbirths (3) and ranking first as a cause of iatrogenic prematurity (4).

In terms of pathophysiology, two entities can be distinguished, on one hand late-onset PE (developed after 34 weeks' gestation) and on the other hand early-onset PE (developed before 34 week's gestation), which is strongly associated with placental insufficiency and maternal systemic endothelial damage conferring the highest maternal and neonatal risks (5–7). In addition, we can classify the disease by the presence of severe features. This severity is defined by laboratory and clinical parameters only from the maternal compartment. Moreover, most of the multi-parametric risk-scores models, such as Prediction of Risks in Early-onset Preeclampsia (PREP) and Preeclampsia Integrated Estimate of Risk (PIERS) have shown promise in the prediction of maternal but not neonatal outcomes (8,9).

Fetal and maternal Doppler has been proposed for predicting neonatal adverse outcome, under the rationale that it may capture the intrauterine stress secondary to the maternal disease. Despite that, in the context of PE several studies have demonstrated that fetal Doppler indices did not accurately predict neonatal outcomes (10–14) and that the natural history of placental insufficiency is less predictable in

80 women with PE (15). Furthermore, Doppler ultrasound surveillance requires trained
81 staff and advanced equipment, which may not be available in all settings.

82 In PE, the endothelial and placental dysfunction leads to increased levels of anti-
83 angiogenic factors (like soluble fms-like tyrosine kinase-1 [s-Flt-1]) and decreased
84 maternal levels of pro-angiogenics factors (like placental growth factor [PlGF]) (16,17).
85 These biochemical markers seem to be helpful for the diagnosis of the disease and have
86 emerged as reliable predictors of adverse perinatal outcomes in women with suspected
87 PE (18–20), although it is not known its role in predicting neonatal complications in
88 women with an established diagnosis of PE (21). PlGF has shown also potential to predict
89 the chances of perinatal survival in cases of early-onset fetal growth restriction (FGR)
90 (22).

91 This study aims to assess the predictive value for adverse neonatal outcomes at
92 admission of Doppler ultrasound, angiogenic factors and multi-parametric risk-score
93 models in women with early-onset PE with severe features.

MATERIALS AND METHODS

Population

Between March 2017 and April 2019, a prospective cohort was created of consecutive singleton pregnancies complicated by early-onset severe PE who were admitted to the Departments of Maternal-Fetal Medicine at BCNatal (Hospital Clínic and Hospital Sant Joan de Déu, Barcelona, Spain). Additional inclusion criteria were the absence of maternal or fetal complications at admission that require immediate delivery.

The study protocol was approved by the Ethics Committee (HCB/2017/0077) and participants provided their written informed consent.

Definitions

PE was defined by the presence of hypertension (systolic blood pressure (BP) of 140 mmHg or higher and/or diastolic BP of 90 mmHg or higher on at least two occasions 4 hours apart) accompanied by proteinuria ($\geq$ 300 mg/24h or a urine protein/creatinine ratio > 0.3 mg/mmol) after 20 weeks of gestation in previously normotensive women (23). Severe PE was defined according to the American College of Obstetricians and Gynecologists as: systolic BP $\geq$ 160 mmHg or diastolic BP $\geq$ 110 mmHg on two occasions at least 4 hours apart, thrombocytopenia (platelet count less than $100x10^9$), impaired liver function (blood concentrations of liver enzymes to twice normal and/or severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses), renal insufficiency (serum creatinine concentration greater than 1.1 mg/dl in absence of other renal diseases), pulmonary edema or new-onset cerebral or visual disturbances (24). Early-onset cases were considered when admission occurred before 34 weeks of gestation and gestational age

117 was calculated according to the crown-rump length at first-trimester ultrasound scan
118 (25).

119 FGR was defined according to the Delphi consensus for early-onset form (26). Severe
120 FGR was defined as persistent (6-hour apart) absent or reversed end-diastolic velocities
121 in the umbilical artery (UA) or ductus venosus (DV) pulsatility index (PI) >95th centile.

122 Adverse neonatal outcome was defined by the presence of any of the following criteria:
123 (i) stillbirth; (ii) neonatal death (before 28 days of age); (iii) neonatal metabolic acidosis
124 (umbilical artery pH≤7.0 plus base deficit ≥ -16); (iv) 5-min Apgar score ≤7; (v)
125 bronchopulmonary dysplasia (oxygen requirement at 36 weeks corrected gestation
126 unrelated to an acute respiratory episode); (vi) necrotizing enterocolitis (including only
127 Bell's stage 2 or 3); (vii) grade III or IV intraventricular hemorrhage; (viii) cystic
128 periventricular leukomalacia; (ix) stage 3-5 retinopathy of prematurity; (x) hypoxic
129 ischemic encephalopathy (10 minutes Apgar score ≤ 5 and/or pH 7.00 in first 60 minutes
130 of life and/or base deficit ≥ -16 in first 60 minutes associated with abnormal conscious
131 level and seizures and/or weak suck and/or hypotonia and/or abnormal reflexes); (xi)
132 acute renal failure (serum creatinine greater than 1.5 mg/dL); and/or (xii) cardiac failure
133 (requiring inotropic agents).

134 Management

135 At admission, all women underwent a physical examination and laboratory work-up
136 according to standard recommendations. Maternal BP was monitored continuously,
137 laboratory tests were assessed at least once a day and fetal assessment was performed
138 by daily cardiotocography and Doppler ultrasound at least twice a week. Magnesium
139 sulfate for seizure prophylaxis was administered to all women and antihypertensive

140 treatment was administered when BP was persistently 160/110 mmHg or higher, with
141 labetalol a first-line drug. Corticosteroid therapy for fetal lung maturity was also
142 administrated.

143 At admission, the risk for complications was estimated according to the Prediction of
144 complications in Early-onset-Preeclampsia (PREP-L) score (9,27), which includes
145 maternal age, maternal medical conditions (pre-existing chronic hypertension, renal
146 disease, diabetes mellitus, autoimmune disease and/or previous history of
147 preeclampsia), systolic BP, biochemical parameters (urine protein/creatinine ratio,
148 serum urea concentration and platelet count), gestational age and need for
149 antihypertensive treatment or magnesium sulfate. In addition, transabdominal Doppler
150 ultrasound was performed at admission. The fetal ultrasound examination at enrolment
151 included: Estimated Fetal Weight (calculated by the Hadlock formula (28)); UA PI; Middle
152 Cerebral Artery (MCA) PI and Ductus venosus (DV) PI (29). The maternal ultrasound
153 included the Mean Uterine Artery (mUtA) PI, calculated as the average PI of the right
154 and left arteries and was considered abnormal when it was >95th centile (30). All Doppler
155 parameters were adjusted by gestational age.

156 Indications for immediate delivery were uncontrollable BP (systolic BP $\geq$ 160 mm Hg or
157 diastolic BP $\geq$ 110 mm Hg not responsive to maximum doses of at least to
158 antihypertensive agents); persistent headaches refractory to treatment; epigastric pain
159 or right upper pain unresponsive to repeat analgesics; visual disturbances, motor deficit
160 or altered sensorium; stroke; myocardial infarction; renal dysfunction; pulmonary
161 edema; eclampsia; suspected placental abruption and/or non-reassuring
162 cardiotocographic reading (31,32). Beyond 26 weeks, indications for delivery also

163 included persistent (>6 hours apart) DV Doppler with reversed diastolic flow; and
164 beyond 30 weeks persistent (>6 hours apart) UA Doppler with reversed end-diastolic
165 flow or DV PI above the 95th centile for gestational age (33). Elective delivery was
166 performed beyond 34 weeks after completion of pulmonary maturation.

167 Vaginal delivery was contraindicated for obstetrical reasons, non-reassuring fetal heart
168 rate patterns, DV PI above the 95th centile for gestational age or reversed diastolic flow,
169 and/or UA Doppler with reversed end-diastolic flow.

170 Samples collection and angiogenic factors measurement

171 At admission, a 5 ml peripheral maternal blood sample was obtained. Serum was
172 separated by centrifugation at 2000 g for 10 min at room temperature, and samples
173 were immediately stored at -80ºC until assayed at an independent laboratory. Clinicians
174 and researchers were unaware of the angiogenic factor levels as they were measured
175 after delivery on stored samples.

176 Maternal serum concentration of sFlt-1 and PlGF was determined by the fully automated
177 Elecsys assays for sFlt-1 and PlGF on an electrochemiluminescence immunoassay
178 platform (Cobas analyzers, Roche Diagnostics). In all the kits, the intra-assay precision
179 was <4% for both assays and the inter-assay precision was 2.3-5.6% and 2.4-4.6% for
180 sFlt-1 and PlGF assays respectively.

181 Statistical analysis

182 Variables were checked for normal distribution by Kolmogorov-Smirnov test.
183 Comparisons between cases with and without adverse neonatal outcomes were
184 performed by Student-T (assuming unequal variances), Mann-Whitney U, Pearson Chi-

185 squared and Fisher-F, as appropriate. In any event, a p value lower than 0.05 was
186 considered statistically significant.

187 The likelihood of neonatal complications was modeled by logistic regression (with robust
188 estimation of the standard errors). The explained uncertainty for the occurrence of
189 adverse neonatal outcomes was calculated as the R^2-Naegelkerke.

190 The predictive performance was determined by receiver–operating characteristic (ROC)
191 curve analysis. Paired ROC curves were compared by the DeLong method (34).

192 Statistical analyses and graph constructions were performed using STATA 13.0
193 (StataCorp LT, Texas, USA) and R 3.1.2 (The R Foundation for Statistical Computing)
194 [package “pROC”].

RESULTS

Eighty-six women were admitted with the diagnosis of early-onset severe PE during the study period, 68 of them fulfilled the inclusion criteria and had no maternal complications and no fetal indication for immediate delivery. Five were excluded for not collecting blood samples for angiogenic factors due to a breach of the study protocol, leaving 63 women for analysis.

A total of 18 (28.6%) pregnancies had an adverse neonatal outcome, non-exclusively including 2 (3.2%) stillbirths, 4 (6.4%) neonatal demise, 1 (1.6%) neonatal acidosis, 9 (14.3%) 5-min Apgar score $\leq$7, 5 (7.9%) bronchopulmonary dysplasia, 1 (1.6%) necrotizing enterocolitis, 1 (1.6%) grade III intraventricular hemorrhage, 2 (3.2%) hypoxic-ischemic encephalopathy, 1 (1.6%) acute renal failure and 3 (4.8%) cardiac failures. Table 1 details the characteristics of the study population, pregnancy outcomes and the at-admission parameters by the occurrence of adverse neonatal outcomes. Of note, among the angiogenic factors (PlGF, sFlt-1 and, sFlt-1/PlGF ratio), the PlGF showed the largest difference between affected and unaffected babies, and it was used in the subsequent multivariate models. Table 2 shows the multivariate analysis for the association between at-admission parameters and adverse neonatal outcomes.

Figure 1 and Table 3 show the predictive performance of different combinations of at-admission predictors. Compared with the PREP-L score, both the PREP-L + severe FGR (p=0.041) and PREP-L + PlGF (0.012) significantly added predictive value. The combination of all parameters (PREP-L score, severe FGR and PlGF) did not improve further the prediction capacity. The formulas for risk estimation according the different models constructed are detailed in the Supplementary Appendix.

DISCUSSION

This study provides evidence that the combination of maternal risk scoring with angiogenic factors or fetal Doppler ultrasound at the time of diagnosis of early-onset PE with severe features has a good performance in the prediction of adverse neonatal outcomes.

To improve the prediction of adverse outcomes related to PE different tools such as the combination of signs and symptoms of PE, the evaluation of fetal and maternal Doppler ultrasound and biochemical markers alone and in combination with clinical factors have been investigated. In 2017, Thangaratinam et al demonstrated that the PREP-model predicts maternal outcomes in patients with clinical early-onset PE, but the prediction of perinatal outcomes was not evaluated (9). In our study, the PREP-L score had a limited predictive value of the adverse neonatal outcomes in early-onset PE with severe features (AUC ROC 0.69 [95% CI 0.51-0.86]).

There is controversy regarding the role of fetal Doppler in PE in predicting adverse neonatal outcome. Rani et al reported that Doppler indices of MCA and UA have good specificity but low sensitivity for detecting adverse perinatal outcomes in PE with or without severe features (13). Two prospective studies, including respectively 100 and 60 patients with severe PE, support CPR as a tool for the prediction of adverse perinatal outcomes but the majority of cases were late-onset PE (mean gestational age at admission 37 weeks of gestation) (10,11). Similarly, Orabona et al in a cohort study on 168 women with PE diagnosed at a mean gestational age of 32^{+6} weeks found that CPR was more accurate than each of their components alone in predicting adverse neonatal outcomes, albeit only marginally (35). The heterogenicity of the women included in

these studies (mixing early and late; and non-severe and severe PE) may account for the inconsistent results. In our population of early-onset PE with severe features, Doppler indices of MCA, DV and CPR were not significantly different between the groups with and without adverse neonatal outcomes, and only the composite proportion of fetuses with advanced Doppler findings (absent/reversed diastolic flow in the UA or pulsatile DV) showed differences between groups. This could be explained by the greater placental involvement in the early-onset cases and the higher association with FGR; and the stronger impact of prematurity in these cases.

In the last years, several studies have shown that angiogenic factors can increase the prediction of PE and its adverse outcomes in patients with impending signs and symptoms of the disease (18,19,36). However, the role of angiogenic factors is not similarly promising in women with established severe PE. In 2014, Pinheiro et al reported a correlation between angiogenic imbalance and poor neonatal outcome in early-onset PE (37). Simon et al demonstrated an association between sFlt-1/PlGF ratio >655 and risk of delivery in less than 48 hours, nevertheless none of the angiogenic factors evaluated were good predictors of adverse maternal or perinatal outcomes (38). In addition, because both the degree of angiogenic imbalance and the neonatal outcomes are highly correlated with the gestational age at onset of the disease (5,21), we propose that the predictive role of these markers should be evaluated as the added value over a baseline risk capturing the gestational age at onset, such as the PREP score.

In 2021, Droge et al found that integrating all available clinical and biochemical markers into a regression model yields the best predictive performance of PE-related adverse outcomes, including both maternal and perinatal (the AUC of blood pressure and

proteinuria was 69%, the AUC of the sFlt-1/PlGF on its own was 85.7% and including all clinical information was 88.7%). The cohort were women with suspected disease (n=1117) and only 351 women (31.4%) had the final diagnosis of PE, most with late-onset disease (39). Gomez-Arriaga et al, in 2014, using a cohort of 51 singleton pregnancies with early-onset PE suggested that the sFlt-1/PlGF ratio in combination with gestational age is useful for the prognostic assessment of neonatal complications (AUC was 89% corresponding to sensitivity, specificity PPV and NPV of 64%, 83%, 57% and 97% respectively), but this combination has limited value for the prediction of maternal complications (12). Reddy et al, in a cohort study with 126 women with suspected PE and 95 women with confirmed PE (regardless of the onset of the disease) demonstrated that the best performing individual marker for predicting adverse perinatal outcome was the sFlt-1/PlGF ratio (AUC 0.87 [95% CI, 0.81-0.93]), also with poor prediction for adverse maternal outcome (AUC 0.69 [95% CI, 0.59 – 0.78]) (40). Rodriguez-Calvo et al demonstrated that the addition of PlGF improves the predictive model for severe neonatal morbidity and mortality in fetus with early-onset (<32 weeks'gestation) FGR but the presence or not of PE was not taken into account (22) Interestingly in both studies, the PlGF values in the group with perinatal adverse outcomes are very similar to those obtained in this study (between 27 and 37 pg/mL). In the present study, we found that the combination of maternal characteristics at admission (PREP-L score) and advanced Doppler or PlGF has a good predictive value (AUC ~ 90%) for the prediction of neonatal complications.

Delivery is the definitive treatment of PE but the optimal time of delivery in severe cases remains controversial because the net benefit between reducing maternal risks by planned delivery and the secondary neonatal risk associated with prematurity is unclear.

Therefore, it is important to develop prognostic tools to counsel the trade-off between neonatal benefits versus maternal risks of expectant management. While patients and health professionals give a similar importance to maternal complications as core outcomes of PE, neonatal complications are seen as more relevant by patients than by professionals or researchers (41). Therefore, to advance towards a patient-centered care and shared decision-making, prediction models for adverse neonatal outcomes are needed in the management of PE. The combination of a maternal risk score (which includes gestational age at onset of PE) and fetal Doppler and/or PlGF predicts with good accuracy those cases at risk of adverse neonatal outcomes.

The strengths of the study are the prospective design, the clinic homogeneity of our population (all with early-onset severe PE), and that all patients were managed per standardized protocols with low variability in care. Additionally, the baseline score-risk we used included de gestational age as a strong predictor of perinatal complications and we tested both angiogenic factors and their ratio. Among the limitations, we acknowledge that nowadays the presence of proteinuria is not mandatory for the definition of PE however at the start of the study it was. Secondly, the relatively small sample size precluded the inclusion of more predictors in the model and the validation of the results. Moreover, the study lacks information on the long-term follow-up of the neonates.

CONCLUSION

In women with early-onset PE with severe features, the combination of a maternal risk score (PREP-L score) and fetal Doppler or PlGF performs well in predicting adverse neonatal outcomes.

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452 **Table 1.** Maternal and perinatal characteristics of the study population.

	Non-adverse neonatal outcome (n=45)	Neonatal adverse outcome (n=18)	p value*
Maternal characteristics			
Maternal age [years]; median (IQR)	34 (6)	34 (8)	0.64¥
Body mass index [kg/m^2]; median (IQR)	25.5 (4.3)	25.7 (10.7)	0.76
White-European ethnicity; n (%)	24 (54.5)	13 (72.2)	0.20
Smoking; n (%)	6 (13.3)	1 (5.6)	0.38
Chronic hypertension; n (%)	7 (15.6)	2 (11.1)	0.65
Renal disease; n (%)	1 (2.2)	2 (11.1)	0.13
Pre-gestational diabetes; n (%)	0	2 (11.1)	0.23
Autoimmune disease; n (%)	1 (2.2)	0	0.52
Nulliparous; n (%)	31 (68.9)	12 (66.7)	0.86
Previous PE; n (%)	5 (11.1)	2 (11.1)	1.00
Previous fetal growth restriction; n (%)	4 (8.9)	0	0.19
Previous stillbirth; n (%)	1 (2.2)	1 (5.6)	0.50
Maternal and perinatal characteristics at admission			
GA at enrolment [weeks]; median (IQR)	31.9 (2.2)	27.2 (4)	0.00¥
Systolic blood pressure [mmHg]; median (IQR)	170 (15)	168 (25)	0.36¥
Diastolic blood pressure [mmHg]; median (IQR)	102 (12)	100 (8)	0.20
24hr urinary protein excretion [mg/24h], median (IQR)	1921 (3595)	1477 (4220)	0.95¥
Aspartate transaminase (IU/L); median (IQR)	25 (21)	24 (28)	0.76¥
Platelet count (x10^9); median (IQR)	224 (85)	168 (90)	0.32
Creatinine (µmol/L); median (IQR)	62 (23.4)	58.8 (22.1)	0.51¥
Oxygen Saturation (%); median (IQR)	98 (2)	99 (3)	0.30¥
Estimated fetal weight centile <10th; n (%)	34 (77.3)	17 (94.4)	0.11
Perinatal outcome			
GA at delivery [weeks]; median (IQR)	33 (2)	27.6 (3.8)	0.00¥
Delivery <32 weeks; n (%)	10 (22.2)	16 (88.9)	0.00
Birthweight [grams]; median (IQR)	1525 (480)	817 (479)	0.00
Birthweight <10th centile; n (%)	36 (80)	17 (94.4)	0.16
Birthweight <3rd centile; n (%)	33 (73.3)	16 (94.1)	0.07
Cesarean section; n (%)	39 (70.9)	16 (88.9)	0.81
Cesarean section for fetal distress; n (%)	14 (31.1)	7 (38.9)	0.55
Umbilical artery pH; median (IQR) $^+$	7.2 (0.1)	7.2 (0.1)	0.15¥
Admission to neonatal unit; n (%) $^+$	36 (80)	15 (93.8)	0.2
Days in the neonatal unit; median (IQR) $^+$	4 (9)	14 (28)	0.01¥

453

454 Data are n (%), mean (standard deviation [SD]), or median (interquartile range [IQR])

455 PE: preeclampsia; GA: gestational age

456 * Student's T- (or Mann-Whitney U¥) or Pearson χ^2 (or Fisher's exact) tests.

457 $^+$ Stillbirths excluded

458 [1] Pulsatility index > 95th centile (30); [2] Pulsatility index >95th centile (29) or absent or reversed end-diastolic
459 flow

460 **Table 2.** Parameters at admission by the occurrence of adverse neonatal outcome.

	Non-adverse neonatal outcome (n=45)	Neonatal adverse outcome (n=18)	p value*
PREP-L risk score; median (IQR)	76.8 (18)	88.5 (8.4)	0.00¥
PlGF [pg/mL]; mean (SD)	63.9 (43.9)	27.7 (18.6)	0.00¥
sFlt-1 [pg/mL]; mean (SD)	15853.9 (10360)	14408.2 (5592.3)	0.98¥
sFlt-1/PlGF ratio; mean (SD)	376 (281.5)	665 (404.8)	0.06
mUtA PI; mean (SD)	1.4 (0.4)	1.7 (0.4)	0.97
mUtA PI >95th centile; n (%)	37 (82.2)	15 (83.3)	0.92
UA PI; mean (SD)	1.3 (0.5)	1.7 (0.7)	0.03¥
UA PI >95th centile; n (%)	7 (15.9)	7 (38.9)	0.05
AEDV or REDV UA; n (%)	2 (4.5)	3 (16.7)	0.11
MCA PI; mean (SD)	1.5 (0.4)	1.4 (0.3)	0.61
MCA PI <5th centile; n (%)	12 (27.3)	10 (55.6)	0.04
CPR; mean (SD)	1.29 (0.5)	0.9 (0.4)	0.00
CPR <5th centile; n (%)	14 (32.6)	16 (88.9)	0.00
DV PI; mean (SD)	0.6 (0.2)	0.7 (0.3)	0.31¥
DV PI >95th centile; n (%)	3 (14.3)	4 (25)	0.41
FGR; n (%)	34 (77.3)	17 (94.4)	0.12
Severe FGR; n (%)	5 (11.1)	7 (38.9)	0.011

461

462 Data are n (%), mean (standard deviation [SD]), or median (interquartile range [IQR])

463 mUtA: mean uterine artery; PI: pulsatility index; UA: umbilical artery; AEDV: absent end-diastolic velocity;
464 REDV: reverse end-diastolic velocity; MCA: middle cerebral artery; CRP: cerebro-placental ratio; DV: ductus
465 venosus; FGR: fetal growth restriction

466 * Student's T- (or Mann-Whitney U¥) or Pearson χ^2 (or Fisher's exact) tests.

467

468 **Table 3.** Multivariate analysis for the association between at-admission parameters and
469 adverse neonatal outcome.

470

Model	R^2 Naegelkerke (%)	Parameters	OR (95% CI)	p
PREP-L score	11.9	PREP-L score	1.13 (0.99-1.29)	0.08
PREP-L + Severe FGR	28.2	PREP-L	1.06(0.93-1.2)	0.39
		Severe FGR	6.4 (1.7-24.4)	0.007
PREP-L + Low PlGF	33.4	PREP-L	1.02 (0.91-1.16)	0.72
		Low PlGF	12.8 (2.2-74.6)	0.005
PREP-L + Severe FGR + Low PlGF	40	PREP-L	1.002 (0.89-1.12)	0.98
		Severe FGR	3.87 (0.93-16.8)	0.06
		Low PlGF	8.7 (1.38-54)	0.021

471

472

473 **Table 4** Predictive performance for adverse neonatal outcome

Model	AUC (95%CI)	FPR	DR	PPV	NPV
PREP-L score	0.69 (0.51-0.86)	10%	37.5(12.5-68.8)	80.2(74.3-89)	57.1(30.8-71)
		20%	56.3(25-81.3)	83.7(75-92.3)	50(30.8-59.1)
		30%	68.8(43.8-87.5)	86.3(77.8-94)	44.9(34.2-50.9)
PREP-L + Severe FGR	0.9 (0.82-0.98)	10%	62.8(26.5-88.2)	86.5(76.4-95.3)	70.4(50-76.9)
		20%	76.5(47.1-100)	90(80-100)	59.1(47.1-65.4)
		30%	88.2(58.8-100)	94(81.8-100)	52.6(42.6-55.7)
PREP-L + Low PlGF	0.91 (0.84-0.98)	10%	58.8(23.5-94.1)	85.3(75.7-97.6)	69(47.1-78.1)
		20%	82.4(58.8-100)	92.3(83.7-100)	60.9(52.6-65.4)
		30%	88.2(70.6-100)	94(86.3-100)	52.6(47.1-55.7)
PREP-L + Severe FGR + Low PlGF	0.91 (0.81-0.98)	10%	58.8(23.5-88.2)	85.3(75.7-95.3)	69(47.1-76.9)
		20%	82.4(47.1-100)	92.3(80-100)	60.9(47.1-65.4)
		30%	88.2(64.7-100)	94(84-100)	52.6(44.9-55.7)

474

Figure 1. ROC curves for different combinations of at-admission predictors

PREP-L score (----); PREP-L score+ Severe FGR (-·-·); PREP-L score+ Low PlGF (····); PREP-L score+ Severe FGR+ Low PlGF (——)

480 **Supplementary Appendix.** Formulas for risk estimation according the different models

481 constructed

Figure 1

Click here to access/download;Figure;Figure 1.jpeg