# Prediction of adverse neonatal outcome at admission for early-onset preeclampsia with severe features: a prospective cohort study.

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**Abstract**

**ABSTRACT 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. **Design:** Prospective cohort study. **Setting:** Maternity units in two Spanish hospitals. **Population:** Women with diagnosis of early-onset severe preeclampsia. **Methods:** A multi-parametric risk score model, Doppler ultrasound, and levels of angiogenic factors were measured at admission. The predictive value for adverse neonatal outcome was calculated. **Main outcome measures:** Composite of adverse neonatal outcome. **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. **Keywords:** Angiogenic factors; Early-onset severe preeclampsia; Hypertension in pregnancy; 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, which is strongly associated with placental insufficiency and maternal systemic endothelial damage confering 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 women with PE (15). Furthermore, Doppler ultrasound surveillance requires trained staff and advanced equipment, which may not be available in all settings.

In PE, the endothelial and placental dysfunction leads to increased levels of anti-angiogenic factors (like soluble fms-like tyrosine kinase-1 [s-Flt-1]) and decreased maternal levels of pro-angiogenics factors (like placental growth factor [PlGF]) (16,17). These biochemical markers seem to be helpful for the diagnosis of the disease and have emerged as reliable predictors of adverse perinatal outcomes in women with suspected PE (18–20), although it is not known its role in predicting neonatal complications in women with an established diagnosis of PE (21).

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

## 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 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 (> 300 mg/24h or a urine protein/creatinine ratio > 0.3 mg/mmol) after 20 weeks of gestation in previously normotensive women (22). Severe PE was defined according to the American College of Obstetricians and Gynecologists as: systolic BP> 160 mmHg or diastolic BP > 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 (23). Early-onset cases were considered when admission occurred before 34 weeks of gestation and gestational age was calculated according to the crown-rump length at first-trimester ultrasound scan (24).

Fetal growth restriction (FGR) was defined according to the Delphi consensus for early-onset form (25). Severe FGR was defined as persistent (6-hour apart) absent or reversed end-diastolic velocities in the umbilical artery (UA) or ductus venosus (DV) pulsatility index (PI) >95th centile.

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

*Management*

At admission, all women underwent a physical examination and laboratory work-up according to standard recommendations. Maternal BP was monitored continuously, laboratory tests were assessed at least once a day and fetal assessment was performed by daily cardiotocography and Doppler ultrasound at least twice a week. Magnesium sulfate for seizure prophylaxis was administered to all women and antihypertensive treatment was administered when BP was persistently 160/110 mmHg or higher, with labetalol a first-line drug. Corticosteroid therapy for fetal lung maturity was also administrated.

At admission, the risk for complications was estimated according to the Prediction of complications in Early-onset-Preeclampsia (PREP-L) score (9,26), which includes maternal age, maternal medical conditions, systolic BP, biochemical parameters (urine protein/creatinine ratio, serum urea concentration and platelet count), gestational age and need for antihypertensive treatment or magnesium sulfate. In addition, transabdominal Doppler ultrasound was performed at admission. The fetal ultrasound examination at enrolment included: Estimated Fetal Weight (calculated by the Hadlock formula (27)); UA PI; Middle Cerebral Artery (MCA) PI and Ductus venosus (DV) PI (28). The maternal ultrasound included the Mean Uterine Artery (mUtA) PI, calculated as the average PI of the right and left arteries and was considered abnormal when it was $>95^{\text{th}}$ centile (29). All Doppler parameters were adjusted by gestational age.

Indications for immediate delivery were uncontrollable BP (systolic BP$>$ 160 mm Hg or diastolic BP $>$110 mm Hg not responsive to antihypertensive medication); persistent headaches refractory to treatment; epigastric pain or right upper pain unresponsive to repeat analgesics; visual disturbances, motor deficit or altered sensorium; stroke; myocardial infarction; renal dysfunction; pulmonary edema; eclampsia; suspected placental abruption and/or non-reassuring cardiotocographic reading (30,31). Beyond 26 weeks, indications for delivery also included persistent (>6 hours apart) DV Doppler with reversed diastolic flow; and beyond 30 weeks persistent (>6 hours apart) UA Doppler with reversed end-diastolic flow or DV PI above the $95^{\text{th}}$ centile for gestational age (32). Elective delivery was performed beyond 34 weeks after completion of pulmonary maturation.

*Samples collection and angiogenic factors measurement*

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

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

*Statistical analysis*

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

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

The predictive performance was determined by receiver–operating characteristic (ROC) curve analysis. Paired ROC curves were compared by the DeLong method (33).

Statistical analyses and graph constructions were performed using STATA 13.0 (StataCorp LT, Texas, USA) and R 3.1.2 (The R Foundation for Statistical Computing) [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< 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.

## DISCUSSION

*Main findings*

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.

*Strengths and Limitations*

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.

*Interpretation in light of other evidence*

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 (34). 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 (18,19,35). 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 (36). 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 (37). 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 (38). 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). 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 (39). 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.

## 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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## DISCLOSURE OF INTERESTS

None declared**.**

## CONTRIBUTION TO AUTHORSHIP

AP, EM and FF: study design. AP, LFB, EM and SH: patient recruitment. LFB, LB, DB and AG: data collection. AP and FF: data analysis. AP, LFB, EM, LB, AG, DB, LY, FC, SH and FF: drafting the manuscript and critical revision. All the authors have seen and approved the final version of the article.

## DETAILS OF ETHICS APPROVAL

This study was approved on 22 March 2017 by the Institu-tional Ethics Committee of Hospital Clinic de Barcelona(Reference number: HCB/2017/0077).

## FUNDING

None.

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## TABLES AND FIGURES CAPTION LIST

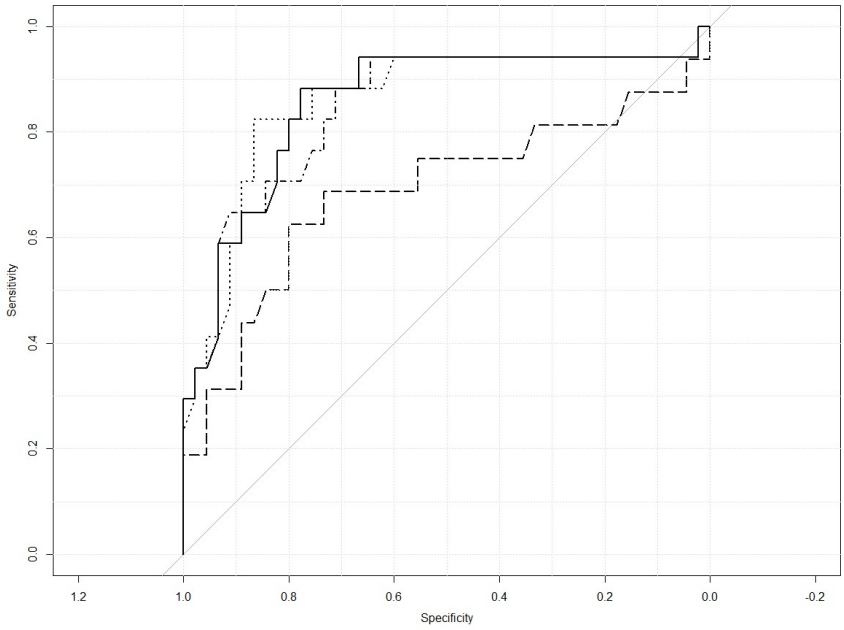
**Table 1.** Maternal and perinatal characteristics of the study population by the occurrence of adverse neonatal outcome.

**Table 2.** Multivariate analysis for the association between at-admission parameters and adverse neonatal outcome.

**Table 3.** Predictive performance for adverse neonatal outcome.

**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 ()

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