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Prognostic indicators of severe disease in late preterm pre-eclampsia to guide decision making on timing of delivery: The PEACOCK study

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ABSTRACT

Objective: To assess the diagnostic performance of angiogenic biomarkers in determining need for delivery in seven days in women with late preterm preeclampsia.

Study design: In a prospective observational cohort study in 36 maternity units across England and Wales, we studied the diagnostic accuracy of placental growth factor (PlGF) and sFlt-1 in determining the risk of complications requiring delivery in late preterm (34^{+0} to 36^{+6} weeks' gestation) preeclampsia. Angiogenic biomarkers were measured using the Quidel (PlGF) and Roche (sFlt-1:PlGF ratio) assays. Additional clinical data was obtained for use within the established 'Prediction of complications in early-onset pre-eclampsia' (PREP)-S prognostic model. Biomarkers were assessed using standard methods (sensitivity, specificity, Receiver Operator Curve areas). Estimated probability of early delivery from PREP-S was compared to actual event rates.

Main outcome measures: Clinically indicated need for delivery for pre-eclampsia within seven days.

Results: PlGF (Quidel) testing had high sensitivity (97.9%) for delivery within seven days, but negative predictive value was only 71.4%, with low specificity (8.4%), with similar results from sFlt-1/PlGF assay. The area under the curve for PlGF was 0.60 (SE 0.03), and 0.65 (0.03), and 0.64 (0.03) for PREP-S in combination with PlGF, and sFlt-1:PlGF, respectively.

Conclusions: Angiogenic biomarkers do not add to clinical assessment to help determine need for delivery for women with late preterm pre-eclampsia. Existing models developed in women with early-onset pre-eclampsia to predict complications cannot be used to predict clinically indicated need for delivery in women with late preterm pre-eclampsia.

1. Introduction

Pre-eclampsia affects around 2–3% of all pregnancies [1], and is associated with potentially serious complications for the woman and baby, including multiple maternal organ dysfunction (severe hypertension, renal and liver impairment, abnormal clotting and stroke or seizures) and fetal morbidity and mortality. Once diagnosed, progression of the syndrome can be unpredictable, and decisions around timing of delivery need to account for evolving maternal complications and perinatal morbidity. We have recently completed the multicentre PHOENIX trial, in which we demonstrated that in women with late preterm pre-eclampsia, planned delivery reduces maternal morbidity, whilst increasing neonatal unit admissions (principally for prematurity as the indication), though with no difference in neonatal morbidity (including need for respiratory support), compared with expectant management [2]. Of women in this gestational age window (34 to 37 weeks of pregnancy) managed expectantly, over half required delivery for clinical indications before they reached 37 weeks' gestation, and pregnancy was prolonged (compared to planned delivery) by three days only.

Current parameters advised by national guidelines for indicating need for delivery in pre-eclampsia are relatively blunt: e.g. uncontrolled

Abbreviations: PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase 1; NICE, National Institute of Health and Care Excellence; PREP-S, Prediction of complications in early-onset pre-eclampsia- survival model.

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severe maternal hypertension, abnormal maternal haematological/biochemical indices or fetal compromise on ultrasound or cardiotocography [3]. Novel blood biomarkers for the diagnosis of preeclampsia are emerging [4–6], but their performance in predicting need for delivery in pregnancies complicated by pre-eclampsia is uncertain. In addition, prognostic models for predicting adverse outcomes in early onset pre-eclampsia are established and have been incorporated in to NICE guidelines [3,7,8] but their applicability to contemporaneous populations of women with confirmed late preterm pre-eclampsia needs further evaluation and validation. If accurate, angiogenic markers could enhance the ability of clinicians to determine who is at greatest risk of need for delivery in late preterm preeclampsia, enabling timely surveillance and decisions around use of antenatal corticosteroids or place of care. Prognostic models that exist to predict complications in early onset preeclampsia (prior to 34 weeks' gestation) warrant prospective assessment of their performance in a cohort of women with late preterm disease. The PREP-S model is a survival model censored at 34 weeks' gestation to predict adverse maternal outcomes from early onset pre-eclampsia at various timepoints.

The aim of this study was to assess the performance of angiogenic biomarkers (placental growth factor (PlGF) and soluble fms like tyrosine kinase 1 (sFlt-1):PlGF ratio, in determining need for delivery in seven days in women with late preterm preeclampsia. In addition, we aimed to assess the performance of the PREP-S model within this cohort.

2. Methods

We undertook a prospective observational cohort study between February 2016 and December 2018, recruiting women from 36 maternity units in England and Wales [2] in women with late preterm pre-eclampsia. The study was approved by South Central – Hampshire B Research Ethics Committee (13/SC/0645).

Women were eligible for this study if they were between 34^{+0} and 36^{+6} weeks' gestation, with a diagnosis of pre-eclampsia (as defined by the International Society for the Study of Hypertension in Pregnancy) [9], with a singleton or dichorionic diamniotic twin pregnancy and at least one viable fetus. Women were aged 18 years or over and gave written informed consent for participation. Exclusion criteria included a decision to deliver within the next 48 hours.

Women were approached and consented individually and asked to provide both plasma (ethylenediaminetetraacetic acid) and serum blood samples at the time of recruitment, which were processed within four hours of sampling. Samples were centrifuged at 1400 × g for 10 min, and the separated supernatant aliquoted and stored at −80 °C. Samples were shipped back to the coordinating centre and processed after completion of all participants in the study on an electronic Triage™ instrument for PlGF (Quidel Cardiovascular Inc: San Diego, CA), and for sFlt-1 and PlGF on the automated Cobas Elecsys™ assay (Roche Diagnostics, GmbH, Mannheim, Germany) according to the manufacturer's instructions. The readings were concealed from the clinical team involved in the woman's care and all laboratory staff were masked to clinical outcomes. Outcomes were collected until the primary hospital discharge of the woman and infant. PlGF and sFlt-1 concentrations at enrolment were evaluated as predictor variables.

In addition, PREP-S is a prediction model that was developed and validated in early onset preeclampsia before 34 weeks' gestation, from 53 maternity units across the United Kingdom [7]. The primary outcome for the original PREP-S study was maternal complications of pre-eclampsia that included maternal death, neurological, hepatic, cardiorespiratory, renal or haematological complications, or delivery before 34 weeks' gestation. All candidate predictors identified in the development of the PREP-S as predictor variables were collected. For the purposes of this study, we sought to determine the performance of PREP-S within our cohort of women with late preterm preeclampsia (a different population from that in which the model was developed), with the primary outcome of delivery for pre-eclampsia within seven days. PREP-S predictor variables were measured at study entry. PREP-S predictor variables, and the prediction model equation are listed in supplementary material.

2.1. Outcomes

Definitions and outcomes were pre-specified in the study protocol (version 4.0). The primary outcome for the PEACOCK study was clinically indicated need for delivery for pre-eclampsia (or delivery for related conditions such as eclampsia or HELLP syndrome) within seven days of assessment. Secondary outcomes included clinically indicated need for delivery for pre-eclampsia within 14 days of assessment, perinatal death, and neonatal unit admission. Customised birthweight centiles were calculated using the INTERGROWTH-21st standards [10]. There were no perinatal deaths in the trial, and further analysis of this secondary outcome did not proceed.

2.2. Sample size

We estimated that the primary outcome (delivery within seven days due to clinical indication) would occur in around 40% of women receiving expectant management, based on our previous work and other literature [4]. The sample size for estimation of the sensitivity (within 7%) and specificity (within 7%), assuming a sensitivity of 0.90, specificity 0.70, and 95% confidence intervals (2-tailed) required 120 women with the primary outcome (and 180 without) in the expectant management arm, giving a minimum of 10 events per candidate variable. We estimated that of 340 women, we expected 134 primary outcome events.

2.3. Statistical analysis

2.3.1. Test performance

Test performance of PlGF and sFlt-1:PlGF was evaluated with sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. When PlGF was assessed as a single predictor, we used a PlGF cut-off of < 100 pg/ml. This was based on the evidence that in those presenting < 35 weeks' gestation, PlGF < 100 pg/ml has a high diagnostic accuracy (0.96; 95% confidence interval, 0.89–0.99) and negative predictive value (0.98; 0.93–0.995) of determining preeclampsia requiring delivery in 14 days [4]. We have previously reported that a PlGF threshold of < 100 pg/mL predicted preeclampsia requiring delivery within 14 days or before 37 weeks' gestation (whichever was sooner) with sensitivity and negative predictive values similar to diagnostic accuracy estimates obtained by using a < 5th centile cut-off [4]. When sFlt-1:PlGF ratio was reported, the threshold was > 38.

2.3.2. PREP-S assessment

Analysis of the PREP model included external validation of the PREP-S model, assessment of the model performance of the updated PREP-S model, assessment of the addition of PlGF and sFlt-1:PlGF to the PREP-S model. Full statistical methods for the assessment of PREP-S are available in the supplementary methods.

The study is reported in accordance with STAndards for the Reporting of Diagnostic accuracy studies (STARD) guidelines.

3. Results

3.1. Pregnancy characteristics

Between 27 April 2016 and 24 December 2018, we recruited 341 women to the PEACOCK study, across 36 maternity units in England and Wales (Fig. S1). Baseline maternal characteristics are presented in Table 1. Maternal and perinatal characteristics at delivery are presented in Table 2. Of 335 women, 319 (95.2%) had a PlGF measurement < 100 pg/ml; 249 of 288 (86.5%) women with sFlt-1:PlGF measurement had

Table 1
Maternal demographics and baseline characteristics at enrolment.

Variable	Expectant Management N = 341
Maternal Age (years), mean (SD)	31.9 (5.7)
Non-white ethnicity n (%)	104 (30.6%)
Multiparous, n (%)	173 (50.7)
Body mass index, Kg/m, mean (SD)	30.2 (7.2)
Maternal History of Pre-eclampsia, n (%)	57 (32.9%)
Chronic Hypertension, n (%)	45 (13.2%)
Chronic Kidney Disease, n (%)	5 (1.5%)
Aspirin use, n (%)	43 (42.1%)
Gestation at enrolment (weeks) mean (SD)	35.4 (0.88)
Maternal BP 48 h prior to enrolment (mmHg), mean (SD)	
Systolic	154 (15)
Diastolic	94 (10)
Highest urinary PCR	
Number with measurement	333
Mean (SD)	166 (289)
Suspected FGR on ultrasound, n (%)	47/341 (13.8%)
Maternal PlGF (pg/mL)	
Number with measurement	335
Mean (SD)	40.16 (140.00)
Median (IQR)	12.0 (12.0–20.6)
PlGF ≥ 100 pg/mL, n (%)	16 (4.8%)
PlGF 12–99 pg/mL, n(%)	136 (40.6%)
PlGF < 12 pg/mL, n (%)	183 (54.6%)
Maternal sFlt-1:PlGF	
Number with measurement	288
Mean (SD)	151.9 (169.12)
Geometric mean (SD)	95.7 (3)
Median (IQR)	108.8 (64.2–183.6)
sFlt-1:PlGF ≤ 38, n (%)	39 (13.5)
sFlt-1:PlGF > 38 < 85, n (%)	70 (24.3)
sFlt-1:PlGF ≥ 85, n(%)	179 (62.2)

SD: standard deviation. BP: blood pressure. PCR: protein:creatinine ratio. FGR: fetal growth restriction. PlGF: Placental growth factor. IQR: Interquartile Range. MD: Mean Difference. RR: Risk Ratio.

Table 2
Maternal and perinatal clinical characteristics at delivery.

Variable	Expectant Management N = 341
Gestation at delivery (weeks), mean (SD)	36.48 (1.03)
Preterm delivery < 37 weeks, n (%)	185 (54.3%)
Delivery within 7 days, n (%)	211 (61.9%)
Delivery within 2 days, n (%)	57 (16.7%)
Delivery within 14 days, n (%)	299 (87.7%)
Antenatal SBP > 160 mmHg, n (%)	204 (60.2%)
Postpartum SBP ≥ 160 mmHg, n (%)	128 (38.1%)
Onset of labour, n (%)	
Spontaneous	18 (5.3%)
Induced	211 (61.9%)
Prelabour Caesarean section	111 (32.6%)
PROM and augmentation	1 (0.3%)
Required clinically indicated delivery, n (%)	176 (51.6%)
Infant Birthweight (grams), mean (SD)	2500 (556)
INTERGROWTH Birthweight Centile, mean (SD)	31.89 (29.61)
INTERGROWTH SGA < 10th centile, n (%)	119 (33.1%)
INTERGROWTH SGA < 3rd centile, n (%)	42 (11.7%)

SD: standard deviation. SBP: systolic blood pressure. PROM: prelabour rupture of membranes. SGA: Small for Gestational Age. MD: Mean Difference. RR: Risk Ratio.

an abnormal result (≤38). 211 of 341 (61.9%) women delivered within seven days due to clinical concerns for maternal or fetal wellbeing. There were no perinatal deaths in the study. The median time to delivery in those recruited at 34–34+, 35–35+, and 36–36+ was 8 days (IQR 3–14 days), 7 days (IQR 3–11 days) and 5 days (IQR 3–7 days) respectively.

3.2. Test performance

For the PlGF test by the Quidel assay, the test performance for PlGF in determining need for delivery within seven days at low (<100 pg/mL) and very low (PlGF < 12 pg/mL) is shown in Table 3. The test performance for PlGF < 100 pg/ml in determining need for delivery within seven days had sensitivity of 97.9% (94.8–99.4%) for delivery within seven days; the negative predictive value was 71.4% (41.9–91.6%) and the specificity was 8.4% (4.1–14.9%). Similar test performance statistics for determining need for delivery within 14 days are shown in Table S1. Evaluation of other thresholds for PlGF did not substantially improve test performance (Table 4) over and above the pre-specified thresholds.

For the sFlt-1:PlGF ratio, the test performance for sFlt-1/PlGF ≥ 38 in determining need for delivery within seven days had sensitivity of 91.4% (86.3–95.1%) for delivery within seven days; the negative predictive value was 60.5% (43.4–76.0%) and the specificity was 20.9% (13.7–29.7%) (Table 3). Similar test performance statistics for determining need for delivery within 14 days are shown in Table S1 and Fig. S2.

The Receiver Operator Curve (ROC) areas for PlGF, sFlt-1:PlGF ratio and PREP-S are shown in Fig. 1, with consideration of the PREP-S model for a dichotomised endpoint (delivery within seven days). PREP-S was also assessed in combination with PlGF, and with the sFlt-1:PlGF ratio, treating PREP-S as a single predictor [7]. The corresponding ROC areas for the clinical prediction model (PREP-S), PlGF and sFlt-1:PlGF in this cohort in determining need for delivery within seven days was 0.64 (standard error (SE) 0.03), 0.60 (SE 0.03), and 0.63 (SE 0.03) respectively. The ROC area for PREP-S in combination with PlGF in determining need for delivery within seven days was 0.65 (SE 0.03), and PREP-S in combination with sFlt-1:PlGF was 0.64 (SE 0.03) (Fig. 1). We did not statistically compare the area under the curves, as all were below 0.7, the level which is determined as having an acceptable level of discrimination for diagnostic tests [11]. PlGF and PREP-S (when used to determine a binary outcome), whether used alone or in combination, have limited clinical applicability in this cohort in determining need for delivery within seven days. Corresponding ROC areas for determining need for delivery in 14 days are presented in Table S2.

The test performance for PlGF < 100 pg/ml, <12, and sFlt-1PlGF > 38 in determining need for neonatal unit admission is described in Table S4.

Table 3
Test performance statistics for low and very low PlGF (Quidel) and sFlt-1:PlGF ratio (Roche) in determining need for delivery within 7 days.

	Delivery within 7 days	
Test performance statistics	PlGF < 100 pg/mL	sFlt-1:PlGF ≥ 38
Sensitivity (%; 95% CI)	97.9 (94.8–99.4)	91.4 (86.3–95.1)
n/N	188/192	160/175
Specificity (%; 95% CI)	8.4 (4.1–14.9)	20.9 (13.7–29.7)
n/N	10/119	23/110
Positive predictive value (%; 95% CI)	63.3 (57.5–68.8)	64.8 (58.5–70.7)
n/N	188/297	160/247
Negative predictive value (%; 95% CI)	71.4 (41.9–91.6)	60.5 (43.4–76.0)
n/N	10/14	23/38
Positive likelihood ratio (95% CI)	1.07 (1.01–1.13)	1.16 (1.04–1.29)
Negative likelihood ratio (95% CI)	0.25 (0.08–0.77)	0.41 (0.22–0.75)
	PlGF < 12 pg/mL	
Sensitivity (%; 95% CI)	62.0 (54.7–68.9)	
n/N	119/192	
Specificity (%; 95% CI)	55.5 (46.1–64.6)	
n/N	66/119	
Positive predictive value (%; 95% CI)	69.2 (61.7–76.0)	
n/N	119/172	
Negative predictive value (%; 95% CI)	47.5 (39.0–51.6)	
n/N	66/139	
Positive likelihood ratio (95% CI)	1.39 (1.11–1.75)	
Negative likelihood ratio (95% CI)	0.69 (0.54–0.87)	

Table 4
Incremental PlGF (Quidel) thresholds for predicting delivery in 7 days.

Threshold for PlGF (pg/mL)	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)
<20	56.6 (51.2–62.0)	54.5 (45.2–63.5)	77.4 (71.7–82.5)	31.3 (25.2–38.0)
<30	74.9 (70.0–79.5)	35.8 (27.3–44.9)	76.3 (71.3–80.7)	34.1 (26.0–43.0)
<40	81.7 (77.2–85.7)	25.2 (17.8–33.8)	75.1 (70.3–79.4)	33.3 (23.9–43.9)
<50	86.4 (82.3–89.9)	18.7 (12.2–26.7)	74.6 (69.9–78.8)	33.3 (22.4–45.7)
<60	88.8 (84.9–91.9)	17.1 (10.9–24.9)	74.7 (70.1–78.9)	35.6 (23.6–49.1)
<70	92.0 (88.6–94.7)	15.4 (9.6–23.1)	75.0 (70.5–79.1)	41.3 (27.0–56.8)
<80	92.0 (88.6–94.7)	13.8 (8.3–21.2)	74.6 (70.2–78.7)	38.6 (24.4–54.5)
<90	93.8 (90.7–96.1)	10.6 (5.7–17.4)	74.3 (69.9–78.4)	38.2 (22.2–56.4)

3.3. PREP-S evaluation

For evaluation of the PREP-S prognostic model in this cohort, baseline predictor variables were assessed in the PEACOCK study cohort and compared with the original PREP-S cohort (Table S3). There were important differences between the two cohorts, particularly relating to gestation at enrolment (as different inclusion criteria were used), definitions used for (and therefore incidence of) adverse maternal outcomes.

The Kaplan-Meier time to delivery estimates for women in the expectant management groups, stratified by four PREP-S risk categories (as observed) are shown in Fig. S3. The recalibrated estimates are shown in Fig. S4.

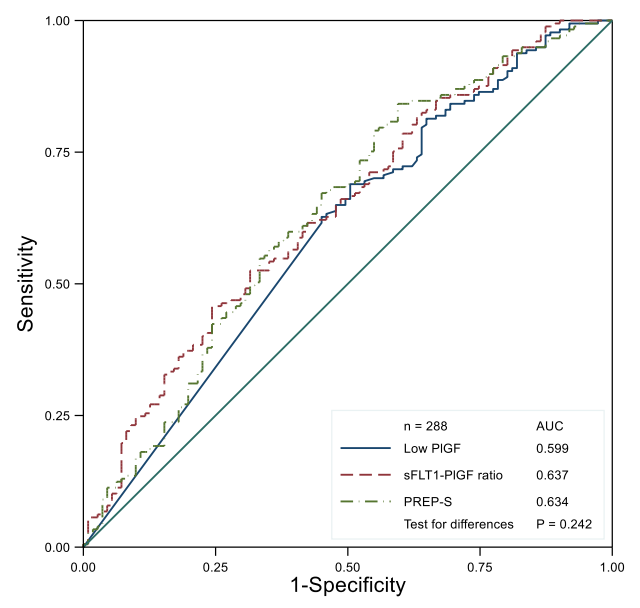
Calibration of the PREP-S model is shown in Table S5, with calibration in the large and of the slope assessed for predicting delivery for preeclampsia within seven days. Calibration of the PREP-S model in this cohort was less good than that achieved in the original PREP-S cohorts. Overall, approximately the same number of women had the outcome as predicted by the model (expected value 0; calculated value −0.13; not significantly different). However, calibration of the slope was 0.375 (expected value 1.0), suggesting that the difference between adverse outcome event rates between low and high risk groups was not as great as the PREP-S model suggested, with PREP-S consistently over-predicting the adverse event rate in the higher risk groups.

4. Discussion

In this group of women with late preterm pre-eclampsia, PlGF and sFlt-1:PlGF measurement do not appear to add to the current clinical methods of assessment to help plan care around timing of delivery. A high proportion of the women already had abnormal angiogenic biomarkers. Although PlGF testing had high sensitivity (97.9%) for determining need for delivery within seven days, the negative predictive value was only 71.4% and the specificity was low (8.4%). The areas under the curve for the clinical prediction model (PREP-S), PlGF and sFlt-1:PlGF in this cohort in determining need for delivery within seven days were all lower than 0.7, below the threshold deemed clinically useful [12]. In addition, test performance for determining need for neonatal unit admission was low, and the PREP-S clinical prognostic model did not perform well in this group.

We originally chose PlGF concentration as a potential predictor, based on our other work describing strong test performance of PlGF <100 pg/ml in women with suspected pre-eclampsia. However we report here that the distribution of PlGF concentration in women with confirmed pre-eclampsia was very different to those presenting with suspected disease, with a high proportion of women (over 95%) having low or very low PlGF values. Although sensitivity of the test remained high, the specificity, predictive values and likelihood ratios were all suboptimal, and the areas under the curve for both PlGF and sFlt-1:PlGF in determining need for delivery in seven days were too low to be clinically useful.

There is good evidence that PlGF is stable in plasma, serum and whole blood, remaining stable through multiple freeze-thaw cycles and for up to 19 h at room temperature [13,14]. Our study protocol specified that the blood was centrifuged and the supernatant frozen at −80 degrees within 4 h of sampling. Samples were subsequently processed at the sponsor hospital research laboratory following transportation on dry ice by courier. Despite the variation in time from sampling to analysis between samples, the stability of PlGF and the rigorous standard operating procedures of the study will have minimised any post sampling



Delivery in 7 days	ROC Area (SE); (95% CI)
PlGF alone	0.60 (0.03); (0.54-0.66)
sFlt-1:PlGF	0.63 (0.03); (0.56 – 0.70)
PREP-S alone	0.64 (0.03); (0.58-0.71)
PREP-S + PlGF	0.65 (0.03); (0.58-0.71)
PREP-S + sFlt-1:PlGF	0.64 (0.03); (0.58-0.71)

Fig. 1. ROC areas for determining need for delivery within seven days. PlGF: Placental growth factor. sFlt-1: soluble fms-like tyrosine kinase-1. PREP: Prediction of complications in early-onset pre-eclampsia study.

variation in serum PlGF levels.

PlGF and sFlt-1:PlGF biomarkers are reasonably 'upstream' in the pathophysiological process of the development of pre-eclampsia. The low overall prognostic performance in this group may be because the need for delivery from pre-eclampsia within seven days is associated with a variety of multi-organ, end-stage clinical parameters, and therefore an 'upstream' biomarkers such as PlGF or sFlt-1:PlGF are unable to discriminate which individuals are at higher risk. In addition, clinicians typically act upon early signs of impending clinical deterioration (such as abnormal liver transaminases) in order to avoid severe hepatic dysfunction (as used within the original PREP-S study, in women with pre-eclampsia prior to 34 weeks' gestation). Treatment paradox (e.g. decision for delivery based on early derangement of liver transaminases) could impact on the performance of prognostic markers or models, as women will have the primary outcome (clinically indicated need for delivery within seven days) without necessarily going on to develop severe maternal adverse outcomes. Although our chosen primary outcome (need for delivery for pre-eclampsia within seven days) acts as a surrogate to represent clinician concern of substantial fetal or maternal compromise, the suboptimal performance of PlGF and sFlt-1:PlGF for predicting delivery in this group may also reflect the complex, multi-pathological nature of this endpoint, and that a single biomarker is unable to determine both fetal and maternal compromise which has considerably different pathology (albeit the same clinical endpoint of early delivery). PlGF measurements have shown considerable potential as a diagnostic adjunct in women with suspected disease [6], in which the distribution of PlGF measurements is across the biological range of values. In contrast, the distribution of abnormal PlGF concentrations in this cohort (with established pre-eclampsia) confirms that women had marked placental dysfunction, but the test does not appear to have strong prognostic value for adverse outcome.

The PREP-S model was developed in early onset pre-eclampsia population (prior to 34 weeks), while the PEACOCK population was those with late preterm pre-eclampsia (34 to 37 weeks). The underlying contributions from maternal and placental pathophysiology may vary across these two groups, and hence the model cannot automatically be transported for use in the different population. Importantly, clinicians are likely to have lower threshold for delivery in women with late preterm pre-eclampsia than early onset pre-eclampsia since the risk of prematurity related complications is lower for births after 34 weeks' gestation. While the PREP-S model has consistently shown accurate performance both in the development dataset, and in two separate validation datasets of early onset pre-eclampsia [7], we found that the model cannot be transported to a late preterm pre-eclampsia population to predict a different outcome.

At the time of conception of this study, there were a number of studies suggesting strong test performance for angiogenic factors measured in pregnancy, but the majority of the studies focused on women with suspected pre-eclampsia and the role of measurement in confirmed pre-eclampsia was under-explored. One early study by Verlohren and colleagues [5] assessed sFlt-1:PlGF in 95 women with pre-eclampsia after 34 weeks' gestation and compared duration of remaining pregnancy between women in the upper and lowest quartiles of sFlt-1:PlGF (but did not report other test performance statistics for this outcome). They reported that women with pre-eclampsia with a sFlt-1:PlGF in the upper quartile had a significantly reduced duration of pregnancy. However, a more recent study by Lou and colleagues [15] found that in women with pre-eclampsia after 34 weeks' gestation, there was no significant difference in sFlt-1:PlGF between those who delivered within seven days compared to those who delivered later. Meler and colleagues [16] similarly concluded that the predictive role of a low PlGF concentration in predicting maternal complications in early onset pre-eclampsia was limited because of both its low specificity and low positive predictive value. More recently, Ukah and colleagues have reported that PlGF does not add incremental value to the fullPIERS externally validated risk prediction model in predicting serious maternal adverse outcomes in women with preeclampsia [17]. It remains unclear if PlGF may add value to the PREP-S model in early onset preeclampsia occurring before 34 weeks' gestation.

PlGF and sFlt-1:PlGF testing, and the PREP-S prediction model, cannot be recommended to help plan care in late preterm pre-eclampsia regarding timing of delivery. A high proportion of women in this cohort already had low PlGF concentrations at the time of confirmed diagnosis, reducing the ability of PlGF measurement to further predict adverse outcomes. This is important and timely information given the current NHS-wide adoption of PlGF based testing as a diagnostic adjunct in the assessment of women with suspected pre-eclampsia, a different population to that studied here. Despite the confirmed diagnostic utility of PlGF in women with suspected pre-eclampsia, PlGF and sFlt-1:PlGF do not appear to have a role in assisting clinicians in determining timing of delivery in women with established preterm pre-eclampsia. The PREP-S model alone, and in combination with both PlGF, and sFlt-1:PlGF appears to have only limited clinical applicability for determining which women would require delivery in seven days from pre-eclampsia in women with late preterm pre-eclampsia.

5. Conclusions

In women with late preterm pre-eclampsia, PlGF and sFlt-1:PlGF measurements are not likely to add to the current clinical assessment to help plan care regarding timing of delivery. Existing prognostic models using clinical data developed in women with early onset pre-eclampsia to predict complications cannot be used to predict clinically indicated need for delivery in women with late preterm pre-eclampsia.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2021.02.012.

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