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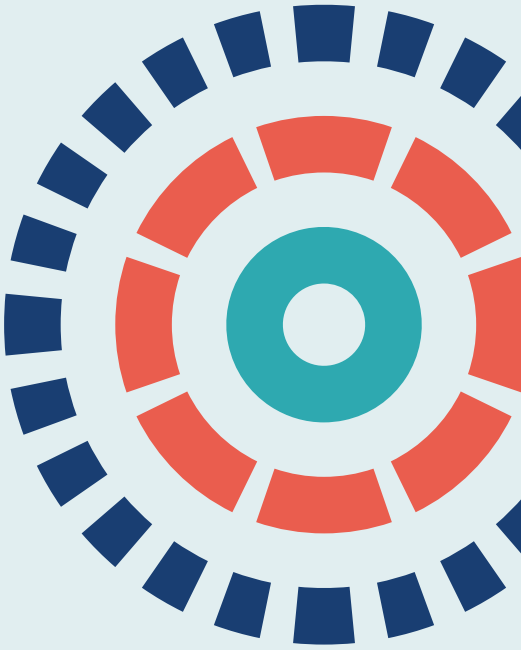

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A prognostic model to guide decision-making on timing of delivery in late preterm pre-eclampsia: the PEACOCK prospective cohort study

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Abstract

A prognostic model to guide decision-making on timing of delivery in late preterm pre-eclampsia: the PEACOCK prospective cohort study

Kate Duhig,[1] Paul T Seed,[1] Anna Placzek,[2] Jenie Sparkes,[1] Carolyn Gill,[1] Anna Brockbank,[1] Andrew Shennan,[1] Shakila Thangaratinam[3] and Lucy C Chappell[1*]

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Background: Pre-eclampsia affects around 2–3% of all pregnancies, and is associated with potential serious complications for the woman and the baby. Once diagnosed, progression of the syndrome can be unpredictable, and decisions around timing of delivery need to take into account evolving maternal complications and perinatal morbidity. Novel prognostic models and blood biomarkers for determination of need for delivery in pregnancies with pre-eclampsia are now emerging.

Objective: The objective of the study was to establish a prognostic model to inform optimal timing of delivery in women with late preterm pre-eclampsia (34^{+0} to 36^{+6} weeks' gestation), comparing novel candidate biomarkers (e.g. placental growth factor) with clinical and routinely collected blood/urinary parameters [incorporated into the PREP-S (Prediction models for Risk of Early-onset Pre-eclampsia – Survival) model] to determine clinically indicated need for delivery for pre-eclampsia (or related complications) within 7 days of assessment.

Methods: Prospective recruitment of women in whom blood samples for placental growth factor and soluble fms-like tyrosine kinase-1 testing was obtained, alongside clinical data, for use within the PREP-S model. Candidate variables were compared using standard methods (sensitivity, specificity, receiver operator curve areas). Estimated probability of early delivery from PREP-S was compared with actual event rates by calibration.

Setting: The PEACOCK (Prognostic indicators of severe disEAse in women with late preterm pre-eClampsia tO guide deCision maKing on timing of delivery) study was a prospective cohort study, nested within the PHOENIX (Pre-eclampsia in HOspital: Early iNductIon or eXpectant management) trial.

Participants: Women between 34^{+0} and 36^{+6} weeks' gestation, with a diagnosis of pre-eclampsia, in whom a plasma (ethylenediaminetetraacetic acid) blood sample for placental growth factor testing was obtained, alongside clinical data for the assessment of variables in a prognostic model.

Main outcome measures: Clinically indicated need for delivery for pre-eclampsia within 7 days of assessment. Statistical analysis: both PREP-S and placental growth factor were assessed and compared using standard methods (sensitivity and specificity for placental growth factor thresholds of 100 pg/ml and < 12 pg/ml, and receiver operating characteristic areas for continuous measurements). The estimated probability of early delivery from PREP-S was compared with actual event rates for women with similar probabilities by calibration. Calibration using logistic regression was also used.

Results: Between 27 April 2016 and 24 December 2018, 501 women were recruited to the study. Although placental growth factor testing had high sensitivity (97.9%) for delivery within 7 days, the negative predictive value was only 71.4% and the specificity was low (8.4%). The area under the curve for the clinical prediction model (PREP-S) and placental growth factor in this cohort in determining need for delivery within 7 days was 0.64 (standard error 0.03) and 0.60 (standard error 0.03), respectively, and 0.65 (standard error 0.03) in combination.

Limitations: A high proportion of women in this cohort already had low placental growth factor concentrations at the time of confirmed diagnosis, which reduced the ability of the biomarker to further predict adverse outcomes.

Conclusions: In this group of women with late preterm pre-eclampsia, placental growth factor measurement is not likely to add to the current clinical assessment to help plan care for late preterm pre-eclampsia regarding timing of delivery. 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.

Future work: Further statistical modelling and subgroup analysis is being considered to assess if improved model performance in the whole cohort or a subgroup can be achieved. Addition of other biomarkers to the model may also be of use and will be explored.

Trial registration: Current Controlled Trials ISRCTN01879376.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 30. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

List of abbreviations

CI	confidence interval
HELLP	haemolysis, elevated liver enzymes, low platelets
NIHR	National Institute for Health Research
PEACOCK	Prognostic indicators of severe disEAse in women with late preterm pre-eClampsia tO guide deCision maKing on timing of delivery
PHOENIX	Pre-eclampsia in HOspital: Early iNductIon or eXpectant management
PlGF	placental growth factor
PPI	patient and public involvement
PREP	Prediction models for Risk of Early-onset Pre-eclampsia
PREP-S	Prediction models for Risk of Early-onset Pre-eclampsia – Survival
ROC	receiver operating characteristic
SE	standard error
sFlt-1	soluble fms-like tyrosine kinase-1

Plain English summary

Why did we do this study?

Pre-eclampsia is a condition occurring in pregnancy. The condition can affect the health of the woman and the baby, often affecting the woman's kidneys and liver and the baby's growth. In severe cases, babies can be stillborn. Once pre-eclampsia is diagnosed, the only cure is to deliver the baby. It is often not possible to identify women and babies at high risk of the severe complications of pre-eclampsia who would benefit from early delivery. We wanted to see if we could improve the way that women with pre-eclampsia are assessed to work out who needs to be delivered early to prevent complications.

What did we do?

A total of 501 women affected by pre-eclampsia took part in our study and we measured substances in their blood. We used these results, along with other clinical measures, to see if we could improve the way that we try and tell which women need delivery soon.

What did we find?

The blood markers were not able to tell us which women needed delivery within 7 days, and they were not able to improve our detection rate of women who need delivery to prevent complications.

What does this mean for women with pre-eclampsia?

These methods cannot be recommended to plan care for women and babies affected by pre-eclampsia between 34 and 37 weeks' gestation to help tell us when the baby should be born. We need to find better tests to help find out which women and babies are most at risk of the complications of pre-eclampsia.

Scientific summary

Background

Pre-eclampsia affects around 2–3% of all pregnancies and is associated with potentially serious complications for the woman and the baby, including multiple maternal organ dysfunction (severe hypertension, renal and liver impairment, abnormal clotting and stroke/seizures), and fetal morbidity and mortality. Once diagnosed, progression of the syndrome can be unpredictable, and decisions around timing of delivery need to take into account evolving maternal complications and perinatal morbidity. We have recently completed the multicentre PHOENIX (Pre-eclampsia in HOspital: Early iNductIon or eXpectant management) trial, in which we demonstrated that, in women with late preterm pre-eclampsia, a planned delivery reduces maternal morbidity while increasing neonatal unit admissions, but there was no difference in neonatal morbidity (including respiratory distress) when compared with expectant management. Of the women in this gestational age window (34 to 37 weeks' gestation) who were managed expectantly, over half required delivery for clinical indications before they reached 37 weeks' gestation, and pregnancy was prolonged over the planned delivery date by 5 days only.

Current parameters advised by national guidelines for indicating need for delivery in pre-eclampsia are relatively blunt (e.g. uncontrolled severe maternal hypertension, abnormal maternal haematological/biochemical indices or fetal compromise on ultrasound or cardiotocography). Novel prognostic models and blood biomarkers for determination of need for delivery in pregnancies with pre-eclampsia are now emerging, but their applicability to contemporaneous populations of women with late preterm pre-eclampsia needs further evaluation and validation. Existing clinical models [e.g. PREP-S (Prediction models for Risk of Early-onset Pre-eclampsia – Survival), derived from the PREP (Prediction models for Risks of complications in Early-onset Pre-eclampsia) study] can accurately predict the risk of complications (including need for delivery before 34 weeks' gestation) in women with early-onset pre-eclampsia before 34 weeks' gestation. If these clinical models and blood markers can also be used in women with late preterm pre-eclampsia, it may enhance the ability of clinicians and women to determine who is at greatest risk of need for delivery, enabling timely surveillance and decisions around use of antenatal corticosteroids or place of care.

Objectives

The objective of the study was to establish a prognostic model to inform optimal timing of delivery in women with late preterm pre-eclampsia (34^{+0} to 36^{+6} weeks' gestation), comparing novel candidate biomarkers (e.g. placental growth factor) with clinical and routinely collected blood/urinary parameters to determine clinically indicated need for delivery for pre-eclampsia (or related complications) within 7 days of assessment.

Methods

We undertook a prospective observational cohort study (PEACOCK; Prognostic indicators of severe disEAse in women with late preterm pre-eClampsia tO guide deCision maKing on timing of delivery), nested within the PHOENIX trial in women with late preterm pre-eclampsia. The PHOENIX trial was a multicentre randomised controlled trial, in which women from 46 units across England and Wales with preterm pre-eclampsia at 34^{+0} to 36^{+6} weeks' gestation were randomly allocated to planned delivery or expectant management. Results of the PHOENIX trial have been reported separately.

Women were eligible for the PEACOCK 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 (ISSHP)], with a singleton or dichorionic diamniotic twin pregnancy and at least one viable fetus. Women were aged ≥ 18 years and gave written informed consent for participation. Exclusion criteria included a decision to deliver within the next 48 hours. All women eligible for the PHOENIX trial were eligible for participation in the PEACOCK study, whether they agreed or declined randomisation to the main PHOENIX trial. The study was approved by the South Central – Hampshire B Research Ethics Committee (reference number 13/SC/0645).

Women were approached individually and asked to provide plasma (ethylenediaminetetraacetic acid) and serum blood samples at the time of recruitment, which was processed within 4 hours of sampling. Samples were centrifuged at 1400 g for 10 minutes, and the separated supernatant aliquoted and stored at −80 °C. Samples were shipped back to the co-ordinating centre, thawed and processed on an electronic Triage™ instrument (Quidel Cardiovascular Inc., San Diego, CA, USA) according to the manufacturer's instructions to give a serum placental growth factor concentration result. The readings were not revealed to the clinical team involved in the woman's care. Definitions and outcomes were prespecified in the study protocol (version 4.0).

Clinical predictor variables

Serum placental growth factor concentration at enrolment was evaluated as a predictor variable. We used clinical predictor variables from a previously validated model (PREP-S), which were measured at study entry. The following PREP-S clinical predictor variables were collected at enrolment: maternal age (years), gestational age (weeks), exaggerated tendon reflexes, medical history (two or more of the following conditions: chronic hypertension, renal disease, previous history of pre-eclampsia, autoimmune disease and diabetes mellitus), systolic blood pressure (mmHg, highest over 6 hours), abnormal oxygen saturation (< 95% on air), platelet count ($\times 10^9$/l), serum alanine aminotransferase level (IU/l), serum urea concentration (mmol/l), serum creatinine concentration (μmol/l), urine protein–creatinine ratio (mg/mmol), any previous treatment with oral/parenteral antihypertensives, and any previous treatment with magnesium sulphate. In the original model, the PREP-S outcome was maternal complications, which included maternal death; neurological, hepatic, cardiorespiratory, renal or haematological complications; or delivery before 34 weeks' gestation. We used the published model equation to evaluate the PREP-S algorithm, but in a new population (34 to 37 weeks' gestation) and with a new primary outcome (clinically indicated need for delivery within 7 days).

Outcomes

The primary outcome was clinically indicated need for delivery for pre-eclampsia [or delivery for related conditions, such as eclampsia or HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome] within 7 days of assessment. Secondary outcomes included clinically indicated need for delivery for pre-eclampsia within 48 hours of assessment and within 14 days of assessment, perinatal deaths and neonatal unit admission.

Sample size estimation

The sample size for estimation of the sensitivity (within 7%) and specificity (within 7%), assuming a sensitivity of 0.90, a specificity of 0.70 and 95% confidence intervals (two-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 two-thirds of the 500 women recruited to the PEACOCK study would receive expectant management (the group on which the model would be validated). We therefore expected 134 events (500 × 67% × 40%).

Statistical analysis

The validation sample for the primary analysis of delivery for pre-eclampsia in 7 days (and secondary analysis evaluating clinically indicated need for delivery for pre-eclampsia within 14 days of assessment) was restricted to women in the PEACOCK study who underwent expectant management, that is

women recruited to the PHOENIX trial (and also enrolled in the PEACOCK study) who were randomised to the expectant management arm and women who declined the PHOENIX trial and were recruited to the PEACOCK study only who underwent the usual care strategy of expectant management. An additional analysis was conducted for evaluating clinically indicated need for delivery for pre-eclampsia within 48 hours of assessment, which included the PEACOCK women randomised to the planned delivery arm in the PHOENIX trial.

The stages of analysis were as follows: external validation of the PREP-S model, limited updating of the PREP-S model by recalibration, assessment of the model performance of the updated PREP-S model, assessment of the predictive performance of placental growth factor concentration, comparison of placental growth factor concentration and PREP-S, and assessment of the addition of placental growth factor concentration to the PREP-S model. The performance of the models was assessed by calibration and discrimination, reported graphically using calibration plots and estimated calibration slopes. The calibration and recalibration of the models were also reported graphically, with estimated and actual event rates (with 95% confidence intervals) compared for different risk groups of women. Model performance in relation to the primary and secondary outcomes was assessed using receiver operating characteristic areas. Test performance of the placental growth factor was evaluated with sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. Kaplan–Meier survival curves of the time from test to delivery were determined, stratified by four categories of risk determined by the PREP-S model. Assessment of PREP-S, placental growth factor concentration and the combined model was conducted on the primary outcome and all secondary outcomes.

Results

Between 27 April 2016 and 24 December 2018, we recruited 501 women to the PEACOCK study across 36 maternity units in England and Wales. Across the participants there were no statistically or clinically relevant differences in baseline characteristics. There were similar outcomes in women randomised to the expectant management group and those participating in the non-randomised expectant management group, whereas outcomes in the planned delivery and randomised expectant management groups reflected those in the larger PHOENIX trial, with earlier gestation at delivery, as expected. Among women managed expectantly, 211 out of 341 (61.9%) delivered within 7 days. There were no perinatal deaths in the study.

The sensitivity of placental growth factor concentration < 100 pg/ml in determining need for delivery within 7 days was 97.9% (95% confidence interval 94.8% to 99.4%), the negative predictive value was 71.4% (95% confidence interval 41.9% to 91.6%) and the specificity of 8.4% (95% confidence interval 4.1% to 14.9%). The area under the curve for the clinical prediction model (PREP-S) and placental growth factor concentration in this cohort in determining need for delivery within 7 days was 0.64 (standard error 0.03) and 0.60 (standard error 0.03), respectively, and 0.65 (standard error 0.03) in combination. Calibration in the large of the PREP-S model was –0.13. The calibration slope was 0.375.

Conclusions

In this group of women with late preterm pre-eclampsia, placental growth factor measurement is not likely to add to the current clinical assessment to help plan care for these women around timing of delivery. The PREP-S model, developed in early-onset pre-eclampsia populations to predict complications (including need for delivery before 34 weeks' gestation), cannot be transferred to predict clinically indicated need for delivery in women with late preterm pre-eclampsia.

The distribution of placental growth factor concentration in women with confirmed pre-eclampsia is very different from the distribution in women presenting with suspected disease, with a high proportion

of women (around 90%) having low or very low placental growth factor results. Although sensitivity of the test remains high, specificity, predictive values and likelihood ratios are all suboptimal, and the areas under the receiver operating characteristic curves for determining need for delivery in 7 days are too low to be clinically useful.

Placental growth factor is a biomarker that is considered reasonably 'upstream' in the pathophysiological process of the development of pre-eclampsia. The poor prognostic performance in this group may be because the need for delivery from pre-eclampsia within 7 days is associated with a variety of multiorgan, end-stage clinical parameters, and therefore an 'upstream' biomarker such as placental growth factor is unable to discriminate which individuals are at a higher risk than others. Although placental growth factor measurements have shown considerable potential as a diagnostic adjunct in women with suspected disease, and the distribution of low and very low placental growth factor concentrations in the PEACOCK cohort confirms that we had participating women with placental dysfunction, the findings suggest that this test does not appear to have strong prognostic value (for need for delivery) in this setting. The PREP-S model was developed in an early-onset pre-eclampsia population (prior to 34 weeks' gestation), whereas women in the PEACOCK trial had late preterm pre-eclampsia (34 to 37 weeks' gestation) and there are known to be important differences in the two populations.

Strengths and weaknesses in relation to other studies, discussing important differences in results

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 underexplored. One early study by Verlohren *et al.* assessed the ratio of soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor 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 the sFlt-1/placental growth factor ratio (but did not report other test performance statistics for this outcome) (Verlohren S, Herraiz I, Lapaire O, Schlembach D, Moertl M, Zeisler H, *et al.* The sFlt-1/placental growth factor ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. *Am J Obstet Gynecol* 2012;**206**:58.e1–8). They reported that women with pre-eclampsia with a sFlt-1/placental growth factor ratio in the upper quartile had a significantly reduced duration of pregnancy. However, a more recent study by Lou *et al.* found that, in women with pre-eclampsia after 34 weeks' gestation, there was no significant difference in the sFlt-1/placental growth factor ratio between those who delivered within 7 days and those who delivered later (Lou WZ, Jiang F, Hu J, Chen XX, Song YN, Zhou XY, *et al.* Maternal serum angiogenic factor sFlt-1 to PlGF ratio in preeclampsia: a useful marker for differential diagnosis and prognosis evaluation in Chinese women. *Dis Markers* 2019;**2019**:6270187). Meler *et al.* similarly concluded that the predictive role of low placental growth factor concentrations in predicting maternal complications in early-onset pre-eclampsia was limited because of both its low specificity and its low positive predictive value (Meler E, Scazzocchio E, Peguero A, Triunfo S, Gratacos E, Figueras F. Role of maternal plasma levels of placental growth factor for the prediction of maternal complications in preeclampsia according to the gestational age at onset. *Prenat Diagn* 2014;**34**:706–10).

Meaning of the study

The evidence suggests that placental growth factor concentration testing and the PREP-S prediction model, developed and validated for use in early-onset pre-eclampsia, is not the best option to help plan care for women with late preterm pre-eclampsia regarding timing of delivery. This is important and timely information given the current NHS-wide adoption of placental growth factor concentration testing as a diagnostic adjunct in the assessment of women with suspected pre-eclampsia, a different population of women in this study, who had confirmed pre-eclampsia. Despite the diagnostic utility of placental growth factor concentration in women with suspected pre-eclampsia, it does 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 both alone and in combination with placental growth factor appears to have limited clinical applicability for determining which women would require delivery in 7 days (from date of assessment), in women with late preterm pre-eclampsia.

Unanswered questions and future research

Statistical modelling

Further statistical analysis of these data is being considered as part of the PREP-S model, with further time-to-event analyses (as the model originally described). We will consider the addition of placental growth factor concentration to this model, and derive the predicted Kaplan–Meier estimates for the PREP-S categories for comparison with the observed estimates. These methods may provide further assessment of the PREP-S model.

Subgroup analysis

Given that placental growth factor is associated with placental pathology, and angiogenic factors have been noted to be imbalanced in pregnancies that are complicated by fetal growth restriction, we will undertake a subgroup analysis for the primary outcome in determining the need for delivery in 7 days for fetal indications.

Angiogenic marker assessment

Maternal serum and urinary sFlt-1 and sFlt-1/placental growth factor ratios have been shown to be correlated with pre-eclampsia disease severity in some small studies. Work is also under way to assess the performance of sFlt-1 and the sFlt-1/placental growth factor ratio to determine if this has superior performance compared with placental growth factor concentration alone in predicting the primary outcome in this cohort.

Trial registration

This trial is registered as ISRCTN01879376.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 30. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Pre-eclampsia affects around 2–3% of all pregnancies[1] and is associated with potentially serious complications for the woman and the baby, including multiple maternal organ dysfunction (severe hypertension, renal and liver impairment, abnormal clotting and stroke/seizures) and fetal morbidity and mortality. Once diagnosed, progression of the syndrome can be unpredictable, and decisions around timing of delivery need to take into account evolving maternal complications and perinatal morbidity. We have recently completed the multicentre PHOENIX (Pre-eclampsia in HOspital: Early iNductIon or eXpectant management) trial, in which we demonstrated that, in women with late preterm pre-eclampsia, a planned delivery reduces maternal morbidity, while increasing neonatal unit admissions, but with no difference in neonatal morbidity (including respiratory distress) when compared with expectant management.[2] Of the women in this gestational age window (34 to 37 weeks' gestation) who were managed expectantly, over half required delivery for clinical indications before they reached 37 weeks' gestation, and pregnancy was prolonged over the planned delivery date by 5 days only.

Current parameters advised by national guidelines for indicating need for delivery in pre-eclampsia are relatively blunt (e.g. uncontrolled severe maternal hypertension, abnormal maternal haematological/biochemical indices or fetal compromise on ultrasound or cardiotocography).[3] Novel prognostic models and blood biomarkers for determination of need for delivery in pregnancies with pre-eclampsia are now emerging,[4,5] but their applicability to contemporaneous populations of women with late preterm pre-eclampsia needs further evaluation and validation. Existing clinical models can accurately predict the risk of complications in women with early-onset pre-eclampsia before 34 weeks' gestation [PREP-S (Prediction models for Risk of Early-onset Pre-eclampsia – Survival)].

These models and blood markers for women with late preterm pre-eclampsia may enhance the ability of clinicians to determine who is at greatest risk of need for delivery, enabling timely surveillance and decisions around use of antenatal corticosteroids or place of care.

The aim of the study was to establish a prognostic model to inform optimal timing of delivery in women with late preterm pre-eclampsia (34^{+0} to 36^{+6} weeks' gestation), comparing novel candidate biomarkers [e.g. placental growth factor (PlGF) concentration] with clinical and routinely collected blood/urinary parameters to determine clinically indicated need for delivery for pre-eclampsia (or related complications) within 7 days of assessment.

Chapter 2 Methods

We undertook a prospective observational cohort study that ran between February 2016 and December 2018, nested within the PHOENIX trial,[2] in women with late preterm pre-eclampsia. The PHOENIX trial was a multicentre randomised controlled trial in which women from 46 units across England and Wales with preterm pre-eclampsia from 34^{+0} to 36^{+6} weeks' gestation were randomly allocated to planned delivery or expectant management. Results of the PHOENIX trial are reported separately.[2]

Development of the original PREP-S model

Prediction models for Risk of Early-onset Pre-eclampsia – Survival (PREP-S) is a prediction model that was developed and validated in early-onset pre-eclampsia arising before 34 weeks' gestation, from 53 maternity units across the UK. The primary outcome for the PREP-S study was maternal complications of pre-eclampsia, which 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 to determine the performance of PREP-S in our cohort of women with late preterm pre-eclampsia.

Women were eligible for the PEACOCK (Prognostic indicators of severe disEAse in women with late preterm pre-eClampsia tO guide deCision maKing on timing of delivery) 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 (ISSHP)],[6] with a singleton or dichorionic diamniotic twin pregnancy and at least one viable fetus. Women were aged $\geq$ 18 years and gave written informed consent for participation. Exclusion criteria included a decision to deliver within the next 48 hours. All women eligible for the PHOENIX trial were eligible for participation in the PEACOCK study, whether they agreed or declined randomisation to the main PHOENIX trial. The study was approved by the South Central – Hampshire B Research Ethics Committee (number 13/SC/0645).

Women were approached individually and asked to provide plasma [ethylenediaminetetraacetic acid (EDTA)] and serum blood samples at the time of recruitment, which was processed within 4 hours of sampling. Samples were centrifuged at 1400 g for 10 minutes, and the separated supernatant aliquoted and stored at −80 °C. Samples were shipped back to the co-ordinating centre, thawed and processed on an electronic Triage™ instrument (Quidel Cardiovascular Inc., San Diego, CA, USA) in accordance with the manufacturer's instructions to give a serum PlGF concentration result. The readings were not revealed to the clinical team involved in the woman's care. Definitions and outcomes were prespecified in the study protocol (version 4.0). Outcomes were collected until the primary hospital discharge of the woman and infant.

Clinical predictor variables

Serum PlGF concentration at enrolment was evaluated as a predictor variable. PREP-S predictor variables were measured at study entry. PREP-S consisted of the following predictor variables, which were collected at diagnosis: maternal age (years), gestational age (weeks), exaggerated tendon reflexes, medical history (two or more of the following conditions: chronic hypertension, renal disease, previous history of pre-eclampsia, autoimmune disease and diabetes mellitus), systolic blood pressure (mmHg, highest over 6 hours), abnormal oxygen saturation (< 95% on air), platelet count ($\times 10^9$/l), serum alanine aminotransferase level (IU/l), serum urea concentration (mmol/l), serum creatinine concentration (μmol/l), urine protein–creatinine ratio (mg/mmol), any previous treatment with oral/parenteral

antihypertensives, and any previous treatment with magnesium sulphate. These were combined using the published model equation:[7]

$$S(t) = S0\,(t)\S\,\hat{}\exp\,((\beta 1^{*}X1 + \cdots + \beta n^{*}Xn)), \quad (1)$$

$$\begin{aligned} S(t) = {} & S0(t)\,\hat{}\exp\,(-0.031^{*}\text{maternal age} + 1.514\,^{*}((\text{Log}(\text{GA at diagnosis}/10))^{-2} - 0.8345136) \\ & + 5.707\,^{*}((\text{Log}(\text{GA at diagnosis}/10))^{-2}\,^{*}\ln((\log(\text{GA at diagnosis}/10)) - 0.0652155) \\ & + 0.122\,(\text{exaggerated tendon reflexes}) - 0.169\,(\text{one pre-existing medical condition}) \\ & - 0.384\,(\text{two or more pre-existing medical conditions}) + 0.016^{*}\text{systolic blood pressure} \\ & + 0.797\,(\text{oxygen saturation} < 94\%\ \text{on air}) - 0.002^{*}\text{platelet count} \\ & + 0.126^{*}\log(\text{alanine amino transferase}) + 0.605^{*}\log(\text{serum urea})^{2} - 0.144^{*}\log(\text{serum urea})^{3} \\ & + 0.265^{*}\log(\text{serum creatinine}) + 0.080^{*}\log(\text{protein–creatinine ratio}) \\ & + 0.176\,(\text{baseline treatment with any antihypertensive}) \\ & + 1.066\,(\text{baseline treatment with magnesium sulfate})). \end{aligned} \quad (2)$$

§S0 (t) – baseline survival adjusted for optimism at time *t*.

S0 (48 hours) = 0.99142, S0 (72 hours) = 0.98542, S0 (1 week) = 0.96492, and S0 (1 month) = 0.87377.

Outcomes

The primary outcome was clinically indicated need for delivery [or delivery for related conditions, such as eclampsia or HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome] within 7 days of assessment. Secondary outcomes included clinically indicated need for delivery for pre-eclampsia within 48 hours of assessment and within 14 days of assessment, perinatal deaths and neonatal unit admission. On analysis of the main trial,[2] it became clear that neonatal unit admissions did not directly reflect neonatal morbidity (as intended), but rather they reflected clinician behaviour. In the PHOENIX trial,[2] the proportions of infants with confirmed morbidity diagnoses were similar, but admission for the indication of prematurity was higher in the planned delivery group. It was therefore decided that neonatal unit admission could not be used in this cohort as a surrogate marker of neonatal morbidity and further analysis of this secondary outcome was not undertaken.

Sample size estimation

It has been recommended that external validation of a prognostic model should ideally involve a minimum of 100 informative events.[8] We estimated that the primary outcome (delivery within 7 days owing to clinical indication) would occur in around 40% of women receiving expectant management, based on our previous work and other literature.[9] The sample size for estimation of the sensitivity (within 7%) and specificity (within 7%), assuming a sensitivity of 0.90, a specificity of 0.70 and 95% confidence intervals (CIs) (two-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 two-thirds of the 500 women recruited to the PEACOCK study would receive expectant management (the group on which the model will be validated). We therefore expected 134 primary outcome events (500 × 67% × 40%).

Statistical analysis

The validation sample for the primary analysis (and secondary analysis evaluating clinically indicated need for delivery for pre-eclampsia within 14 days of assessment) was restricted to women in the PEACOCK study who underwent expectant management, that is women recruited to the PHOENIX trial (and also enrolled in the PEACOCK study) who were randomised to the expectant management arm and women who declined the PHOENIX trial and who were recruited to the PEACOCK study only who underwent the usual care strategy of expectant management. An additional analysis was conducted for evaluating clinically indicated need for delivery for pre-eclampsia within 48 hours of assessment, which included the PEACOCK women randomised to the planned delivery arm in the PHOENIX trial.

The stages of analysis were as follows: external validation of the PREP-S model, limited updating of the PREP-S model by recalibration, assessment of the model performance of the updated PREP-S model, assessment of the predictive performance of PlGF, comparison of PlGF and PREP-S, and assessment of the addition of PlGF to the PREP-S model. The performance of the models was assessed by calibration and discrimination. Model discrimination was assessed primarily using receiver operating characteristic (ROC) areas (areas under the curve), and calibration was assessed and reported graphically using calibration plots and estimated calibration slopes. The recalibrations were additionally reported graphically, with actual event rates compared with predicted rates for specified risk groups. Model performance in relation to the primary and secondary outcomes was determined using ROC areas. Test performance of PlGF was evaluated with sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. We used a PlGF concentration cut-off point of < 100 pg/ml. This was based on the evidence that, in those presenting at < 35 weeks' gestation, a PlGF concentration < 100 pg/ml has a high diagnostic accuracy (0.96, 95% CI 0.89 to 0.99) and negative predictive value (0.98, 95% CI 0.93– to 0.995) for determining pre-eclampsia necessitating delivery in 14 days. We have previously reported that a PlGF concentration < 100 pg/ml predicted pre-eclampsia 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 point.[9] Kaplan–Meier survival curves of the time from test to delivery were determined, stratified by four categories of risk determined by the PREP-S model. Assessment of PREP-S, PlGF and the combined model was conducted on the primary outcome and all secondary outcomes.

Missing data

In line with the approach used in the original Prediction models for Risk of Early-onset Pre-eclampsia (PREP) study, missing variables were handled as follows:

- Where measurement of serum alanine aminotransferase levels were not available, aspartate aminotransferase was used instead (like for like).
- Oxygen saturation was assumed to be normal if not recorded in clinical care.
- No women had exaggerated tendon reflexes, which was imputed as no, as such women were ineligible for the PHOENIX trial.
- Urinary protein-to-creatinine ratio was derived from 24-hour urinary protein excretion when there were sufficient data to derive a conversion factor.
- Missing values for serum urea concentrations were be replaced by a value derived from serum creatinine concentrations by linear regression (serum urea $= 0.053883 \times$ serum creatinine $+ 0.7874831$; numbers derived from linear regression, as described, in those with sufficient data, the correlation between the measurements was 0.5434 for 264 observations).

Chapter 3 Results

Between 27 April 2016 and 24 December 2018, we recruited 501 women to the PEACOCK study, across 36 maternity units in England and Wales (*Figure 1*). Across the participants who received expectant management as usual care outside the trial ($n = 182$) and within the PHOENIX trial allocation arm ($n = 159$), there were no statistically or clinically relevant differences (*Table 1*). Women in the two PHOENIX trial allocation arms (presented here as women in the planned delivery group included for secondary analysis) were, as expected, balanced for baseline characteristics (*Table 2*).

There were similar outcomes in women randomised to the expectant management group and those participating in the non-randomised expectant management group (*Table 3*), whereas outcomes in the planned delivery and randomised expectant management groups (*Table 4*) reflect those in the larger PHOENIX trial, with earlier gestation at delivery, as expected.[2] In women receiving expectant management, 81 (50.9%) of those randomised and 95 (52.2%) of those non-randomised (i.e. outside the trial) had indicated delivery due to clinical concerns for maternal or fetal well-being. Among women managed expectantly, 211 out of 341 (61.9%) delivered within 7 days. There were no perinatal deaths in the study.

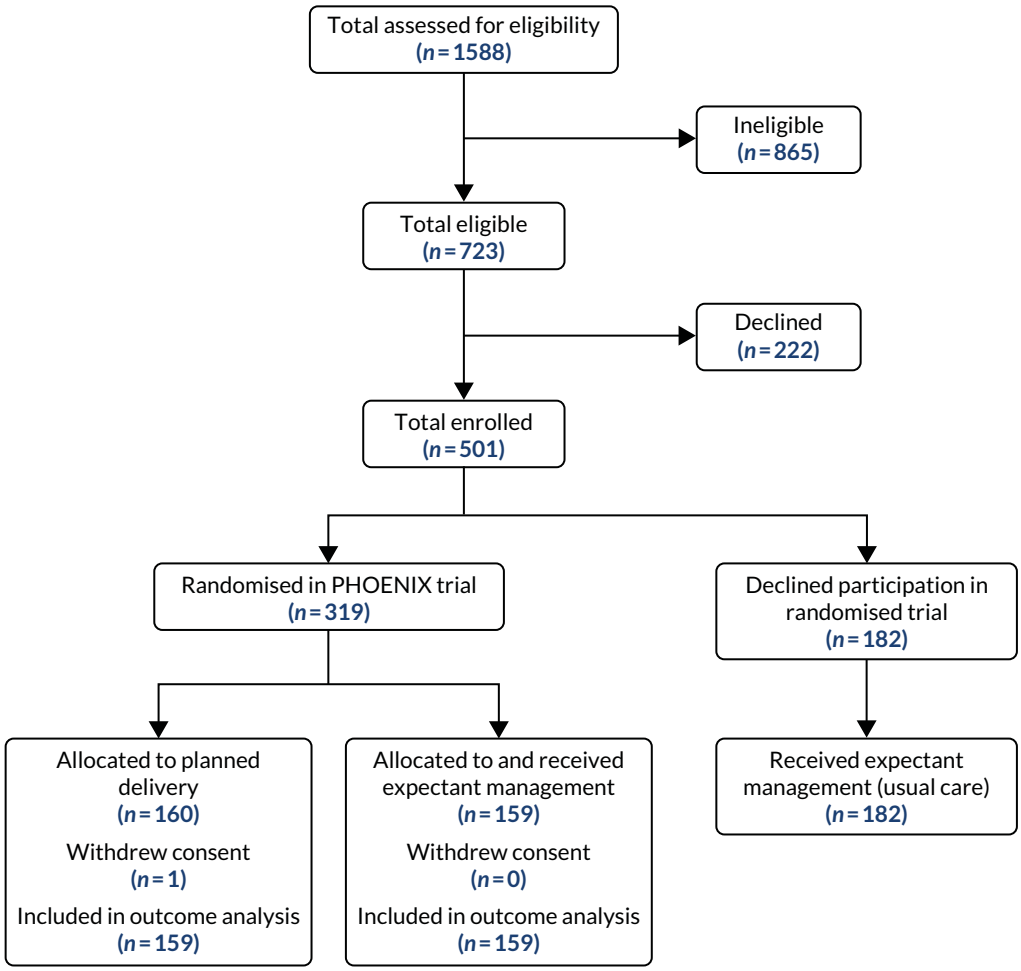

FIGURE 1 The flow diagram of participants. Reproduced with permission from Duhig *et al.*[10] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. This includes minor additions and formatting changes to the original.

TABLE 1 Maternal clinical characteristics prior to enrolment (by expectant management groups)

	Non-randomised (expectant management) (*N* = 182)	Randomised (expectant management) (*N* = 159)	Comparison (95% CI)	All (expectant management) (*N* = 341)
Maternal age (years), mean (SD)	32.7 (5.3)	31.1 (6.1)	MD 0.8 (0.2 to 1.5)	31.9 (5.7)
Ethnicity, *n* (%)				
White	122 (67.0)	114 (71.7)	–	236 (69.4)
Black	24 (13.2)	18 (11.4)	–	42 (12.4)
Asian	28 (15.4)	13 (8.2)	–	41 (12.1)
Mixed	4 (2.2)	8 (5.1)	–	12 (3.5)
Other	4 (2.2)	5 (3.2)	–	9 (2.6)
Non-white ethnicity	60 (33.0)	44 (27.8)	RR 1.18 (0.85 to 1.64)	104 (30.6)
Multiparous, *n* (%)	90 (49.5)	83 (52.2)	RR 0.95 (0.77 to 1.17)	173 (50.7)
Body mass index (kg/m^2), mean (SD)	30.2 (6.5)	30.1 (7.9)	MD 0.1 (–0.7 to 0.8)	30.2 (7.2)
Smoking, *n* (%)				
Never	146 (80.2)	114 (71.7)	–	260 (76.2)
Quit before pregnancy	21 (11.5)	32 (20.1)	–	53 (15.5)
Smoking at booking	12 (6.6)	11 (6.9)	–	23 (6.7)
Unknown	3 (1.6)	2 (1.3)	–	5 (1.5)
Smoking ever	33 (18.1)	43 (27.0)	RR 0.67 (0.45 to 1.00)	76 (22.6)
Maternal history of pre-eclampsia, *n* (%)	28 (31.1)	29 (34.9)	RR 0.84 (0.53 to 1.35)	57 (32.9)
Chronic hypertension, *n* (%)	20 (11.0)	25 (15.7)	RR 0.70 (0.40 to 1.21)	45 (13.2)
Chronic kidney disease, *n* (%)	3 (1.6)	2 (1.3)	RR 1.31 (0.22 to 7.74)	5 (1.5)
Maternal history of autoimmune disease, *n* (%)	0 (0.0)	0 (0.0)	–	0 (0.0)
Maternal medical comorbidities, *n* (%)				
0	132 (72.5)	113 (71.1)	–	245 (71.8)
1	35 (19.2)	29 (18.2)	–	64 (18.8)
2	14 (7.7)	16 (10.1)	–	30 (8.8)
3	1 (0.5)	1 (0.6)	–	2 (0.6)
Aspirin use, *n* (%)	75 (41.4)	68 (42.8)	RR 0.97 (0.75 to 1.24)	43 (42.1)
Gestation at enrolment (weeks), mean (SD)	35.4 (0.86)	35.5 (0.89)	MD –0.1 (–0.2 to 0.04)	35.4 (0.88)
Gestation at enrolment (weeks), *n* (%)				
34^{+0}–34^{+6}	69 (37.9)	51 (32.1)	–	120 (35.2)
35^{+0}–35^{+6}	55 (30.2)	48 (30.2)	–	103 (30.2)
36^{+0}–36^{+6}	58 (31.9)	60 (37.7)	–	118 (34.6)

TABLE 1 Maternal clinical characteristics prior to enrolment (by expectant management groups) (*continued*)

	Non-randomised (expectant management) (*N* = 182)	Randomised (expectant management) (*N* = 159)	Comparison (95% CI)	All (expectant management) (*N* = 341)
Singleton, *n* (%)	174 (95.6)	147 (92.5)	–	321 (94.1)
Twin, *n* (%)	8 (4.4)	12 (7.5)	RR 0.76 (0.49 to 1.18)	20 (5.9)
Maternal blood pressure 48 hours prior to enrolment (mmHg), mean (SD)				
Systolic	153 (15)	155 (16)	MD −0.8 (−2.4 to 0.8)	154 (15)
Diastolic	94 (10)	95 (11)	MD −0.3 (−1.4 to 0.8)	94 (10)
Highest urinary protein-to-creatinine ratio				
Number with measurement, mean (SD)	177, 145 (238)	156, 189 (337)	MD −22 (−54 to 10)	333, 166 (289)
Suspected fetal growth restriction on ultrasound, *n* (%)	22 (12.1)	25 (15.7)	RR 0.77 (0.45 to 1.31)	47 (13.8)
Maternal hyperreflexia, *n* (%)	0 (0.0)	0 (0.0)	–	0 (0.0)
Maternal blood oxygen level < 95%, *n* (%)	8 (4.4)	2 (1.3)	RR 3.49 (0.75 to 16.2)	10 (2.9)
Maternal platelet count (10^9/l)				
Number with measurement, mean (SD)	182, 218 (64)	159, 217 (61)	MD 0.6 (−6.2 to 7.2)	341, 218 (62)
Maternal alanine transaminase (IU/l)				
Number with measurement, mean (SD)	174, 30 (44)	154, 23 (41)	MD 3.7 (−0.8 to 8.3)	341, 27 (43)
Maternal urea (mmol/l)				
Number with measurement, mean (SD)	87, 4.2 (1.4)	88, 3.9 (1.5)	MD 0.1 (−0.03 to 0.2)	175, 4.1 (1.4)
Maternal creatinine (μmol/l)				
Number with measurement, mean (SD)	182, 64 (19)	159, 61 (14)	MD 1.4 (−0.4 to 3.2)	341, 62 (17)
Maternal PlGF (pg/ml)				
Number with measurement	178	157	MD −3.3 (−18.5 to 11.9)	335
Mean (SD)	37.1 (134.1)	43.6 (146.7)		40.16 (140.00)
Median (IQR)	12.0 (12.0–18.6)	12.6 (12.0–24.1)		12.0 (12.0–20.6)
PlGF concentration ≥ 100 pg/ml, *n* (%)	9 (5.1)	7 (4.5)	RR 1.60 (0.64 to 4.02)	18 (5.8)
PlGF concentration 12–100 pg/ml, *n* (%)	67 (37.6)	75 (47.8)	RR 0.91 (0.71 to 1.16)	142 (45.7)
PlGF concentration < 12 pg/ml, *n* (%)	76 (42.7)	75 (47.8)	RR 1.03 (0.82 to 1.30)	151 (48.6)

IQR, interquartile range; MD, mean difference; RR, risk ratio; SD, standard deviation.

TABLE 2 Maternal clinical characteristics prior to enrolment (by randomised group)

	Randomised (planned delivery) (*N* = 160)	Randomised (expectant management) (*N* = 159)	Comparison (95% CI)	All (*N* = 319)
Maternal age (years), mean (SD)	30.3 (6.0)	31.1 (6.1)	MD −0.7 (−2.0 to 0.6)	30.7 (6.0)
Ethnicity, *n* (%)				
White	123 (76.9)	114 (71.7)	–	237 (74.5)
Black	17 (10.6)	18 (11.4)	–	35 (11.0)
Asian	16 (10.0)	13 (8.2)	–	29 (9.1)
Mixed	3 (1.9)	8 (5.1)	–	11 (3.5)
Other	1 (0.6)	5 (3.2)	–	6 (1.9)
Non-white ethnicity	37 (23.1)	44 (27.8)	RR 0.83 (0.57 to 1.21)	81 (25.5)
Multiparous, *n* (%)	99 (61.9)	83 (52.2)	RR 1.19 (0.98 to 1.44)	182 (57.1)
Body mass index (kg/m^2), mean (SD)	30.6 (8.1)	30.1 (7.9)	MD 0.4 (−1.3 to 2.2)	30.36 (8.0)
Smoking, *n* (%)				
Never	120 (75.0)	114 (71.7)	–	234 (73.4)
Quit before pregnancy	26 (16.3)	32 (20.1)	–	58 (18.2)
Smoking at booking	14 (8.8)	11 (6.9)	–	25 (7.8)
Unknown	0 (0.0)	2 (1.3)	–	2 (0.6)
Smoking ever	40 (25.0)	43 (27.0)	RR 0.91 (0.63 to 1.32)	83 (26.2)
Maternal history of pre-eclampsia, *n* (%)	30 (30.3)	29 (34.9)	RR 1.03 (0.65 to 1.63)	59 (32.4)
Chronic hypertension, *n* (%)	18 (11.3)	25 (15.7)	RR 0.72 (0.41 to 1.26)	43 (13.5)
Chronic kidney disease, *n* (%)	2 (1.3)	2 (1.3)	RR 0.99 (0.14 to 6.97)	4 (1.3)
Maternal history of autoimmune disease, *n* (%)	0 (0.0)	0 (0.0)	–	0 (0.0)
Maternal medical comorbidities, *n* (%)				
0	114 (71.3)	113 (71.1)	–	227 (71.2)
1	33 (20.6)	29 (18.2)	–	62 (19.4)
2	12 (7.5)	16 (10.1)	–	28 (8.8)
3	1 (0.6)	1 (0.6)	–	2 (0.6)
Aspirin use, *n* (%)	67 (41.9)	68 (42.8)	RR 0.98 (0.76 to 1.27)	135 (42.3)
Gestation at enrolment (weeks), mean (SD)	35.5 (0.85)	35.5 (0.89)	MD 0.02 (−0.2 to 0.2)	35.49 (0.87)
Gestation at enrolment (weeks), *n* (%)				
34^{+0}–34^{+6}	48 (30.0)	51 (32.1)	–	99 (31.0)
35^{+0}–35^{+6}	52 (32.5)	48 (30.2)	–	100 (31.3)
36^{+0}–36^{+6}	60 (37.5)	60 (37.7)	–	120 (37.6)

TABLE 2 Maternal clinical characteristics prior to enrolment (by randomised group) (*continued*)

	Randomised (planned delivery) (*N* = 160)	Randomised (expectant management) (*N* = 159)	Comparison (95% CI)	All (*N* = 319)
Singleton, *n* (%)	147 (91.9)	147 (92.5)	–	294 (92.2)
Twin, *n* (%)	13 (8.1)	12 (7.5)	RR 1.08 (0.51 to 2.29)	25 (7.8)
Maternal blood pressure 48 hours prior to enrolment (mmHg), mean (SD)				
Systolic	154 (15)	155 (16)	MD −1.1 (−4.4 to 2.3)	154 (15)
Diastolic	96 (10)	95 (11)	MD 1.0 (−1.3 to 3.3)	95 (10)
Highest urinary protein-to-creatinine ratio				
Number with measurement, mean (SD)	158, 149 (168)	156, 189 (337)	MD −39 (−97 to 19)	314, 169 (266)
Suspected fetal growth restriction on ultrasound, *n* (%)	25 (15.6)	25 (15.7)	RR 0.99 (0.60 to 1.65)	50 (15.7)
Maternal hyperreflexia, *n* (%)	0 (0.0)	0 (0.0)	–	0 (0.0)
Maternal blood oxygen level < 95%, *n* (%)	1 (0.6)	2 (1.13)	–	3 (0.9)
Maternal platelet count (10^9/l)				
Number with measurement, mean (SD)	160, 225 (87)	159, 217 (61)	MD 8.0 (−8.6 to 24.6)	319, 221 (75)
Maternal alanine transaminase (IU/l)				
Number with measurement, mean (SD)	155, 23 (24)	154, 23 (41)	MD 0.4 (−7.8 to 7.0)	309, 23 (34)
Maternal urea (mmol/l)				
Number with measurement, mean (SD)	92, 4.0 (1.5)	88, 4.0 (1.5)	MD −0.05 (−0.3 to 0.2)	180, 4.0 (1.5)
Maternal creatinine (μmol/l)				
Number with measurement, mean (SD)	160, 60 (15)	159, 61 (14)	MD −1.5 (−4.7 to 1.7)	319, 60 (14)
Maternal PlGF (pg/ml)				
Number with measurement	154	157	MD 4.3 (−29.5 to 38.0)	311
Mean (SD)	47.9 (155.5)	43.6 (146.7)		45.7 (150.9)
Median (IQR)	12.3 (12.0–25.3)	12.6 (12.0–24.1)		12.0 (12.0–20.6)
PlGF concentration ≥ 100 pg/ml, *n* (%)	11 (7.1)	7 (4.5)	RR 1.60 (0.64 to 4.02)	18 (6)
PlGF concentration 12–100 pg/ml, *n* (%)	67 (43.5)	75 (47.8)	RR 0.91 (0.71 to 1.16)	142 (46)
PlGF concentration < 12 pg/ml, *n* (%)	76 (49.4)	75 (47.8)	RR 1.03 (0.82 to 1.30)	151 (49)

IQR, interquartile range; MD, mean difference; RR, risk ratio; SD, standard deviation.

TABLE 3 Maternal and perinatal characteristics at delivery by expectant management groups

	Non-randomised (expectant management) (*N* = 182)	Randomised (expectant management) (*N* = 159)	Comparison (95% CI)	All (expectant management) (*N* = 341)
Mean number of weeks' gestation at delivery (SD)	36.4 (1.05)	36.5 (1.00)	MD −0.02 (−0.1 to −0.1)	36.48 (1.03)
Preterm delivery before 37 weeks' gestation, *n* (%)	101 (55.5)	84 (52.8)	RR 1.05 (0.86 to 1.28)	185 (54.3)
Delivery within 7 days, *n* (%)	108 (59.3)	103 (64.8)	–	211 (61.9)
Delivery within 2 days, *n* (%)	28 (15.4)	29 (18.2)	–	57 (16.7)
Delivery within 14 days, *n* (%)	158 (86.8)	141 (88.7)	–	299 (87.7)
Antenatal systolic blood pressure > 160 mmHg, *n* (%)	106 (58.9)	98 (61.6)	–	204 (60.2)
Postpartum systolic blood pressure ≥ 160 mmHg, *n* (%)	67 (37.9)	61 (38.4)	–	128 (38.1)
Antihypertensive medication prior to delivery, *n* (%)	170 (93.4)	145 (91.2)	RR 1.02 (0.96 to 1.09)	315 (92.4)
Onset of labour, *n* (%)				
Spontaneous	11 (6.0)	7 (4.4)	–	18 (5.3)
Induced	110 (60.4)	101 (63.5)	–	211 (61.9)
Prelabour caesarean section	61 (33.5)	50 (31.4)	–	111 (32.6)
PROM and augmentation	0 (0.0)	1 (0.6)	–	1 (0.3)
Required indicated delivery, *n* (%)	95 (52.2)	81 (50.9)		176 (51.6)
Indication for delivery, *n* (%)				
Severe maternal hypertension	40 (22.0)	45 (28.3)	–	85 (24.9)
Maternal haematological abnormality	9 (4.9)	6 (3.8)	–	15 (4.4)
Maternal biochemical abnormality	21 (11.5)	21 (13.2)	–	42 (12.3)
Fetal concerns on US	30 (16.5)	17 (10.7)	–	47 (13.8)
Fetal concerns on CTG	24 (13.2)	18 (11.3)	–	42 (12.3)
Severe maternal symptoms	13 (7.1)	17 (10.7)	–	30 (8.8)
Reaching 37 weeks' gestation	76 (41.8)	71 (44.7)	–	147 (43.1)
Mean infant birthweight (grams) (SD)	2489 (558)	2513 (520)	MD −12 (−70 to 45)	2500 (556)
Mean intergrowth centile (SD)	32.2 (31)	31.6 (23)	MD 0.3 (−2.8 to 3.4)	31.89 (29.61)
Intergrowth SGA < 10th centile, *n* (%)	69 (36.5)	50 (29.2)	RR 1.18 (0.95 to 1.47)	119 (33.1)
Intergrowth SGA < 3rd centile, *n* (%)	30 (15.9)	12 (7.0)	RR 1.58 (1.12 to 2.24)	42 (11.7)

CTG, cardiotocography; MD, mean difference; PROM, prelabour rupture of membranes; RR, risk ratio; SD, standard deviation; SGA, small for gestational age; US, ultrasound.

TABLE 4 Maternal and perinatal clinical characteristics at delivery by randomised group

	Randomised (planned delivery) (*N* = 159)	Randomised (expectant management) (*N* = 159)	Comparison (95% CI)	All (randomised) (*N* = 318)
Mean number of weeks' gestation at delivery (SD)	35.9 (0.88)	36.5 (1.00)	MD −0.6 (−0.8 to −0.4)	36.2 (0.99)
Preterm delivery before 37 weeks' gestation, *n* (%)	139 (87.4)	84 (52.8)	RR 1.65 (1.41 to 1.94)	223 (70.1)
Delivery within 7 days, *n* (%)	154 (99.4)	103 (64.8)	–	257 (80.8)
Delivery within 2 days, *n* (%)	77 (48.4)	29 (18.2)	–	106 (33.3)
Delivery within 14 days, *n* (%)	158 (99.4)	141 (88.7)	–	299 (94.0)
Antenatal systolic blood pressure > 160 mmHg, *n* (%)	67 (42.1)	98 (61.6)	–	165 (51.9)
Postpartum systolic blood pressure ≥ 160 mmHg, *n* (%)	50 (31.4)	61 (38.4)	RR 0.71 (0.60 to 0.85)	111 (34.9)
Antihypertensive medication prior to delivery, *n* (%)	138 (86.8)	145/159 (91.2)	RR 0.95 (0.88 to 1.03)	283 (89.0)
Onset of labour, *n* (%)				
Spontaneous	0 (0.0)	7 (4.4)	–	7 (2.2)
Induced	108 (67.9)	101 (63.5)	–	209 (65.7)
Prelabour caesarean section	50 (31.4)	50 (31.4)	–	100 (31.4)
PROM and augmentation	1 (0.6)	1 (0.6)	–	2 (0.6)
Required indicated delivery, *n* (%)	–	81 (50.9)	–	–
Indication for delivery, *n* (%)				
Severe maternal hypertension	4 (2.5)	45 (28.3)	–	49 (15.4)
Maternal haematological abnormality	0 (0.0)	6 (3.8)	–	6 (1.9)
Maternal biochemical abnormality	5 (3.1)	21 (13.2)	–	26 (8.2)
Fetal concerns on US	3 (1.9)	17 (10.7)	–	20 (6.3)
Fetal concerns on CTG	12 (7.5)	18 (11.3)	–	30 (9.4)
Severe maternal symptoms	3 (1.9)	17 (10.7)	–	20 (6.3)
Reaching 37 weeks' gestation	1 (0.6)	71 (44.7)	–	72 (22.6)
Trial allocation	159 (100)	0 (0.0)	–	159 (50.0)
Mean infant birthweight (grams) (SD)	2450 (465)	2513 (520)	MD −63 (−168 to 42)	2482 (494)
Mean intergrowth centile (SD)	36.8 (29)	31.6 (23)	MD 5.3 (−0.9 to 11.3)	34.2 (28.8)
Intergrowth SGA < 10th centile, *n* (%)	41 (24.0)	50 (29.2)	RR 0.82 (0.58 to 1.17)	91 (26.6)
Intergrowth SGA < 3rd centile, *n* (%)	12 (7.0)	12 (7.0)	RR 1.00 (0.46 to 2.16)	24 (7.0)

CTG, cardiotocography; MD, mean difference; PROM, prelabour rupture of membranes; RR, risk ratio; SD, standard deviation; SGA, small for gestational age; US, ultrasound.

The test performance for PlGF in determining the need for delivery within 7 days at low (< 100 pg/ml) and very low PlGF concentrations (< 12 pg/ml) is shown in *Table 5*. The sensitivity of placental growth factor concentration < 100 pg/ml in determining need for delivery within 7 days was 97.9% (95% CI 94.8% to 99.4%), the negative predictive value was 71.4% (95% CI 41.9% to 91.6%) and the specificity of 8.4% (95% CI 4.1% to 14.9%). Similar test performance statistics for determining need for delivery within 14 days are shown in *Table 6* and need for delivery within 2 days are shown in *Table 7* ($n = 501$ women). Although the test had high sensitivity for delivery within 7 days, the negative predictive value was only 71% and the specificity was low (8%).

For evaluation of the PREP-S prognostic model in this cohort, baseline predictor variables were assessed in the PEACOCK study cohort and the original PREP-S cohort (*Table 8*). There were important differences between the two cohorts, particularly relating to gestation at enrolment, definitions used for and, therefore, incidence of adverse maternal outcomes.

The ROC areas for PlGF and PREP-S are shown in *Table 9* and *Figure 2*, with consideration of the PREP-S model for a dichotomised end point (delivery within 7 days), not a time-to-survival model as originally described, and assessment of PlGF concentration and PREP-S in combination, treating PREP-S as a single predictor.[4] The area under the curve for the clinical prediction model (PREP-S) concentration and PlGF in this cohort in determining need for delivery within 7 days was 0.64 [standard error (SE) 0.03] and 0.60 (SE 0.03), respectively, and 0.65 (SE 0.03) in combination. Both PREP-S (when used to determine a binary outcome and PlGF concentration have limited clinical applicability in this cohort in determining need for delivery within 7 days.

Performance of the PREP-S model and PlGF concentration is similar in determining delivery in 2 and 14 days in this cohort (*Table 10* and *Figures 3* and *4*), and these predictors have limited clinical applicability in this setting.

TABLE 5 Test performance statistics for low and very low concentrations of PlGF in determining need for delivery within 7 days in the expectant management groups (non-randomised and randomised)

	Delivery within 7 days
< 100 pg/ml	
Sensitivity (%) (95% CI); *n/N*	97.9 (94.8 to 99.4); 133/135
Specificity (%) (95% CI); *n/N*	8.4 (4.1 to 14.9); 10/119
Positive predictive value (%) (95% CI); *n/N*	63.3 (57.5 to 68.8); 188/297
Negative predictive value (%) (95% CI); *n/N*	71.4 (41.9 to 91.6); 10/14
Positive likelihood ratio (95% CI)	1.07 (1.01 to 1.13)
Negative likelihood ratio (95% CI)	0.25 (0.08 to 0.77)
< 12 pg/ml	
Sensitivity (%) (95% CI); *n/N*	62.0 (54.7 to 68.9); 119/192
Specificity (%) (95% CI); *n/N*	55.5 (46.1 to 64.6); 66/119
Positive predictive value (%) (95% CI); *n/N*	69.2 (61.7 to 76.0); 119/172
Negative predictive value (%) (95% CI); *n/N*	47.5 (39.0 to 51.6); 66/139
Positive likelihood ratio (95% CI)	1.39 (1.11 to 1.75)
Negative likelihood ratio (95% CI)	0.69 (0.54 to 0.87)

TABLE 6 Test performance statistics for low and very low concentrations of PlGF in determining need for delivery within 14 days in the expectant management groups (non-randomised and randomised)

	Delivery within 14 days
< 100 pg/ml	
Sensitivity (%) (95% CI); *n/N*	97.4 (94.8 to 99.0); 266/273
Specificity (%) (95% CI); *n/N*	18.4 (7.7 to 34.3); 7/38
Positive predictive value (%) (95% CI); *n/N*	89.6 (85.5 to 92.8); 266/297
Negative predictive value (%) (95% CI); *n/N*	50.0 (23.0 to 77.0); 7/14
Positive likelihood ratio (95% CI)	1.19 (1.03 to 1.39)
Negative likelihood ratio (95% CI)	0.14 (0.05 to 0.38)
< 12 pg/ml	
Sensitivity (%) (95% CI); *n/N*	58.6 (52.5 to 64.5); 160/273
Specificity (%) (95% CI); *n/N*	68.4 (51.3 to 82.5); 26/39
Positive predictive value (%) (95% CI); *n/N*	93.0 (88.1 to 96.3); 160/172
Negative predictive value (%) (95% CI); *n/N*	18.7 (12.6 to 26.2); 26/139
Positive likelihood ratio (95% CI)	1.86 (1.15 to 2.99)
Negative likelihood ratio (95% CI)	0.60 (0.47 to 0.78)

TABLE 7 Test performance statistics for low and very low concentrations of PlGF in determining need for delivery in 2 days in the PEACOCK cohort

	Delivery within 2 days
< 100 pg/ml	
Sensitivity (%) (95% CI); *n/N*	95.2 (89.8 to 98.2); 119/125
Specificity (%) (95% CI); *n/N*	5.6 (3.4 to 8.7); 19/337
Positive predictive value (%) (95% CI); *n/N*	27.2 (23.1 to 31.7); 119/337
Negative predictive value (%) (95% CI); *n/N*	76.0 (54.9 to 90.6); 19/25
Positive likelihood ratio (95% CI)	1.01 (0.96 to 1.06)
Negative likelihood ratio (95% CI)	0.85 (0.35 to 2.08)
< 12 pg/ml	
Sensitivity (%) (95% CI); *n/N*	54.4 (45.3 to 63.3); 68/125
Specificity (%) (95% CI); *n/N*	47.2 (41.7 to 52.7); 159/338
Positive predictive value (%) (95% CI); *n/N*	27.6 (22.2 to 33.7); 68/246
Negative predictive value (%) (95% CI); *n/N*	73.6 (67.2 to 79.4); 159/216
Positive likelihood ratio (95% CI)	1.03 (0.85 to 1.24)
Negative likelihood ratio (95% CI)	0.97 (0.77 to 1.21)

TABLE 8 Comparison of baseline variables and outcomes in the PEACOCK study and original PREP cohorts

Variable	PEACOCK: all expectant management (*N* = 341)	PREP-S cohort (*N* = 954)	Comparison
Maternal age (years)			
Number with measurement, mean (SD)	341, 31.9 (5.7)	954, 30.2 (6.1)	$p < 0.0001$
Multiparous			
Number with measurement, *n* (%)	341, 173 (50.7)	954, 403 (42)	$p = 0.006$
Maternal history of pre-eclampsia			
Number with measurement, *n* (%)	341, 57 (32.9)	336, 169 (43)	$p < 0.0001$
Chronic hypertension			
Number with measurement, *n* (%)	341, 45 (13.2)	944, 139 (15)	$p = 0.43$
Maternal medical comorbidities			
Number with measurement	341	953	$p < 0.0009$
1 +, *n* (%)	96 (27.9)	352 (37)	$p = 0.53$
2 +, *n* (%)	32 (9.6)	101 (11)	
Maternal blood pressure 48 hours prior to enrolment (mmHg)			
Number with measurement	341	949	$p < 0.0001$
Systolic, mean (SD)	154 (15)	159 (19)	$p < 0.0001$
Diastolic, mean (SD)	94 (10)	99 (12)	
Gestation at enrolment (weeks)			
Number with measurement, mean (SD)	341, 35.4 (0.88)	954, 30.5 (2.9)	$p < 0.0001$
Maternal hyperreflexia			
Number with measurement, *n* (%)	–	601, 147 (24)	
Maternal blood oxygen level < 94%			
Number with measurement, *n* (%)	177, 3 (1.7)	433, 4 (0.9)	$p = 0.23$
Highest urinary protein-to-creatinine ratio			
Number with measurement, mean (SD)	333, 166 (289)	845, 273 (492)	$p < 0.0001$
Maternal platelet count (10^9/l)			
Number with measurement, mean (SD)	341, 218 (62)	913, 226 (78)	$p = 0.006$
Maternal alanine transaminase (IU/l)			
Number with measurement, mean (SD)	341, 27 (43)	879, 31 (71)	$p < 0.0001$
Maternal urea (mmol/l)			
Number with measurement, mean (SD)	175, 4.1 (1.4)	884, 4.6 (4.4)	$p < 0.0001$
Maternal creatinine (μmol/l)			
Number with measurement, mean (SD)	341, 62 (17)	916, 61 (18)	$p = 0.54$
Baseline treatment with magnesium			
Number with measurement, *n* (%)	–	954, 144 (15)	–
Delivery before 34 weeks' gestation (%)	–	61.3	–
Delivery before 37 weeks' gestation (%)	54.3	–	–
PEACOCK adverse maternal outcome (%)	19.5[a]	–	–
PREP-S adverse maternal outcome (%)	–	15.1[b]	–

SD, standard deviation.
a PEACOCK definition of maternal adverse outcome: composite of maternal morbidity of fullPIERs outcomes with the addition of systolic blood pressure > 160 mmHg at any time post study entry.
b PREP-S definition of adverse maternal outcome: composite of maternal morbidity of fullPIERs outcomes with the addition of delivery before 34 weeks' gestation.

TABLE 9 The ROC areas (SE) for PREP-S and PlGF in determining delivery in 7 days singly and in combination

	ROC area (SE) (95% CI)	Harrell's C-index (95% CI)	Comparison (vs. PREP-S alone)
PREP-S alone	0.64 (0.03) (0.58 to 0.71)	0.61 (0.57 to 0.64)	–
PlGF alone	0.60 (0.03) (0.54 to 0.66)	–	$p = 0.314$
PREP-S + PlGF	0.65 (0.03) (0.58 to 0.71)	–	$p = 0.776$

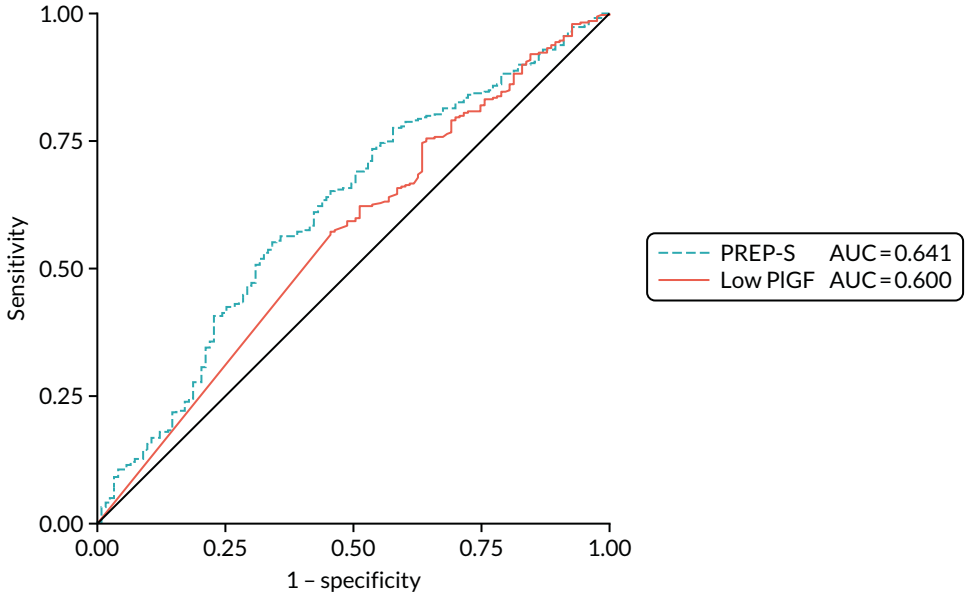

FIGURE 2 The ROC areas for PlGF and PREP-S in determining need for delivery within 7 days. AUC, area under the curve. Reproduced with permission from Duhig *et al.*[10] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. This includes minor additions and formatting changes to the original.

TABLE 10 The ROC areas (SE) for PREP-S and PlGF in determining delivery in 14 days and in 2 days, both singly and in combination

Delivery time	ROC area (SE) (95% CI)	Comparison (vs. PREP-S alone)
In 14 days		
PREP-S alone	0.72 (0.05) (0.63 to 0.82)	
PlGF alone	0.67 (0.05) (0.58 to 0.77)	$p = 0.352$
PREP-S + PlGF	0.74 (0.05) (0.65 to 0.83)	$p = 0.080$
In 2 days		
PREP-S alone	0.71 (0.04) (0.64 to 0.79)	
PlGF alone	0.53 (0.04) (0.45 to 0.61)	$p = 0.0002$
PREP-S + PlGF	0.72 (0.04) (0.64 to 0.79)	$p = 0.639$

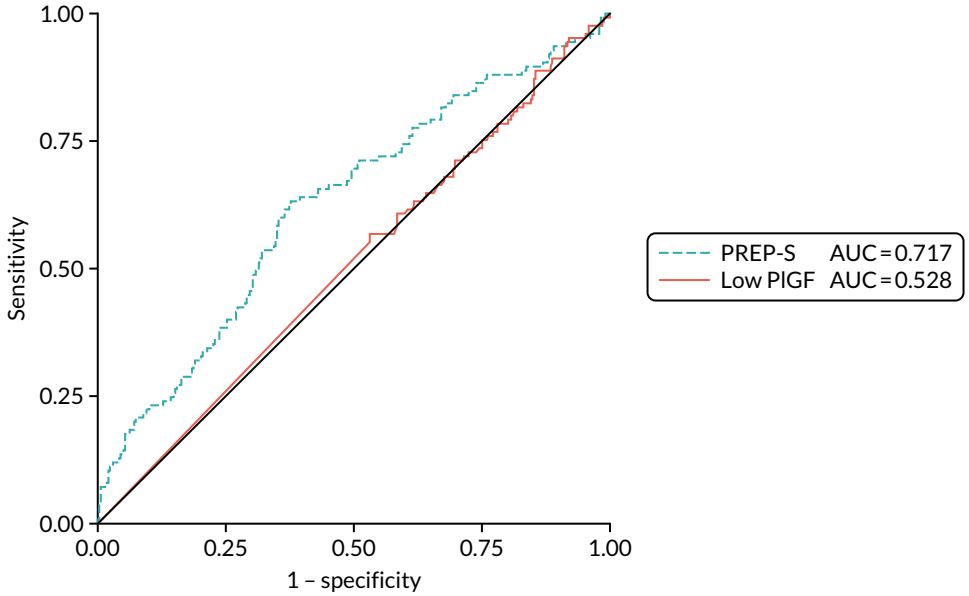

FIGURE 3 The ROC areas for PlGF and PREP-S in determining need for delivery within 2 days. AUC, area under the curve. Reproduced with permission from Duhig *et al.*[10] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. This includes minor additions and formatting changes to the original.

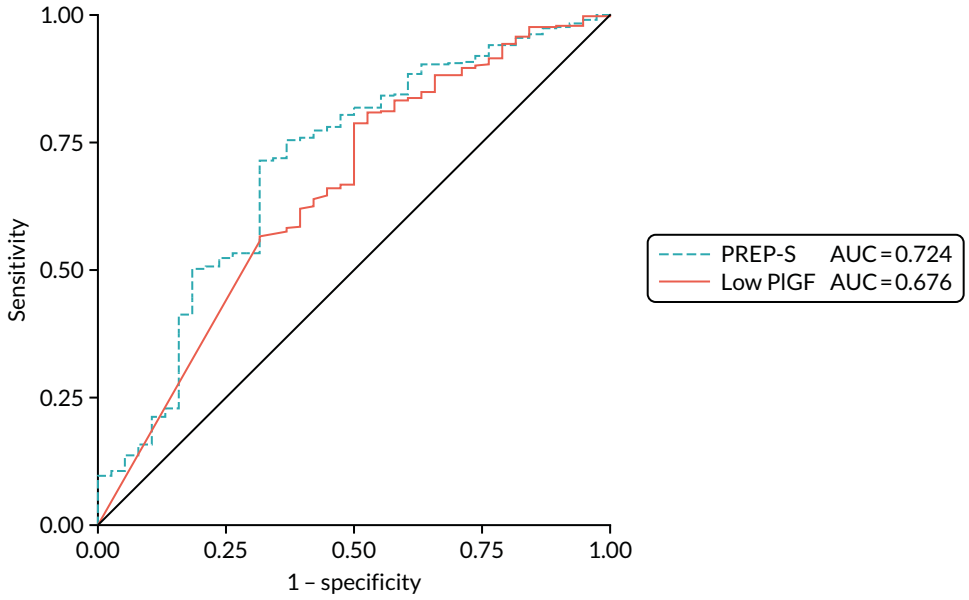

FIGURE 4 The ROC areas for PlGF and PREP-S in determining need for delivery within 14 days. AUC, area under the curve. Reproduced with permission from Duhig *et al.*[10] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. This includes minor additions and formatting changes to the original.

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 *Figure 5*, and the recalibrated estimates are shown in *Figure 6*.

Calibration of the PREP-S model is shown in *Table 11*, with calibration in the large and of the slope assessed for predicting delivery for pre-eclampsia within 7 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 did have the outcome that was predicted by the model (expected value 0;

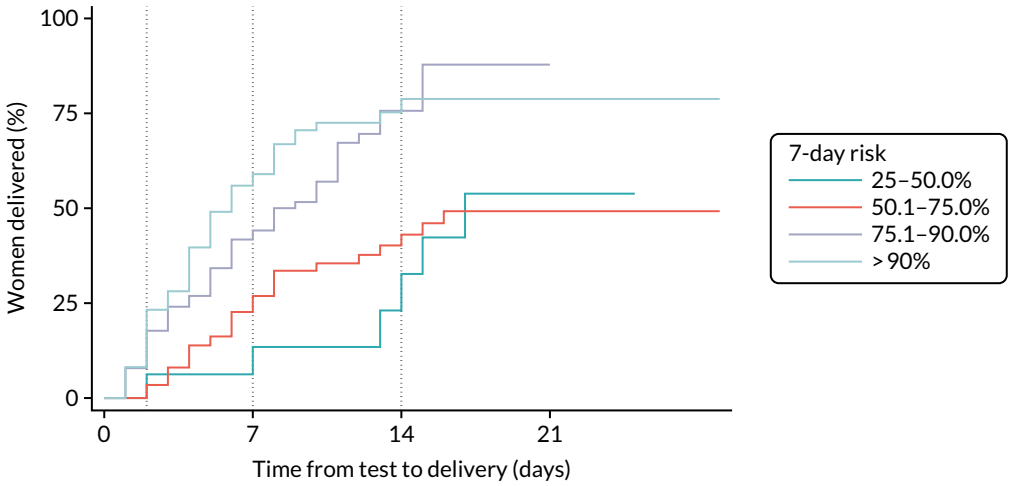

FIGURE 5 Observed risks for time-to-delivery Kaplan–Meier failure estimates by four 7-day PREP-S risk categories. Reproduced with permission from Duhig *et al.*[10] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. This includes minor additions and formatting changes to the original.

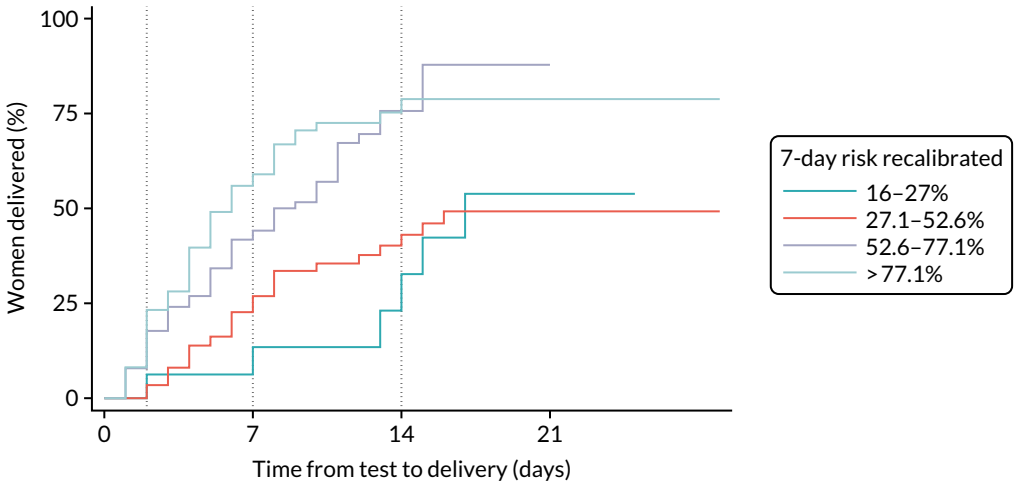

FIGURE 6 Recalibrated risks for time-to-delivery Kaplan–Meier failure estimates by four 7-day PREP-S risk categories. Reproduced with permission from Duhig *et al.*[10] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. This includes minor additions and formatting changes to the original.

TABLE 11 The PREP calibrations

	Delivery within 7 days	Delivery within 2 days	Delivery within 14 days
In the large	−0.13 ($p = 0.52$)	−1.07 ($p < 0.0001$, Z −5.78)	0.41 ($p = 0.29$)
In the large – recalibrated	0.24 ($p = 0.075$)	0.10 ($p = 0.79$)	0.89 ($p = 0.001$, Z = 3.32)
Of the slope	0.375 ($p < 0.00001$, Z = −5.7)	1.18 ($p = 0.483$)	0.49 ($p < 0.0001$, Z = −4.06)

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 overpredicting the adverse event rate in the higher-risk groups. Recalibration of the model had no impact on the ROC areas, but slightly improved the calibration of the PREP-S probabilities so that the notional probabilities were slightly closer to the actual event rate in the various subgroups.

Calibrations plots are shown for PREP-S for delivery within 7 days (*Figure 7* and *Table 12*), 2 days (*Figure 8* and *Table 13*) and 14 days (*Figure 9* and *Table 14*). These are used as a prognostic model to determine time to delivery within a certain number of days as a binary outcome, not as a time-to-survival model. Without recalibration, there is poor agreement between the predicted and the actual event rates in each risk group. After recalibration, there is some improvement, particularly in the overall average, but substantial differences remain. For example, in *Figure 7b*, only the third group is correctly aligned, and the fourth group remains substantially unaligned.

Evaluation of other thresholds (undertaken post hoc following a reviewer request) for PlGF did not substantially improve test performance over and above the prespecified thresholds (*Table 15*).

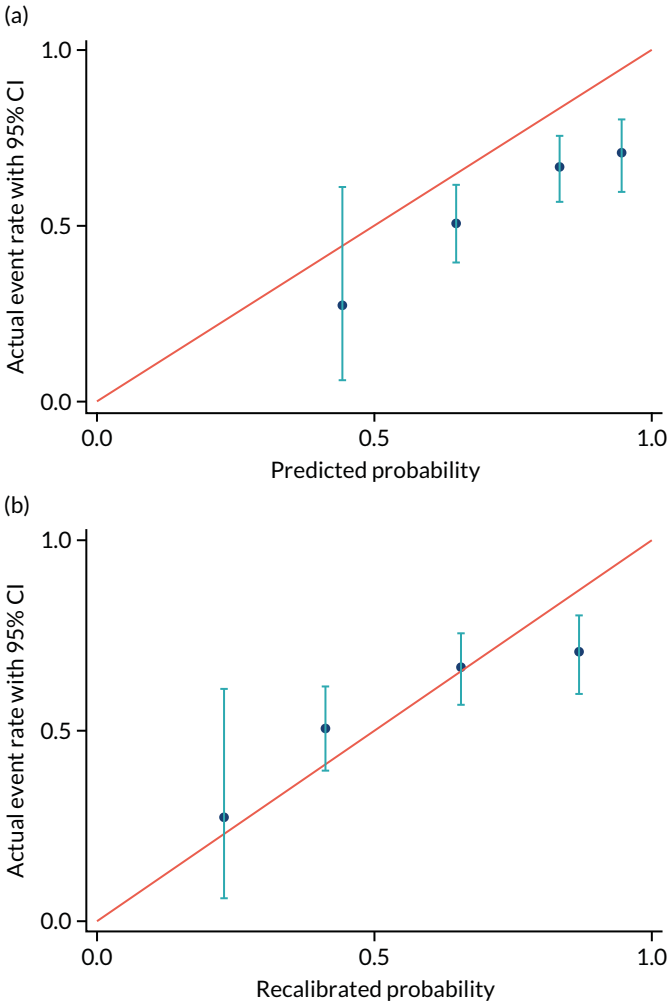

FIGURE 7 Calibration plot for delivery within (a) 7 days and (b) recalibrated. Reproduced with permission from Duhig *et al.*[10] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. This includes minor additions and formatting changes to the original.

TABLE 12 Probability of delivery in 7 days compared with observed event rate

	Predicted probability group			
Event rate	**0.25–0.50**	**0.51–0.75**	**0.76–0.90**	**> 0.90**
Number of women	**11**	**85**	**105**	**82**
Original predicted event rate, mean (95% CI)	0.44 (0.36 to 0.50)	0.65 (0.50 to 0.75)	0.83 (0.75 to 0.90)	0.95 (0.90 to 1.00)
Recalibrated predicted event rate, mean (95% CI)	0.23 (0.17 to 0.27)	0.41 (0.27 to 0.53)	0.66 (0.53 to 0.77)	0.87 (0.77 to 0.99)
Actual event rate, proportion (*n*)	0.27 (3)	0.51 (167)	0.67 (70)	0.71 (58)

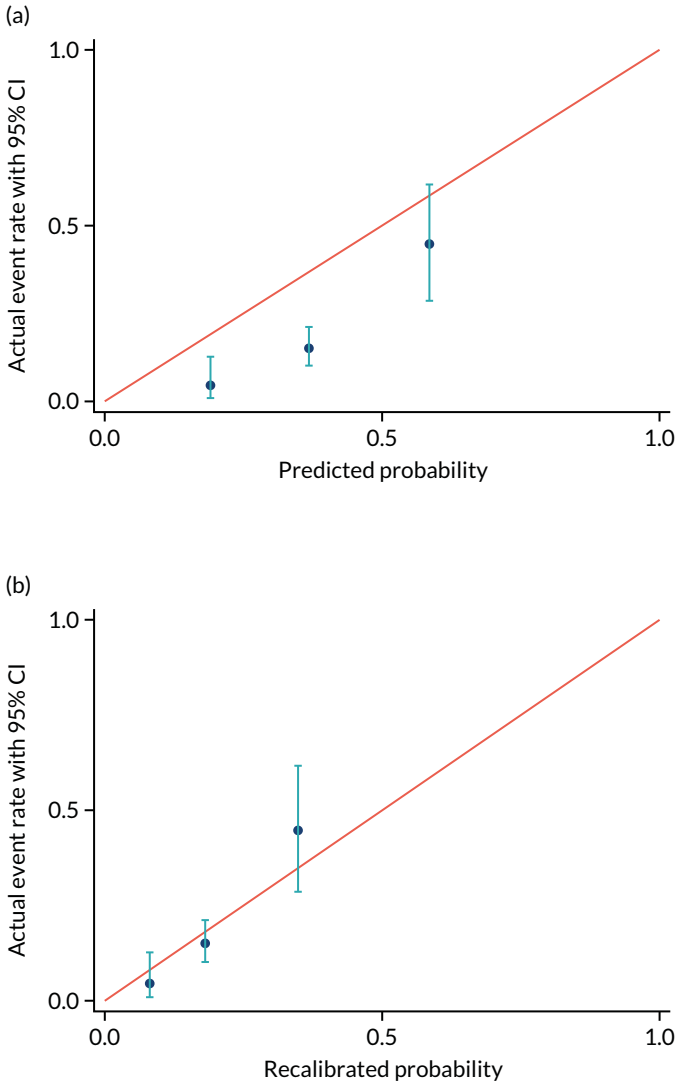

FIGURE 8 Calibration plot for delivery within (a) 2 days and (b) recalibrated. Reproduced with permission from Duhig *et al.*[10] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. This includes minor additions and formatting changes to the original.

TABLE 13 Probability of delivery in 2 days compared with observed event rate

	Predicted probability group		
Event rate	**< 0.25**	**0.25–0.50**	**> 0.50**
Number of women	**66**	**179**	**38**
Original predicted event rate, mean (95% CI)	0.19 (0.10 to 0.25)	0.37 (0.25 to 0.50)	0.59 (0.50 to 0.74)
Recalibrated predicted event rate, mean (95% CI)	0.08 (0.40 to 0.11)	0.18 (0.11 to 0.27)	0.35 (0.27 to 0.51)
Actual event rate, proportion (*n*)	0.05 (3)	0.15 (27)	0.45 (17)

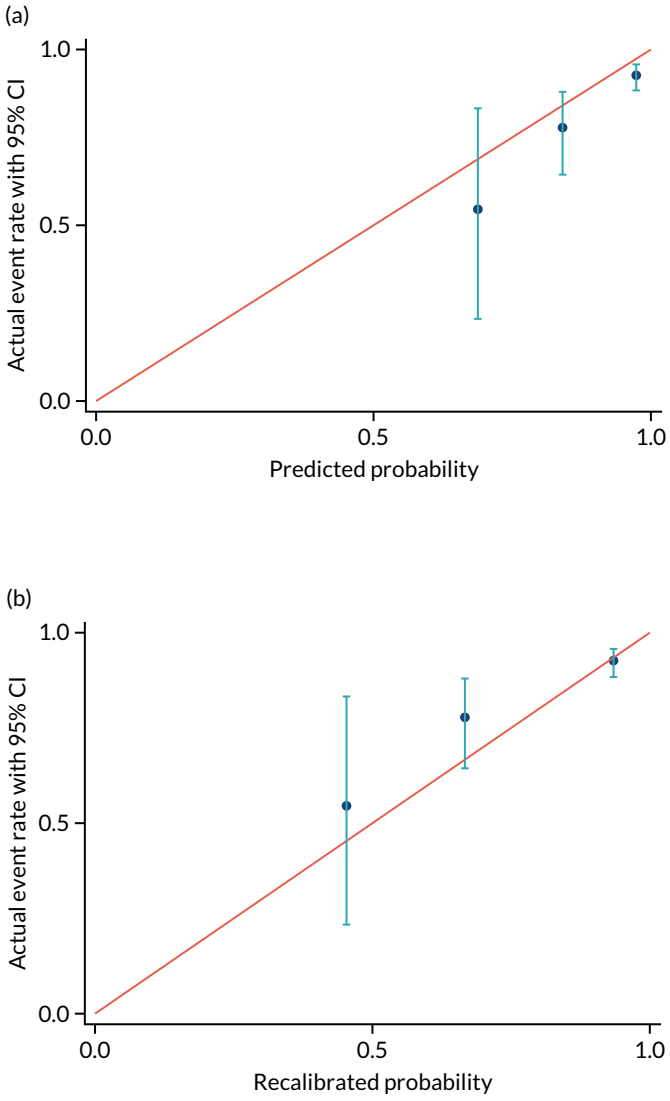

FIGURE 9 Calibration plot for delivery within (a) 14 days and (b) recalibrated. Reproduced with permission from Duhig *et al.*[10] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. This includes minor additions and formatting changes to the original.

TABLE 14 Probability of delivery in 14 days compared with observed event rate

	Predicted probability group		
Event rate	**0.50–0.75**	**0.76–0.90**	**> 0.90**
Number of women	**11**	**54**	**218**
Original predicted event rate, mean (95% CI)	0.69 (0.59 to 0.75)	0.84 (0.75 to 0.90)	0.97 (0.91 to 0.99)
Recalibrated predicted event rate, mean (95% CI)	0.45 (0.36 to 0.53)	0.67 (0.53 to 0.77)	0.93 (0.78 to 0.99)
Actual event rate, proportion (*n*)	0.55 (6)	0.77 (42)	0.93 (203)

TABLE 15 Incremental PlGF 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 to 62.0)	54.5 (45.2 to 63.5)	77.4 (71.7 to 82.5)	31.3 (25.2 to 38.0)
< 30	74.9 (70.0 to 79.5)	35.8 (27.3 to 44.9)	76.3 (71.3 to 80.7)	34.1 (26.0 to 43.0)
< 40	81.7 (77.2 to 85.7)	25.2 (17.8 to 33.8)	75.1 (70.3 to 79.4)	33.3 (23.9 to 43.9)
< 50	86.4 (82.3 to 89.9)	18.7 (12.2 to 26.7)	74.6 (69.9 to 78.8)	33.3 (22.4 to 45.7)
< 60	88.8 (84.9 to 91.9)	17.1 (10.9 to 24.9)	74.7 (70.1 to 78.9)	35.6 (23.6 to 49.1)
< 70	92.0 (88.6 to 94.7)	15.4 (9.6 to 23.1)	75.0 (70.5 to 79.1)	41.3 (27.0 to 56.8)
< 80	92.0 (88.6 to 94.7)	13.8 (8.3 to 21.2)	74.6 (70.2 to 78.7)	38.6 (24.4 to 54.5)
< 90	93.8 (90.7 to 96.1)	10.6 (5.7 to 17.4)	74.3 (69.9 to 78.4)	38.2 (22.2 to 56.4)

NPV, negative predictive value; PPV, positive predictive value.

Chapter 4 Discussion

Statement of principal findings

The findings from this research indicate that, in this group of women with late preterm pre-eclampsia, PlGF measurement and the PREP-S model are not likely to add to the current clinical assessment to help plan care for these women around timing of delivery.

Strengths and weaknesses of the study

The PEACOCK study was nested within a larger trial (PHOENIX), which evaluated timing of delivery in women with late preterm pre-eclampsia. We were necessarily constrained by the design of the PHOENIX trial such that we studied women who had reached a higher number of gestational weeks (from 34 up to 37 weeks' gestation) than those in the original PREP study (who had reached up to 34 weeks' gestation). In addition, we chose a different, binary, outcome (clinically indicated need for delivery by 7 days) and a different initial statistical analysis (presenting ROC areas). Further statistical analysis is under way to derive the predicted Kaplan–Meier estimates for the PREP-S categories for comparison with the observed estimates. These methods will provide further measure of the PREP-S model using a time-to-survival approach (as originally described).[4] We originally chose measurement of PlGF concentrations as a potential predictor, based on our other work describing strong test performance of PlGF concentrations in women with suspected pre-eclampsia.[9] However, the distribution of PlGF concentrations in women with confirmed pre-eclampsia is very different from the distribution of those presenting with suspected disease, with a high proportion of women (> 90%) having low or very low PlGF results. Although sensitivity of the test remains high, specificity, predictive values and likelihood ratios are all suboptimal, and the areas under the ROC curves for determining need for delivery in 7 days are too low to be clinically useful.

Placental growth factor is a biomarker that is considered reasonably 'upstream' in the pathophysiological process of the development of pre-eclampsia. The poor prognostic performance in this group may be because the need for delivery from pre-eclampsia within 7 days is associated with a variety of multiorgan, end-stage clinical parameters and, therefore, an 'upstream' biomarker such as PlGF is unable to discriminate which individuals are at a higher risk than others. In addition, clinicians act on the early signs of impending clinical deterioration (e.g. abnormal liver transaminases) to avoid severe hepatic dysfunction (as used in the original PREP-S study). If these blood test results are considered good at predicting severe adverse outcomes, then the treatment paradox (e.g. decision for delivery based on early derangement of liver transaminases) could have an impact on the performance of prognostic markers or models, as women will have the primary outcome (clinically indicated need for delivery within 7 days) without necessarily going on to develop severe maternal adverse outcomes. Although our chosen primary outcome (need for delivery for pre-eclampsia within 7 days) acts as a surrogate to represent clinician concern of substantial fetal or maternal compromise, the suboptimal performance of PlGF for predicting delivery in this group may also reflect the complex, multipathological nature of this end point, and that a single biomarker is unable to determine both fetal and maternal compromise, which have considerably different pathology (albeit the same clinical end point of early delivery). It remains to be determined if PlGF may perform better at predicting fetal indications for delivery such as fetal growth restriction or acute placental compromise, given that fetal complications reflect a placental phenotype of pre-eclampsia. Although PlGF measurements have shown considerable potential as a diagnostic adjunct in women with suspected disease,[11] and the distribution of low and very low PlGF concentrations in the PEACOCK cohort confirms that we had participating women with placental dysfunction, the findings suggest that this test does not appear to have strong prognostic value (for need for delivery) in this setting.

The PREP-S model was developed in an early-onset pre-eclampsia population (prior to 34 weeks' gestation), whereas the PEACOCK population was women with late preterm pre-eclampsia (34 to 37 weeks' gestation). The underlying pathophysiology of the condition is likely to vary across these two groups, and hence the model cannot automatically be transferred for use in the different population. PREP-S was mainly developed to predict neurological, hepatic, renal, haematological and cardiorespiratory complications, and delivery before 34 weeks' gestation, as clinicians would consider delivery before 34 weeks' gestation only if the risks of complications are considered to outweigh the risks of prematurity. In the PEACOCK study, we assessed women with late preterm pre-eclampsia, including only those who either developed pre-eclampsia after 34 weeks' gestation or remained undelivered after 34 weeks' gestation if they did develop pre-eclampsia prior to this gestation. Both of these groups are different from those in which the model was developed for PREP-S. Importantly, clinicians are likely to have lower threshold for delivery in women with late preterm pre-eclampsia than early-onset pre-eclampsia because the risk of prematurity-related complications is lower for births after than before 34 weeks' gestation. Although the PREP-S model has consistently shown accurate performance both in the development data set and in two separate validation data sets of early-onset pre-eclampsia,[4] we found that the model cannot be transferred to a late preterm pre-eclampsia population to predict a different outcome.

There was a very small proportion of missing data. We chose a pragmatic approach to reflect the scenario of using a prediction model with an individual woman in clinical practice. For a scenario such as having an aspartate aminotransferase result (rather than a serum alanine aminotransferase result), single-value substitution was more appropriate than multiple imputation, which was not practical in clinical practice.

Strengths and weaknesses in relation to other studies, discussing important differences in results

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 underexplored. One early study by Verlohren *et al.*[12] assessed the ratio of the soluble fms-like tyrosine kinase-1 (sFlt-1) to 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 the sFlt-1/PlGF ratio (but did not report other test performance statistics for this outcome). They reported that women with pre-eclampsia with a sFlt-1/PlGF ratio in the upper quartile had a significantly reduced duration of pregnancy. However, a more recent study by Lou *et al.*[13] found that, in women with pre-eclampsia after 34 weeks' gestation, there was no significant difference in sFlt-1/PlGF ratio between those who delivered within 7 days and those who delivered later. Meler *et al.*[14] similarly concluded that the role of a low PlGF concentration in predicting maternal complications in early-onset pre-eclampsia is limited because of both its low specificity and its low positive predictive value.

Meaning of the study

PlGF testing and the PREP-S prediction model cannot be recommended to help plan care for late preterm pre-eclampsia regarding timing of delivery. This is important and timely information given the current NHS-wide adoption of PlGF testing as a diagnostic adjunct in the assessment of women with suspected pre-eclampsia, a different population of women in this study, who had confirmed pre-eclampsia. Despite the confirmed diagnostic utility of PlGF in women with suspected pre-eclampsia, PlGF does 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 both alone and in combination with PlGF appears to have limited clinical applicability for determining which women would require delivery in 7 days (from date of assessment), in women with late preterm pre-eclampsia.

Unanswered questions and future research

Statistical modelling

Further statistical analysis of these data, considering the PREP-S model with a time-to-event analysis (as the model originally described) could be undertaken. We will consider the addition of PlGF to this model, and derive the predicted Kaplan–Meier estimates for the PREP-S categories for comparison with the observed estimates. These methods may provide further measures of the PREP-S model. We will consider rebuilding the PREP-S model within this data set, using PlGF as a candidate predictor.

Subgroup analysis

Given that PlGF is associated with placental pathology, and angiogenic factors have been observed to be imbalanced in pregnancies complicated by fetal growth restriction,[9,15] we will undertake a subgroups analysis for the primary outcome in determining need for delivery in 7 days for fetal indications.

Angiogenic marker assessment

Maternal serum and urinary sFlt-1 and sFlt-1/PlGF ratios have been shown to be correlated with pre-eclampsia disease severity in some small studies.[16] Work is also under way to assess the performance of sFlt-1 and the sFlt-1/PlGF ratio to determine if this has superior performance to PlGF alone in predicting the primary outcome in this cohort.

Patient and public involvement

The research question for the PEACOCK study was identified with the involvement of women from our Hypertension in Pregnancy patient and public involvement (PPI) group, alongside the charity Action on Pre-eclampsia. With their input, we have identified a research question related to the uncertainties of the clinical course of pre-eclampsia that they deem extremely relevant to the physical and emotional well-being of women. Given that there is no reliable, robust way of determining which women and babies will become seriously unwell from pre-eclampsia, there is significant anxiety for women, with uncertainty as to who will deteriorate (and in what time frame). This also results in prolonged hospital stays for women who remain well, which has an impact on their existing family life.

Action on Pre-eclampsia were consulted on an ongoing basis for the duration of the PHOENIX trial and the PEACOCK study, advising on the execution of the study, particularly relating to approaching women for participation. We will consult with our PPI group and the charity when the results of the PEACOCK study are ready for dissemination.

Acknowledgments

Contributions of authors

Kate Duhig (https://orcid.org/0000-0001-9176-5671) (Clinical Research Fellow) contributed to the analysis and writing of the study. She also wrote the report.

Paul T Seed (https://orcid.org/0000-0001-7904-7933) (Statistician) wrote the later versions of the statistical analysis plan and undertook the statistical analysis.

Anna Placzek (https://orcid.org/0000-0002-6745-5996) (Study Manager) assisted with day-to-day running of the trial.

Jenie Sparkes (https://orcid.org/0000-0002-9973-544X) (Research Midwife) supported site research midwives and related activities.

Carolyn Gill (https://orcid.org/0000-0003-0012-5105) (Senior Research Technician) co-ordinated sample movement and analysis.

Anna Brockbank (https://orcid.org/0000-0002-2764-0556) (Research Technician) undertook sample logistics and analysis.

Andrew Shennan (https://orcid.org/0000-0001-5273-3132) (Professor, Obstetrics) conceived the study, contributed to study design and interpretation, and was involved in securing funding for the study.

Shakila Thangaratinam (https://orcid.org/0000-0002-4254-460X) (Professor, Obstetrics) conceived the study, contributed to study design, analysis and interpretation, and was involved in securing funding for the study.

Lucy C Chappell (https://orcid.org/0000-0001-6219-3379) (NIHR Research Professor, Obstetrics) conceived the study, was the chief investigator and was involved in securing funding for the study. She also wrote the report.

All authors reviewed, contributed to and approved the final version of the report.

Contributions of others

Pollyanna Hardy was listed as a co-investigator on the initial grant application, but moved to Birmingham CTU soon after the study commenced and handed over to Louise Linsell. Louise Linsell and Virginia Chiocchia wrote early drafts of a statistical analysis plan. The statistical analysis then transferred to King's College London and new drafts of the statistical analysis plan were written by Paul Seed.

Publication

Duhig KE, Seed PT, Placzek A, Sparkes J, Hendy E, Gill C, *et al.* Prognostic indicators of severe disease in late preterm pre-eclampsia to guide decision making on timing of delivery: the PEACOCK study. *Pregnancy Hypertens* 2021;**24**:90–5.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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