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]*

[1]Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, UK
[2]National Perinatal Epidemiology Unit Clinical Trials Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[3]Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

*Corresponding author lucy.chappell@kcl.ac.uk

Declared competing interests of authors: Lucy C Chappell's institution received funding from the National Institute for Health Research (NIHR) for this work. Lucy C Chappell is also the chairperson of the NIHR Health Technology Assessment Clinical Evaluation and Trials Committee, a member of the NIHR Efficacy and Mechanism Evaluation Strategic Advisory Group, and a member of the NIHR Journals Library Design group. Andrew Shennan is a member of the NIHR Health Technology Assessment Commissioning Committee.

Published May 2021
DOI: 10.3310/hta25300

Scientific summary

The PEACOCK prospective cohort study

Health Technology Assessment 2021; Vol. 25: No. 30
DOI: 10.3310/hta25300

NIHR Journals Library www.journalslibrary.nihr.ac.uk

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.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 15/59/06. The contractual start date was in April 2016. The draft report began editorial review in October 2019 and was accepted for publication in May 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).