

Development and validation of Prediction models for Risks of complications in Early-onset Pre-eclampsia (PREP): a prospective cohort study

Shakila Thangaratinam,^{1,2,3*} John Allotey,^{1,2,3}
Nadine Marlin,³ Ben W Mol,⁴ Peter Von Dadelszen,⁵
Wessel Ganzevoort,⁶ Joost Akkermans,⁷ Asif Ahmed,⁸
Jane Daniels,⁹ Jon Deeks,¹⁰ Khaled Ismail,¹¹
Ann Marie Barnard,¹² Julie Dodds,^{1,2,3} Sally Kerry,³
Carl Moons,¹³ Richard D Riley¹⁴ and Khalid S Khan^{1,2,3}
on behalf of the PREP study group

¹Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

²Multidisciplinary Evidence Synthesis Hub (MESH), Queen Mary University of London, London, UK

³Pragmatic Clinical Trials Unit, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

⁴School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, SA, Australia

⁵Institute of Cardiovascular and Cell Sciences, University of London, London, UK

⁶Department of Obstetrics and Gynaecology, Academic Medical Centre, Amsterdam, the Netherlands

⁷Department of Obstetrics, Leiden University Medical Centre, Leiden, the Netherlands

⁸School of Life and Health Sciences, Aston University, Birmingham, UK

⁹Birmingham Clinical Trials Unit, University of Birmingham, Birmingham, UK

¹⁰School of Health and Population Sciences, University of Birmingham, Birmingham, UK

¹¹Birmingham Centre for Women's and Children's Health, University of Birmingham, Birmingham, UK

¹²Action on Pre-eclampsia Charity (APEC), Evesham, UK

¹³Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands

¹⁴Research Institute for Primary Care and Health Sciences, Keele University, Keele, UK

*Corresponding author s.thangaratinam@qmul.ac.uk

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Scientific summary

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Scientific summary

Background

Women with early-onset pre-eclampsia (before 34 weeks' gestation) are at high risk of maternal and fetal complications. Early identification of pregnancies at high risk is required to plan transfer of mothers to a tertiary care unit, commence intense monitoring and administer corticosteroids for fetal lung maturity.

Objectives

Primary

To develop prediction models to assess the overall risk of composite maternal outcomes in women with early-onset pre-eclampsia by postnatal discharge and at various time points after the diagnosis of the condition and to validate the performance of these prediction models in external data sets for assessment of transportability.

Secondary

To assess the predictive value of baseline maternal and fetal characteristics and tests for fetal and neonatal complications at birth and by discharge.

Methods

We developed and externally validated two prediction models: a logistic model (PREP-L) to assess the risk of any maternal complication until postnatal discharge and a survival analysis model (PREP-S) to predict the risk of composite maternal outcome at various time points after diagnosis and until 34 weeks' gestation.

Development of the models

Data source

We undertook a prospective observational study [Prediction of Risks in early-onset Pre-eclampsia (PREP)]. Consecutive eligible women with early-onset pre-eclampsia were recruited from 53 secondary and tertiary care maternity units in the UK. Pregnant women presenting with uncomplicated early-onset pre-eclampsia before 34 weeks' gestation were recruited to the study if they satisfied the following inclusion criteria:

- new-onset pre-eclampsia, defined as new-onset hypertension [systolic blood pressure (BP) of ≥ 140 mmHg or diastolic BP of ≥ 90 mmHg on two occasions between 4 and 6 hours apart] after 20 weeks of pregnancy and new-onset proteinuria (2+ or more on a urine dipstick or urine protein-to-creatinine ratio (PCR) of > 30 mg/mmol or 300 mg of protein excretion in 24 hours)
- superimposed pre-eclampsia diagnosed in women with chronic hypertension before 20 weeks' gestation and new-onset proteinuria. In women with significant proteinuria before 20 weeks' gestation, we defined superimposed pre-eclampsia as elevated serum alanine aminotransferase concentration (> 70 units per litre) or worsening hypertension (either two diastolic BP measurements of at least 110 mmHg 4 hours apart or one diastolic BP measurement of at least 110 mmHg if the woman had been treated with an antihypertensive drug) and one of the following: increasing proteinuria, persistent severe headaches or epigastric pain
- haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome
- one episode of eclamptic seizures with no hypertension or proteinuria.

Additionally, we recruited women with suspected pre-eclampsia, with new-onset hypertension and 1+ proteinuria on a urine dipstick. Only those women whose diagnosis of pre-eclampsia was confirmed subsequently with significant proteinuria (PCR > 30 mg/mmol or 24-hour urine protein concentration > 300 mg) were included in the primary models.

Candidate predictors

We evaluated the predictive ability of tests that were routinely performed in women with pre-eclampsia. We identified 22 maternal and 27 fetal predictors a priori through systematic reviews and Delphi surveys for their association with adverse outcomes and their availability in the UK NHS.

We evaluated the following:

- maternal characteristics including age, gestation at diagnosis of pre-eclampsia and number of fetuses in pregnancy
- medical history including pre-existing hypertension, renal disease, diabetes mellitus, autoimmune disease and/or history of pre-eclampsia in previous pregnancies
- symptoms including headache and/or visual disturbance, epigastric pain, nausea and/or vomiting, chest pain and dyspnoea
- bedside examination findings and tests including BP, clonus, tendon reflex, oxygen saturation and urine dipstick
- laboratory investigations including haemoglobin levels, platelet counts, urine PCR serum and concentrations of alanine aminotransaminase (ALT), serum aspartate transaminase (AST), serum uric acid, serum urea and serum creatinine
- treatment measures including administration of antihypertensives and magnesium sulphate.

In addition, we considered estimated fetal weight and liquor volume by ultrasound, uterine artery Doppler, cardiotocography findings and administration of steroids for prediction of fetal outcomes.

Outcomes

The primary outcome, established using Delphi surveys of experts in the field, was a composite maternal outcome which included at least one of the following: eclamptic seizures, Glasgow Coma Scale score of < 13, stroke or reversible ischaemic neurological deficit (RIND), cortical blindness, retinal detachment, posterior reversible encephalopathy, Bell's palsy, hepatic dysfunction, liver haematoma or rupture, need for positive inotrope support, myocardial ischaemia or infarction, at least 50% fraction of inspired oxygen (FiO_2) for > 1 hour, intubation, pulmonary oedema, acute renal insufficiency, dialysis, transfusion of any blood product, abruptio placentae and postpartum haemorrhage and delivery before 34 weeks' gestation.

The secondary outcome was a composite fetal outcome, which included one or more of the following: perinatal or infant mortality, bronchopulmonary dysplasia, necrotising enterocolitis, grade III/IV intraventricular haemorrhage, cystic periventricular leukomalacia, stage 3–5 retinopathy of prematurity, hypoxic–ischaemic encephalopathy, stillbirth and admission to the neonatal intensive care unit.

Sample size

We aimed to evaluate 10 candidate predictors in our multivariable model, with at least 10 events per candidate predictor variable. We assumed that 20% of women with early-onset pre-eclampsia would have adverse maternal outcomes, with the objective to continue recruitment until 100 events were reached. Prior to the analysis, we included preterm delivery before 34 weeks as an outcome and we were able to study over 20 predictors.

Analysis

Candidate predictors that did not show a normal distribution were log-transformed to improve model fit. We dealt with missing data by multiple imputation for missing predictor values, except for oxygen saturation, missing values of which were assumed to be normal. The backward selection procedure was done to identify predictors for inclusion in the models. Non-linear terms were identified using fractional polynomials. PREP-L was used to predict risks of any adverse outcome by discharge, and a flexible parametric model censored at 34 weeks' gestation was used for PREP-S. The apparent model performance was evaluated for its ability to discriminate those with and without the outcome (Harrell's *c*-statistic for survival model and the *c*-statistic for the logistic model) and for calibration defined as the agreement between observed and predicted risks (by visual inspection of calibration plots).

We internally validated the model by using bootstrapping techniques that quantified the model's potential for overfitting, and the amount of optimism in the model's performance. We then calculated the optimism-adjusted *c*-statistic for each model and reduced the predictor effects in the final models by a uniform shrinkage factor to adjust for optimism.

External validation of the model

We assessed the performance of the models to predict adverse maternal outcomes in the two external cohorts from the Pre-eclampsia Integrated Estimate of RiSk for mothers (PIERS) and the Pre-Eclampsia TRIal Amsterdam (PETRA) studies. Owing to the missing predictors in the PETRA and PIERS cohorts, it was necessary to reduce the number of predictor variables in the original PREP models, and the reduced logic model and survival model (rPREP-L and rPREP-S, respectively) were externally validated.

Results

Between December 2011 and April 2014, 1101 women with suspected or confirmed early-onset pre-eclampsia were recruited to the study. Of these, the diagnosis was confirmed and maternal outcomes were known in 946 women. Two-thirds (633/946, 66.9%) experienced at least one adverse maternal outcome by discharge and 584 (61.7%) experienced an adverse outcome before 34 weeks' gestation.

Prediction of adverse maternal outcomes

Apparent performance of the PREP-L model

The model included maternal age, gestational age at diagnosis, summary score for medical history (1 point for pre-existing chronic hypertension, renal disease, diabetes mellitus, autoimmune disease or previous history of pre-eclampsia), systolic BP, urine PCR, platelet count, serum urea concentration, baseline treatment with any antihypertensive drug and administration of magnesium sulphate. The apparent performance of the model showed an optimism-adjusted *c*-statistic of 0.82 [95% confidence interval (CI) 0.80 to 0.84] for composite adverse maternal outcomes.

Apparent performance of the PREP-S model

In addition to the predictors included in the PREP-L model, the PREP-S model included exaggerated tendon reflexes, and concentrations of serum ALT and serum creatinine. The model showed a discrimination (Harrell's *c*-statistic) of 0.75 (95% CI 0.73 to 0.78) for maternal complication after adjusting for optimism.

Performance of the models in external data sets

Data on exaggerated tendon reflexes, serum urea concentration and autoimmune disease in medical history were not available in the external cohorts. Therefore, we used reduced rPREP-L and rPREP-S models without these predictors for validation.

The rPREP-L model showed good discrimination in the PIERS and PETRA data sets, with a c-statistic of 0.81 (95% CI 0.77 to 0.85) and 0.75 (95% CI 0.64 to 0.86), respectively, for maternal complications. The calibration slope was 0.93 (95% CI 0.72 to 1.10) in the PIERS and 0.90 (95% CI 0.48 to 1.32) in the PETRA cohort.

The rPREP-S model showed a discrimination of 0.71 (95% CI 0.67 to 0.75) in the PIERS cohort, and a calibration slope of 0.67 (95% CI 0.56 to 0.79) for adverse maternal outcomes, which suggested large overprediction of the reduced PREP-S model. We did not validate the PREP-S model in the PETRA data set because of a lack of information on the timing of outcomes.

Prediction of fetal complications

Multivariable analysis of predictors showed that an increased gestational age at diagnosis of pre-eclampsia reduced the odds of fetal complications [odds ratio (OR) 0.09, 95% CI 0.01 to 0.61]. A medical history of pre-existing chronic hypertension, diabetes mellitus, autoimmune disease or renal disease or a history of pre-eclampsia in previous pregnancies reduced the odds of composite adverse fetal outcomes (OR 0.65, 95% CI 0.44 to 0.98) for one pre-existing medical condition and (OR 0.43, 95% CI 0.25 to 0.77) for two or more pre-existing medical conditions. The odds of fetal complications were significantly increased in women with raised urine PCR (OR 1.29, 95% CI 1.11 to 1.50) or serum urea concentration (OR 1.72, 95% CI 1.07 to 2.76), in women being treated with antihypertensive drugs (OR 1.56, 95% CI 1.04 to 2.37) or magnesium sulphate (OR 2.40, 95% CI 1.04 to 5.57), in women in whom uterine artery Doppler scanning was abnormal (OR 1.94, 95% CI 1.08 to 3.51) and when expected fetal weight was less than the 10th centile, as determined by ultrasound scanning (OR 2.54, 95% CI 1.46 to 4.40).

Conclusions

The PREP-L model provides accurate predictions of the overall severity of the disease, and will be crucial to plan subsequent care, such as regular follow-ups and admission of high-risk individuals and outpatient management of those at low risk. The reduced PREP-L model has excellent discrimination and calibration, even when transported to external validation data sets outside the UK. We expect the full PREP-L model to have similar, if not better, performance.

The PREP-S model can provide individual risk estimates for adverse maternal outcomes, at various time points after a diagnosis of early-onset pre-eclampsia to plan management. External validation of the reduced PREP-S model in a non-UK population shows similar discrimination, but recalibration may be required to improve the accuracy of predicted risks in populations outside the UK.

Future work recommendations

Further research may examine the impact of implementing the PREP-S and PREP-L models into clinical practice, in terms of their uptake by clinicians and their impact on patient outcomes.

Trial registration

This trial is registered as ISRCTN40384046.

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