Accuracy of clinical characteristics, biochemical and ultrasound markers in the prediction of preeclampsia: an Individual Patient Data (IPD) Meta-analysis

Summary

Despite advances in maternal medicine, pre-eclampsia continues to be a major contributor to maternal, fetal and neonatal mortality and morbidity. Pre-eclampsia is not a single disorder but a syndrome. The early onset disease is more severe, and is considered to have a different pathophysiology than the late onset disease. It is unlikely that one single model will accurately predict both early and late onset disease. A HTA brief called for synthesis of available evidence to identify the most accurate tests, separately and in combination for the prediction of pre-eclampsia, including the early onset type. We have identified over 50 published evidence synthesis projects on this topic, and they are unable to provide clear conclusions on the performance of the tests due to the limitations in the published data.

The technique of combining the data from individual patients in studies to generate estimates of benefit is known as an Individual Patient Data (IPD) Meta-analysis. An IPD meta-analysis will allow us to assess the differential accuracy of the tests in various subgroups according to the risk status. It will provide us with sufficient sample size to develop and validate a multivariable prediction model, for the clinically important outcome of early onset pre-eclampsia. By taking into account the clustering within studies, the developed model will avoid the model performance deterioration encountered in aggregate meta-analysis, when the individual's baseline risk is different from the average estimated during model development.

We will obtain the individual data of all participants in relevant studies, through our International Prediction of Pre-eclampsia IPD Collaborative (IPPIC) Network. The Network comprises of researchers involved in studies on this topic and we have the support of more than 70 researchers, with access to data from over 400,000 women.

The IPPIC Network is strengthened by support from the Global Obstetrics Research Network (GONet), a group of international investigators that perform clinical trials and observational studies in maternal fetal medicine and obstetrics (www.globalobstetricsnetwork.org). All collaborators will be involved in providing input into the project and will be co-authors in any publication arising from the project.

Aims and objectives

We will develop separate prediction models for a. early (<34 weeks' gestation) and b. any pre-eclampsia.

Primary

1. To update our systematic review on prediction models for pre-eclampsia and externally validate the most accurate and robust models on IPD.
2. To estimate the prognostic value of individual clinical, biochemical and ultrasound markers in the prediction of pre-eclampsia analysis
3. To use IPD from multiple studies to develop and externally validate (using internal-external cross-validation) multivariable prediction models for a. early (<34 weeks' gestation) and b. any pre-eclampsia based on (i) clinical characteristics only, and in combination with (ii) biochemical markers, (iii) ultrasound markers (iv) both ultrasound and biochemical markers
4. To assess the differential performance of the predictors in subgroups based on population characteristics (unselected vs selected), timing of test (first trimester vs any trimester) in predicting pre-eclampsia, and treatment strategies

Secondary

5. To evaluate the predictive accuracy of the individual tests and models for maternal and fetal complications of pre-eclampsia

To study the added role of novel biomarkers on the accuracy of the developed model and to validate the model

Methods

We will evaluate the performance of the identified (and relevant) published models based on our systematic review.

External validation: The validation cohort will be from our large IPD database of the IPPIC Collaborative Network. For each external validation, we will quantify the predictive performance of the existing models, and assess the extent to which they need to be improved or tailored for the target population to assess the risk of early, late and any preeclampsia. For example, recalibration techniques will be considered. This includes intercept or baseline hazard (depending on type of prediction model) and adjustment of individual predictor weights (regression coefficients). Using these data, the probability of early, late and any pre-eclampsia for each individual patient in our validation cohort will be calculated. We expect the sample sizes to be adequate; as for such validation often only one parameter (the linear predictor of the original model) is fitted, with 100 events needed for validating dichotomous outcomes. Missing data will be multiple imputed and conform to

current guidelines. The performance of the models will be assessed using discrimination and calibration statistics.

We will identify the relevant population from the IPPIC- IPD studies recruited, develop (or improve) and validate the models using the internal-external cross-validation (IECV) approach. A set of candidate predictors will be identified a priori, based on prior evidence and clinical judgement. A suitable multivariable modelling framework will be chosen, for example logistic regression for binary outcomes or a survival model for time-to-event outcomes, such as Cox regression or preferably a (flexible) parametric model.

Dissemination

Once completed the findings will be disseminated to healthcare policy makers through the HTA report, national guidelines, publications in peer reviewed journals and presentations in national and international conferences. We anticipate the findings of this project to provide specific national and international recommendations on early identification of women at risk of pre-eclampsia. The Chief Investigator will work closely with the collaborative partners and co-ordinate dissemination of data from this trial. All publications using data from this trial to undertake original analyses will be submitted to the Project Steering Committee (PSC) for review before release. To safeguard the scientific integrity of the trial, data will not be presented in public before the main results are published without the prior consent of the PSC.