2016

The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: a systematic review

Z Al-Rubaie

L Askie

J Ray

H Hudson

S Lord
University of Notre Dame Australia, sally.lord@nd.edu.au

This article was originally published as:
Al-Rubaie, Z., Askie, L., Ray, J., Hudson, H., & Lord, S. (2016). The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: a systematic review. *BJOG: an International Journal of Obstetrics and Gynaecology, Early View (Online First)*.

Original article available here:
http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.14029/abstract

The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: a systematic review

Ziad TA Al-Rubaie, MBChB MPH
ziad.alrubaie1@my.nd.edu.au
School of Medicine, The University of Notre Dame Australia, Sydney, NSW, Australia
Postal address: School of Medicine, The University of Notre Dame Australia
160 Oxford Street, Darlinghurst NSW 2010
Tel: +61 2 8204 4212

Lisa M Askie, MPH PhD
lisa.askie@ctc.usyd.edu.au
NHMRC Clinical Trial Centre, University of Sydney, Sydney, NSW, Australia
Postal address: NHMRC Clinical Trials Centre, Sydney Medical School, University of Sydney
Level 6 Medical Foundation Building, 92 Parramatta Road, Locked Bag 77, Camperdown NSW 2050 Australia
T +61 2 9562 5000

Joel G Ray, MD FRCPC
rayj@smh.ca
Departments of Medicine, Health Policy Management and Evaluation, and Obstetrics and Gynecology, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
Postal address: Department of Medicine, St. Michael's Hospital
30 Bond Street, Toronto, Ontario, M5B 1W8
T (416) 864-6060, Ext 77442

H Malcolm Hudson, BSc (hons) PhD
malcolm.hudson@ctc.usyd.edu.au
NHMRC Clinical Trial Centre, University of Sydney, Sydney, NSW, Australia
Department of Statistics, Macquarie University, Sydney, NSW, Australia
Postal address: NHMRC Clinical Trials Centre, Sydney Medical School, University of Sydney
Level 6 Medical Foundation Building, 92 Parramatta Road, Camperdown NSW 2050 Australia
T +61 2 9562 5000

Sarah J Lord, MBBS MS (Epi)
sally.lord@nd.edu.au
School of Medicine, The University of Notre Dame Australia, Sydney, NSW, Australia
NHMRC Clinical Trial Centre, University of Sydney, Sydney, NSW, Australia
Postal address: School of Medicine, The University of Notre Dame Australia
160 Oxford Street, Darlinghurst NSW 2010
Tel: +61 2 8204 4212

Corresponding author contact details:
Ziad TA Al-Rubaie
Postal address: School of Medicine, The University of Notre Dame Australia
160 Oxford Street, Darlinghurst NSW 2010
Tel: +61 2 8204 4212, E-mail: ziad.alrubaie1@my.nd.edu.au

Word count: Total: 3806/4000, Abstract: 247/250, Introduction: 393/400, Discussion: 1200/1200

ABSTRACT

Background

Risk prediction models may be valuable to identify women at risk of pre-eclampsia to guide aspirin prophylaxis in early pregnancy.

Objective

To assess the performance of 'simple' risk models for pre-eclampsia that use routinely collected maternal characteristics; compare to 'specialised' models that include specialised tests; and to guideline recommended decision rules.

Search Strategy

MEDLINE, Embase and PubMed were searched to June 2014.

Selection Criteria

We included studies that developed or validated pre-eclampsia risk models using maternal characteristics with or without specialised tests and reported model performance.

Data collection and analysis

We extracted data on study characteristics; model predictors, validation and performance including area under the curve (AUC), sensitivity and specificity.

Main Results

We identified 29 studies that developed 70 models including 22 simple models. Studies included 151-9149 women with pre-eclampsia prevalence 1.2-9.5%. No single predictor was included in all models. Four simple models were externally validated, with a model using parity, pre-eclampsia history, race, chronic hypertension and conception method to predict early-onset pre-eclampsia achieving the highest AUC (0.76, 95% CI 0.74-0.77). Nine studies comparing simple versus specialized models in the same population reported AUC favouring specialized models. A simple model achieved fewer false positives than a guideline recommended risk factor list, but sensitivity to classify risk for aspirin prophylaxis was not assessed.

Conclusion

Validated simple pre-eclampsia risk models demonstrate good risk discrimination that can be improved

with specialised tests. Further research is needed to determine their clinical value to guide aspirin prophylaxis compared to decision rules.

Key words

Aspirin, pre-eclampsia, risk factors, risk prediction models, systematic review, validation

Running title

Risk prediction models for pre-eclampsia

Tweetable abstract

Pre-eclampsia risk models using maternal factors show good risk discrimination to guide aspirin prophylaxis

Introduction

Pre-eclampsia is a major international maternal health problem, affecting 1-8% of pregnancies worldwide with serious adverse maternal and fetal consequences (1-4). Despite advances in obstetric care, it still represents a leading cause of maternal death in both developed and developing countries (1,5). The United Nations Millennium Development Goals recognise that more effort needs to be spent toward decreasing maternal mortality, through the prevention of pregnancy complications including pre-eclampsia (6).

Randomised controlled trials demonstrate that antiplatelet therapy such as acetylsalicylic acid (aspirin) is effective for pre-eclampsia prevention. A meta-analysis using individual patient-level data reported a 10% relative risk reduction in pre-eclampsia (7), and subsequent meta-analyses estimate larger gains when aspirin is commenced prior to 17 weeks' gestation (8,9). Clinical practice guidelines recommend antenatal assessment of risk factors for pre-eclampsia, but provide little guidance about their use to recommend aspirin prophylaxis.

The National Institute for Health and Care Excellence (NICE) recommends a list of maternal risk factors that can be used as a clinical prediction decision rule to identify women at high risk for pre-eclampsia in whom aspirin should be started at 12 weeks' gestation (10). Clinical risk prediction models have also been developed to combine risk factors and quantify a woman's risk of pre-eclampsia. These include risk models based on readily available maternal characteristics ('simple models'); and more complex models that include specialised tests ('specialised models'), such as developed by the Fetal Medicine Foundation (https://fetalmedicine.org/calculator/preeclampsia). Most of these tests, such as uterine artery Doppler, are not routinely performed or readily available in general antenatal settings.

Simple models and prediction rules have the advantage of being widely available to guide aspirin prophylaxis in non-specialised settings; including low-income countries where pre-eclampsia outcomes are poorest (3). However, the predictive performance of these tools has not been adequately assessed to inform clinical guidelines. Furthermore, in settings where clinicians may have access to specialised

tests, given the costs of these tests, a comparison of the performance of simple versus specialised models is needed to assess the added advantage.

The objective of this study is to identify and assess the characteristics and performance of simple risk models that can be applied in the first 16 weeks of pregnancy to identify women at increased risk of pre-eclampsia who may benefit from antiplatelet prophylaxis; and compare their performance to models that include specialised tests; and to clinical decision rules recommended by guidelines.

METHODS

Eligibility criteria

We included all published studies that developed or validated a multivariable risk prediction tool for pre-eclampsia that used maternal characteristics with or without specialised tests that can be obtained in early pregnancy – defined here as before 17 weeks' gestation. We included prospective or retrospective cohort studies, case-control studies, trial-based analyses, and systematic reviews. We defined pre-eclampsia as the presence of hypertension with new onset proteinuria at or beyond 20 weeks' gestation. We included multivariable risk prediction models, defined as statistical models that include two or more predictor variables using logistic regression or other statistical methods; and clinical prediction rules or algorithms based on the combination of two or more risk factors that were not developed using statistical methods.

We included all studies conducted in women who were pregnant or planning pregnancy, including nulliparous and multiparous women, singleton and multiple pregnancies. We included studies that reported on early-onset pre-eclampsia (onset or required delivery <34 weeks) or late-onset pre-eclampsia (onset or delivery ≥34 weeks). The primary outcomes used to measure model discrimination were receiver operating characteristic (ROC), area under the curve (AUC), and sensitivity and specificity. We excluded studies that: did not report the model algorithm for pre-eclampsia risk calculation; or did

not report on risk model performance by presenting AUC, or sensitivity and specificity. This systematic review protocol was not registered on a public database such as PROSPERO.

Search strategy

We searched MEDLINE , PubMed, Embase from their inception to June 2014 using a combination of MeSH terms and keywords related to pre-eclampsia and risk prediction models including: Pre-Eclampsia, Hypertension, Pregnancy-Induced, Risk Factors, Risk, Risk Assessment, risk*, predict* rule*, models, statistical, Nomograms, Logistic Models, logistic*, regress*, combinat*, multivar*, algorithm*, Area Under Curve*, ROC Curve* and Receiver Operating Characteristic* (Appendix S1). We limited our search to studies published in English. We also checked the reference lists of relevant articles and citations of included studies.

All articles identified were screened for eligibility using pre-specified criteria. One reviewer (ZA) conducted the preliminary screening of abstracts to exclude ineligible articles based on title and abstract. Two reviewers (ZA, SL) independently checked potentially eligible articles to identify studies requiring retrieval for further screening. Disagreements were resolved with discussion.

Data extraction and assessment of risk of bias

One reviewer (ZA) extracted study and population characteristics, model predictors, risk of bias, and model performance measures of discrimination, calibration, classification and internal and external validation from each eligible study into pre-defined data extraction tables. A second reviewer (SL) checked the accuracy of data entered from each study. If multiple models were developed within the same study, the best performing model was selected for analysis. If multiple studies developed models using the same population, data were extracted from each study but the study reporting the best performing model was selected for the primary analysis. If studies compared the performance of the study model with other published models or clinical decision rules, measures of discrimination,

classification and calibration were extracted for each model or rule. For studies comparing model performance with the NICE decision rule, unless otherwise stated by the study authors, we defined the latter as follows: the presence of one or more high risk factors (hypertensive disease in previous pregnancy, chronic kidney disease, autoimmune disease, diabetes and chronic hypertension) or two or more moderate risk factors (1st pregnancy, age ≥40 years, pregnancy interval of >10 years, BMI ≥35 kg/m^2 at first visit, family history of pre-eclampsia and multiple pregnancy) (10).

We assessed the risk of bias for each primary model development study using criteria adapted from Hayden et al. (11). We classified models as 'low risk of bias' for studies that used prospective data collection and pre-defined predictors, reported missing data, had <5% exclusions due to missing predictors or outcome, included ≥10 events per variable, and performed external validation. Studies not meeting these criteria were assessed as 'high risk of bias' or 'unclear' if information for assessment of low risk was not reported.

Data synthesis

Discrimination performance for each model was summarized by plotting the AUC and 95% confidence interval (CI) on a forest plot, categorized by outcome (any pre-eclampsia onset, early-onset pre-eclampsia, late-onset pre-eclampsia) and by the type of model (simple, specialised). Model sensitivity and specificity were not plotted because studies reported sensitivity estimates at different fixed specificities or did not report cut-point for classification of high risk. Differences in performance (AUC, sensitivity and specificity) between simple versus specialised models and with clinical decision rules was described as reported from studies that performed direct comparisons in the same population; and, if provided, by calculating the percentage of patients correctly reclassified as high or low risk to assess clinical value. Where available, we focused interpretation on data from external validation studies.

RESULTS

Study selection

The search strategy identified 3657 articles, of which 32 articles met inclusion criteria (Figure S1). No systematic reviews were identified that addressed our research questions

Study characteristics

Twenty nine eligible model development studies were identified. These included 15 prospective cohort studies, six case-control studies, five nested case-control studies and three retrospective cohort studies. Study characteristics and types of models are summarized in Table S1. Overall, these 29 studies reported on 70 models: 17 models to predict pre-eclampsia, 31 to predict early-onset pre-eclampsia, and 22 to predict late-onset pre-eclampsia. Of the 70 models; 22 were simple models; and 48 were specialised models. Another three studies reported on the external validation of 10 of the models developed from the same United Kingdom (UK) study population. Two of the three model validation studies used a prospective cohort design (42,43) and one used a retrospective cohort design (41).

The 29 model development studies were conducted in 14 different populations. A total of 27,958 pregnant women were assessed in model development studies, ranging from 151 to 9149 women per study.

Nine study populations included both nulliparous and multiparous women; one study was conducted in nulliparous women only (21); one study was restricted to multiparous women with a past history of pre-eclampsia (20); and three studies did not report parity status. Ten study populations excluded women with multiple pregnancies and four studies did not report selection criteria. Pre-eclampsia prevalence ranged 1.2-9.5%.

Thirteen study populations were drawn from high-income countries and one study was conducted in a middle-income country (14).

All studies defined pre-eclampsia as the onset of hypertension and proteinuria >20 weeks' gestation. Of 19 studies assessing early-onset pre-eclampsia, 16 defined it as requiring delivery <34 weeks, and three studies as the onset of pre-eclampsia <34 weeks.

No single predictor was included in every model. Maternal characteristics included in at least half the 14 best-performing models from each study population were parity, race, past history of hypertension, BMI and blood pressure (Table 1). Serum pregnancy associated protein-A (PAPP-A) was included in eight of these studies; and uterine artery Doppler was included in seven studies (Table 1). Predictors included in simple and specialised models from all studies are listed in Table S2.

Assessment of risk of bias

Of the 14 model development studies, two studies were classified as having a low risk of bias, both of which reported simple models (21,24). Twelve studies were classified as high risk of bias (Table S3). Common important sources of bias were lack of: external validation (13 studies); internal validation (11 studies); reporting on model calibration (eight studies); accounting for overfitting (11 studies) (Figure S2). Of the three model development studies that performed internal validation, one used boot strapping technique (20), one used split sample approach (12) and one used a 10-fold cross validation method (21), with only the latter study reporting internal validation for the development of a simple model (Table S4).

Data synthesis

Model performance varied across studies with AUC ranging from 0.64 to 0.96. At a descriptive level, model performance also varied for different classifications of pre-eclampsia with more modest performance observed for prediction of all pre-eclampsia compared to early-onset pre-eclampsia. Sensitivity for detection of pre-eclampsia ranged between 29% and 100% and specificity from 26% to 96% (Table S4).

Simple models

The performance of simple models to predict women who have pre-eclampsia versus no pre-eclampsia ranged from AUC 0.67-0.90 (Figure 1). Of these, four models were externally validated (Table 2). None of these validation studies assessed model performance to predict any pre-eclampsia. Park et al. (41) validated the two Poon et al. (29) simple models for early-onset pre-eclampsia and late-onset pre-eclampsia and reported good performance for prediction of early-onset pre-eclampsia (AUC 0.76; 95% CI 0.74-0.77) but poorer performance for prediction of late-onset pre-eclampsia in the validation population (AUC 0.68; 95% CI 0.66-0.69) compared to the model development population (AUC for early-onset pre-eclampsia 0.79; 95% CI 0.72-0.87; late-onset pre-eclampsia 0.80; 0.76-0.83). Herraiz et al. (43) validated the Plascencia et al. (39) simple models for early-onset pre-eclampsia and late-onset pre-eclampsia and reported good performance for the early-onset pre-eclampsia model (AUC 0.74; 95% CI 0.60-0.89) compared to the development study (0.78; 95% CI 0.77 to 0.80); and poor performance for the late-onset pre-eclampsia model (0.65; 95% CI 0.49-0.80) compared to the development study (0.80; 95% CI 0.79-0.81). Farina et al. (42) validated the Plascencia et al. (39) simple model for late-onset pre-eclampsia and reported poorer performance (AUC 0.72; 95% CI 0.62-0.82) than the development study (0.80; 95% CI 0.79-0.81).

Predictors included in both externally validated simple models for early-onset pre-eclampsia included parity, past history of pre-eclampsia and race (29,39). The best performing externally validated simple model for early-onset pre-eclampsia also included history of chronic hypertension and conception method (29,41). The sensitivity and specificity of these models to detect pre-eclampsia in women classified as low or high risk based on a defined cut-off risk level was not reported, but receiver operating characteristic curves for both models indicate a sensitivity of more than 70% to predict pre-eclampsia could be achieved at specificity 70% (29,39).

Comparison with specialised models

The performance of specialised models to predict pre-eclampsia ranged from AUC 0.65-0.96 (Figure 1, Table S4). Of these, six specialised models developed from the same UK population were externally validated (Table S4). None of these validation studies assessed model performance to predict any pre-eclampsia. For predicting early-onset pre-eclampsia, two validation studies reported good performance for two different models (AUC 0.78 to 0.93). Of these, the best performing validated model achieved AUC 0.93, sensitivity 92% at fixed specificity 90% (41). Predictors in this model were: parity, past history of pre-eclampsia, race, chronic hypertension, conception method, mean arterial pressure (MAP), uterine artery-pulsatility index (UtA-PI) and PAPP-A (24).

For predicting late-onset pre-eclampsia, two validation studies reported good performance for two models (AUC 0.75 to 0.93); and poorer performance for two other models (AUC 0.64 to 0.70) (Table S4). The best performing validated model achieved AUC 0.93, sensitivity 85% at fixed specificity 90% (42). Predictors in this model were: parity, past history of pre-eclampsia, race, maternal age, family history of pre-eclampsia , BMI, MAP and UtA-PI.

Seven model development studies and two validation studies directly compared simple versus specialised models and reported model equations and corresponding AUCs with 95% CI for each model. At a descriptive level, 16 of the 17 model comparisons reported a higher AUC with the addition of specialised tests (Figure 2). The size of the difference in AUC varied widely between each of these model comparisons, ranging from -0.005 to 0.24 in favour of specialised models. Improvements in discrimination were more modest for models predicting any pre-eclampsia and late-onset pre-eclampsia than for models predicting early-onset pre-eclampsia. Improvements were also more modest for model validation studies than model development studies, with one model validation study reporting no improvement in discrimination between a specialised versus simple model for predicting late-onset pre-eclampsia .

Ten model development studies and two validation studies directly compared specialised versus simple models and reported sensitivity and specificity. The median difference in sensitivity was 18% (0-56%) in favour of specialised models; with a fixed specificity of 90% or 95% used for both simple and specialised models in 11 studies and improved specificity of 8% to 10% in one study (24). Inspection of ROC curves comparing models also showed this difference varies at different cut-points. For example, in the Poon et al. (24) study, model sensitivity to detect early-onset pre-eclampsia at a fixed 10% fixed false positive rate (FPR) was 45% higher using the specialised model than the corresponding simple model. However, by fixing the FPR at 30%, the gap in sensitivity between the two models narrowed to 25%.

Comparison with the NICE clinical decision rule

One study compared the performance of a simple risk model with the NICE decision rule to identify women at elevated risk of pre-eclampsia warranting aspirin prophylaxis (Table 2). Poon et al. (29) compared the performance of a simple model that included parity, past history of pre-eclampsia, race, history of chronic hypertension and conception method versus the NICE rule and reported model sensitivity of 37% (95% CI 13-50%) for detection of early-onset pre-eclampsia at a FPR of 5% (corresponding to a specificity of 95%) compared to a sensitivity of 89% (75-97%) and FPR of 64% (corresponding to a specificity of 36%) using the NICE rule in the same study population. Reading from the ROC curve, the sensitivity of the study model was approximately 95% when fixed at the same FPR as the NICE rule; and 70% when the FPR was fixed at 30%.

DISCUSSION

Main findings

This systematic review identified 22 risk models that combine simple maternal characteristics to predict risk of pre-eclampsia. Overall, there was a wide variation in risk predictors used by models developed in different populations with no single risk factor included in every model. The performance of simple

models to discriminate between high versus low risk women also ranged widely from poor to good (AUC 0.67-0.90).

Two simple models demonstrated good discrimination to predict early-onset pre-eclampsia in validation cohorts (AUC 0.74-0.76) (41,43). Predictors included in both these models were parity, past history of pre-eclampsia and race (29,39); with one model also including chronic hypertension and conception method (29). Simple models performed more poorly for prediction of late-onset pre-eclampsia in validation cohorts. In contrast, two 'specialised' models demonstrated excellent discrimination for predicting early-onset and late-onset pre-eclampsia on external validation (AUC 0.93) (41,42).

Our finding that specialised models provided a median gain in sensitivity of 18% compared to simple models can be interpreted as an additional 18 per 100 women who subsequently have a diagnosis of pre-eclampsia being correctly identified as high risk and recommended aspirin prophylaxis. Inspection of ROC curves for models with and without specialised tests such as shown in Poon et al. (24), indicates this sensitivity gain may be more modest if a false positive rate of >10% is deemed acceptable to guide aspirin decisions.

Data to compare performance of simple models versus clinical decision rules, such the current NICE guidelines were limited. Poon et al's validation of the NICE rule demonstrates it can provide high sensitivity, but a simple risk model that applies weights to each individual risk factor can provide fewer false positive risk classifications (29).

This review identifies important methodological limitations affecting the validity and applicability of model performance estimates to routine antenatal care. Model calibration and internal validation were rarely performed, and only study performed bootstrapping - the recommended method for internal validation (44). External validation was only performed for models developed in one UK study population. These limitations have previously been described in a systematic review of the quality of 38 risk models for pre-eclampsia (45).

Limitations for applicability include that all models were developed and validated for women with a singleton pregnancy. Given that a twin pregnancy may not be determined at the first antenatal visit and has a 2-4 times higher risk of pre-eclampsia (46), model performance may be lower in routine antenatal settings. Secondly, most published models were developed to predict either early-onset or late-onset pre-eclampsia, with less promising findings and no validation studies for simple models to predict a woman's risk of any (early or late) pre-eclampsia which would provide the most clinically relevant measure of its performance to guide aspirin decisions. Furthermore, no models were developed or validated in low-income populations.

Strengths and limitations

The major strength of this study is that it provides a timely systematic review of the performance of simple risk models to predict pre-eclampsia before 17 weeks pregnancy. After completing our review we reran the search strategy from June 2014 to 16 November 2015 to check for new studies that may alter our results. We identified two new studies reporting three simple models that met our inclusion criteria (47,48). Of these, one study compared model performance with a specialised model and reported similar improvements to our findings (47). No external validation of these new models was identified. One additional study externally validated a simple model that used different predictors to the validated models presented here and reported poor performance (model algorithm not reported) (49) .

The main limitation is that studies did not report model sensitivity and specificity to identify women above the pre-eclampsia risk level where aspirin is recommended to allow an assessment of clinical value. The majority of studies did not report on model calibration and reported model sensitivity at a fixed specificity of 90% or 95% (corresponding to a 5% or 10% false positive rate).

Interpretation

For clinicians working in general antenatal care settings, our finding that simple risk models have been validated to demonstrate good discrimination to predict pre-eclampsia suggest that they may have a

role in guiding aspirin prophylaxis. For clinicians with access to specialised tests, our findings that risk prediction models including these tests provide improved discrimination support their use. However, given the additional costs of these tests, their clinical and cost-effectiveness to guide aspirin use still needs to be determined to recommend their use.

We identified limited evidence to assess the difference in sensitivity using a simple model to guide aspirin use versus the NICE rule. However, a study published after our search was completed reported a simple model correctly predicted 40% of pre-eclampsia cases compared to 35% using the NICE decision rule supporting the potential role for simple models (50).

Our findings also have important implications for researchers. Given the wide range of model predictors identified and methodological limitations of existing studies, future validation studies should aim to identify the optimal combination of simple maternal risk factors. Certainly, those factors need to be readily determined in the first trimester of pregnancy, based on a woman's past medical and obstetric history, or evident at the early prenatal visit.

To assess the clinical value of any proposed risk models to inform aspirin prophylaxis, performance should be validated and compared with simple risk factor rules by examining how well it classifies women as being above the risk threshold where aspirin can be recommended. Current USPSTF guidelines recommend aspirin for women at ≥8% risk based on the risk profile of populations included in trials demonstrating its effectiveness (51). A recent analysis also suggests that, given its efficacy, safety and low cost, aspirin can be recommended for women with at least a 6-10% probability of pre-eclampsia (52). At this risk level, women with single high risk factor such as a past history of pre-eclampsia can be recommended for aspirin without requiring additional assessment. Thus, a critical research question is how much more accuracy is provided by simple models to classify risk levels for women with moderate risk factors (eg. nulliparity, older age, obesity) than approaches such as the NICE rule that classify all women with more than one of these factors as high risk. For these women, a simple risk model that can quantify level of risk may be considered very helpful to inform aspirin use. Additionally, women

approaching the NICE decision rule thresholds, eg. age 35-39 years or BMI 30-34 kg/m^2 may reasonably ask their risk level in order to consider aspirin prophylaxis. The recent publication of the TRIPOD reporting guidelines could help to guide the development and reporting of models in these populations (53).

Conclusion

Risk models using simple maternal characteristics demonstrate good discrimination to identify women at elevated risk of pre-eclampsia with fewer false positives than the NICE decision rule. Their performance is improved with the addition of tests. However their clinical value to guide aspirin prophylaxis compared to specialised models or clinical decision rules still needs to be determined. Given specialised tests are not feasible in many antenatal settings, further research should focus on developing and validating the optimal simple risk tool for use in a wide range of settings including low-income countries where pre-eclampsia outcomes are poorest.

Acknowledgements

We thank Ms Morgann Quilty, medical librarian, the University of Notre Dame Australia for her help with the literature search and reference manager software.

Disclosure of interests

None declared.

Contribution to authorship

ZA, SL, LA, JR and MH contributed to development of research question and review design. ZA led literature search, data extraction, analysis, interpretation of results and writing. SL contributed to literature search and data extraction. SL LA MH and JR contributed to data analysis, interpretation of results and writing.

Details of ethics approval

Not required.

Funding

ZA is supported by an Australian Postgraduate Award and an Australian Collaborative Research Network PhD Scholarship.

Supporting Information: Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy.

Table S1. Characteristics of model development studies, *n* = 29 studies.

Table S2. List of predictors of pre-eclampsia risk prediction models.

Table S3. Risk of bias assessment, *n* = 14 model development studies.

Table S4. Model performance and validation, *n* = 29 studies

Figure S1. Quorum Flowchart.

Figure S2. Risk of bias assessment of studies reporting risk prediction models for pre-eclampsia, *n* = 14 studies.

REFERENCES

1. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066-74.
2. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. American journal of obstetrics and gynecology. 2000;183(1):S1-s22.

3. Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP. Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis. PloS one. 2014;9(3):e91198.
4. Roberts CL, Ford JB, Algert CS, Antonsen S, Chalmers J, Cnattingius S, et al. Population-based trends in pregnancy hypertension and pre-eclampsia: an international comparative study. BMJ open. 2011;1(1):e000101.
5. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. The Lancet Global health. 2014;2(6):e323-33.
6. The Millennium Development Goals: Report 2015. New York, United Nations, 2015.
7. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet. 2007;369(9575):1791-8.
8. Roberge S, Villa P, Nicolaides K, Giguere Y, Vainio M, Bakthi A, et al. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. Fetal diagnosis and therapy. 2012;31(3):141-6.
9. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. Obstetrics and gynecology. 2010;116(2 Pt 1):402-14.
10. National Institute for Health and Care Excellence. NICE quality standard 35. Hypertension in pregnancy. NICE, 2013.
11. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. Annals of internal medicine. 2013;158(4):280-6.
12. Goetzinger KR, Tuuli MG, Cahill AG, Macones GA, Odibo AO. Development and Validation of a Risk Factor Scoring System for First-Trimester Prediction of Preeclampsia. American Journal of Perinatology. 2014 31(12):1049-56.
13. Caradeux J, Serra R, Nien JK, Perez-Sepulveda A, Schepeler M, Guerra F, et al. First trimester prediction of early onset preeclampsia using demographic, clinical, and sonographic data: a cohort study. Prenatal diagnosis. 2013;33(8):732-6.
14. Direkvand-Moghadam A, Khosravi A, Sayehmiri K. Predictive factors for preeclampsia in pregnant women: A Receiver Operation Character approach. Archives of Medical Science. 2013;9(4):684-9.
15. Keikkala E, Vuorela P, Laivuori H, Romppanen J, Heinonen S, Stenman UH. First trimester hyperglycosylated human chorionic gonadotrophin in serum - A marker of early-onset preeclampsia. Placenta. 2013;34(11):1059-65.
16. Kuc S, Koster MP, Franx A, Schielen PC, Visser GH. Maternal characteristics, mean arterial pressure and serum markers in early prediction of preeclampsia. PloS one. 2013;8(5):e63546.
17. Parra-Cordero M, Rodrigo R, Barja P, Bosco C, Rencoret G, Sepulveda-Martinez A, et al. Prediction of early and late pre-eclampsia from maternal characteristics, uterine artery Doppler and markers of vasculogenesis during first trimester of pregnancy. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2013;41(5):538-44.
18. Scazzocchio E, Figueras F, Crispi F, Meler E, Masoller N, Mula R, et al. Performance of a first-trimester screening of preeclampsia in a routine care low-risk setting. American journal of obstetrics and gynecology. 2013;208(3):203.e1-.e10.
19. Di Lorenzo G, Ceccarello M, Cecotti V, Ronfani L, Monasta L, Vecchi Brumatti L, et al. First trimester maternal serum PlGF, free beta-hCG, PAPP-A, PP-13, uterine artery Doppler and maternal history for the prediction of preeclampsia. Placenta. 2012;33(6):495-501.
20. Kuijk SMJV, Nijdam ME, Janssen KJM, Sep SJS, Peeters LL, Delahaije DHJ, et al. A model for preconceptional prediction of recurrent early-onset preeclampsia: Derivation and internal validation. Reproductive Sciences. 2011;18(11):1154-9.

21. North RA, McCowan LME, Dekker GA, Poston L, Chan EHY, Stewart AW, et al. Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. BMJ (Clinical Research Ed). 2011;342:d1875-d.
22. Odibo AO, Zhong Y, Goetzinger KR, Odibo L, Bick JL, Bower CR, et al. First-trimester placental protein 13, PAPP-A, uterine artery Doppler and maternal characteristics in the prediction of pre-eclampsia. Placenta. 2011;32(8):598-602.
23. Goetzinger KR, Singla A, Gerkowicz S, Dicke JM, Gray DL, Odibo AO. Predicting the risk of pre-eclampsia between 11 and 13 weeks' gestation by combining maternal characteristics and serum analytes, PAPP-A and free beta-hCG. Prenatal diagnosis. 2010;30(12-13):1138-42.
24. Poon LCY, Stratieva V, Piras S, Piri S, Nicolaides KH. Hypertensive disorders in pregnancy: Combined screening by uterine artery Doppler, blood pressure and serum PAPP-A at 11-13 weeks. Prenatal diagnosis. 2010b;30(3):216-23.
25. Emonts P, Seaksan S, Seidel L, Thoumsin H, Gaspard U, Albert A, et al. Prediction of maternal predisposition to preeclampsia. Hypertension in pregnancy : official journal of the International Society for the Study of Hypertension in Pregnancy. 2008;27(3):237-45.
26. Poon LCY, Kametas NA, Valencia C, Chelemen T, Nicolaides KH. Hypertensive disorders in pregnancy: screening by systolic diastolic and mean arterial pressure at 11-13 weeks. Hypertension In Pregnancy: Official Journal Of The International Society For The Study Of Hypertension In Pregnancy. 2011;30(1):93-107.
27. Foidart JM, Munaut C, Chantraine F, Akolekar R, Nicolaides KH. Maternal plasma soluble endoglin at 11-13 weeks' gestation in pre-eclampsia. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2010;35(6):680-7.
28. Poon LC, Akolekar R, Lachmann R, Beta J, Nicolaides KH. Hypertensive disorders in pregnancy: screening by biophysical and biochemical markers at 11-13 weeks. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2010c;35(6):662-70.
29. Poon LC, Kametas NA, Chelemen T, Leal A, Nicolaides KH. Maternal risk factors for hypertensive disorders in pregnancy: a multivariate approach. Journal of human hypertension. 2010a;24(2):104-10.
30. Leal AM, Poon LC, Frisova V, Veduta A, Nicolaides KH. First-trimester maternal serum tumor necrosis factor receptor-1 and pre-eclampsia. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2009;33(2):135-41.
31. Poon LCY, Karagiannis G, Leal A, Romero XC, Nicolaides KH. Hypertensive disorders in pregnancy: screening by uterine artery Doppler imaging and blood pressure at 11-13 weeks. Ultrasound In Obstetrics & Gynecology: The Official Journal Of The International Society Of Ultrasound In Obstetrics And Gynecology. 2009e;34(5):497-502.
32. Poon LCY, Staboulidou I, Maiz N, Plasencia W, Nicolaides KH. Hypertensive disorders in pregnancy: screening by uterine artery Doppler at 11-13 weeks. Ultrasound In Obstetrics & Gynecology: The Official Journal Of The International Society Of Ultrasound In Obstetrics And Gynecology. 2009d;34(2):142-8.
33. Poon LCY, Nekrasova E, Anastassopoulos P, Livanos P, Nicolaides KH. First-trimester maternal serum matrix metalloproteinase-9 (MMP-9) and adverse pregnancy outcome. Prenatal diagnosis. 2009c;29(6):553-9.
34. Poon LCY, Kametas NA, Maiz N, Akolekar R, Nicolaides KH. First-trimester prediction of hypertensive disorders in pregnancy. Hypertension. 2009b;53(5):812-8.
35. Poon LCY, Maiz N, Valencia C, Plasencia W, Nicolaides KH. First-trimester maternal serum pregnancy-associated plasma protein-A and pre-eclampsia. Ultrasound In Obstetrics & Gynecology: The Official Journal Of The International Society Of Ultrasound In Obstetrics And Gynecology. 2009a;33(1):23-33.

36. Akolekar R, Zaragoza E, Poon LC, Pepes S, Nicolaides KH. Maternal serum placental growth factor at 11 + 0 to 13 + 6 weeks of gestation in the prediction of pre-eclampsia. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2008;32(6):732-9.
37. De Paco C, Kametas N, Rencoret G, Strobl I, Nicolaides KH. Maternal cardiac output between 11 and 13 weeks of gestation in the prediction of preeclampsia and small for gestational age. Obstetrics and gynecology. 2008;111(2 Pt 1):292-300.
38. Poon LC, Kametas NA, Pandeva I, Valencia C, Nicolaides KH. Mean arterial pressure at 11(+0) to 13(+6) weeks in the prediction of preeclampsia. Hypertension. 2008;51(4):1027-33.
39. Plasencia W, Maiz N, Bonino S, Kaihura C, Nicolaides KH. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks in the prediction of pre-eclampsia. Ultrasound In Obstetrics & Gynecology: The Official Journal Of The International Society Of Ultrasound In Obstetrics And Gynecology. 2007;30(5):742-9.
40. Myers JE, Kenny LC, McCowan LME, Chan EHY, Dekker GA, Poston L, et al. Angiogenic factors combined with clinical risk factors to predict preterm pre-eclampsia in nulliparous women: a predictive test accuracy study. BJOG: An International Journal Of Obstetrics And Gynaecology. 2013;120(10):1215-23.
41. Park FJ, Leung CHY, Poon LCY, Williams PF, Rothwell SJ, Hyett JA. Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2013;53(6):532-9.
42. Farina A, Rapacchia G, Freni Sterrantino A, Pula G, Morano D, Rizzo N. Prospective evaluation of ultrasound and biochemical-based multivariable models for the prediction of late pre-eclampsia. Prenatal diagnosis. 2011;31(12):1147-52.
43. Herraiz I, Arbues J, Camano I, Gomez-Montes E, Graneras A, Galindo A. Application of a first-trimester prediction model for pre-eclampsia based on uterine arteries and maternal history in high-risk pregnancies. Prenatal diagnosis. 2009;29(12):1123-9.
44. Steyerberg EW, Harrell FE, Jr. Prediction models need appropriate internal, internal-external, and external validation. Journal of clinical epidemiology. 2016;69:245-7.
45. Brunelli VB, Prefumo F. Quality of first trimester risk prediction models for pre-eclampsia: a systematic review. BJOG : an international journal of obstetrics and gynaecology. 2015;122(7):904-14.
46. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. Bmj. 2005;330(7491):565.
47. Crovetto F, Figueras F, Triunfo S, Crispi F, Rodriguez-Sureda V, Dominguez C, et al. First trimester screening for early and late preeclampsia based on maternal characteristics, biophysical parameters, and angiogenic factors. Prenatal diagnosis. 2015;35(2):183-91.
48. Baschat AA, Magder LS, Doyle LE, Atlas RO, Jenkins CB, Blitzer MG. Prediction of preeclampsia utilizing the first trimester screening examination. American journal of obstetrics and gynecology. 2014;211(5):514.e1-7.
49. Skrastad RB, Hov GG, Blaas HG, Romundstad PR, Salvesen K. Risk assessment for preeclampsia in nulliparous women at 11-13 weeks gestational age: prospective evaluation of two algorithms. BJOG : an international journal of obstetrics and gynaecology. 2015;122(13):1781-8.
50. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. American journal of obstetrics and gynecology. 2015;213(1):62.e1-10.
51. LeFevre ML. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Annals of internal medicine. 2014;161(11):819-26.
52. Bartsch E, Park AL, Kingdom JC, Ray JG. Risk threshold for starting low dose aspirin in pregnancy to prevent preeclampsia: an opportunity at a low cost. PloS one. 2015;10(3):e0116296.

53. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Annals of internal medicine. 2015;162(1):W1-73.

Author, year	n/N*	Model	Outcome	AUC (95% CI)
			Pre-eclampsia	
Direkvand-Moghadam et al. (2013)[14]	58/610	MC		0.67 (0.59-0.76)
North et al. (2011)[21]	186/3529	MC		0.71 (0.706-0.714)
Plasencia et al. (2007)[39]	107/6015	MC		0.81 (0.80-0.82)
Keikkala et al. (2013)[15**]	159/586	MC+BT		0.76 (0.72-0.81)
Goetzinger et al. (2010)[23]	293/3716	MC+BT		0.70 (0.65-0.72)
Leal et al. (2009)[30**]	128/1138	MC+D		0.82 (0.79-0.85)
De Paco et al. (2008)[37]	83/4293	MC+Echo		0.83 (0.77-0.89)
Plasencia et al. (2007)[39]	107/6015	MC+D		0.85 (0.84-0.86)
Goetzinger et al. (2014)[12]	88/1200	MC+D+BT		0.76 (0.69-0.83)
Odibo et al. (2011)[22]	42/452	MC+D+BT		0.77 (0.63-0.81)
			Early-onset pre-eclampsia	
Myers et al. (2013)[40]	47/3529	MC		0.76 (0.67-0.84)
Poon et al. (2011)[26]	37/8366	MC		0.90 (0.85-0.95)
Foidart et al. (2010)[27**]	30/270	MC		0.75 (0.69-0.81)
Poon et al. (2010c)[28**]	26/402	MC		0.72 (0.65-0.77)
Poon et al. (2010a)[29]	37/8366	MC		0.79 (0.72-0.87)
Plasencia et al. (2007)[39]	NR/6015	MC		0.78 (0.77-0.80)
Keikkala et al. (2013)[15**]	29/586	MC+BT		0.86 (0.79-0.94)
Myers et al. (2013)[40]	47/3529	MC+BT		0.84 (0.77-0.91)
Kuijk et al. (2011)[20]	28/407	MC+BT		0.65 (0.56-0.74)
Poon et al. (2009e)[31]	37/8366	MC+D		0.95 (0.92-0.99)
Poon et al. (2009d)[32]	37/8366	MC+D		0.91 (0.86-0.96)
Plasencia et al. (2007)[39]	NR/6015	MC+D		0.91 (0.90-0.92)
Scazzocchio et al. (2013)[18]	26/5170	MC+D		0.95 (0.94-0.98)
Foidart et al. (2010)[27**]	30/270	MC+D+BT		0.95 (0.91-0.98)
Poon et al. (2010c)[28**]	26/402	MC+D+BT		0.96 (0.93-0.98)
Poon et al. (2010b)[24]	37/8366	MC+D+BT		0.96 (0.956-0.964)
Poon et al. (2009c)[33**]	29/1138	MC+D+BT		0.91 (0.84-0.97)
Poon et al. (2009a)[35]	32/8051	MC+D+BT		0.85 (0.84-0.86)
Akolekar et al. (2008)[36**]	29/824	MC+D+BT		0.94 (0.88-0.99)
			Late-onset pre-eclampsia	
Poon et al. (2011)[26]	128/8366	MC		0.85 (0.83-0.88)
Poon et al. (2010c)[28**]	90/402	MC		0.78 (0.73-0.82)
Poon et al. (2010a)[29]	128/8366	MC		0.80 (0.76-0.83)
Plasencia et al. (2007)[39]	NR/6015	MC		0.80 (0.79-0.81)
Poon et al. (2009a)[35]	124/8051	MC+BT		0.79 (0.78-0.80)
Scazzocchio et al. (2013)[18]	110/5170	MC+BT		0.71 (0.66-0.76)
Poon et al. (2010b)[24]	128/8366	MC+D		0.863 (0.855-0.87)
Poon et al. (2009e)[31]	128/8366	MC+D		0.863 (0.855-0.87)
Poon et al. (2009d)[32]	128/8366	MC+D		0.81 (0.78-0.85)
Plasencia et al. (2007)[39]	NR/6015	MC+D		0.84 (0.83-0.85)
Poon et al. (2010c)[28**]	90/402	MC+D+BT		0.86 (0.82-0.90)
Poon et al. (2009c)[33**]	99/1138	MC+D+BT		0.81 (0.77-0.86)
Akolekar et al. (2008)[36**]	98/824	MC+D+BT		0.82 (0.77-0.86)

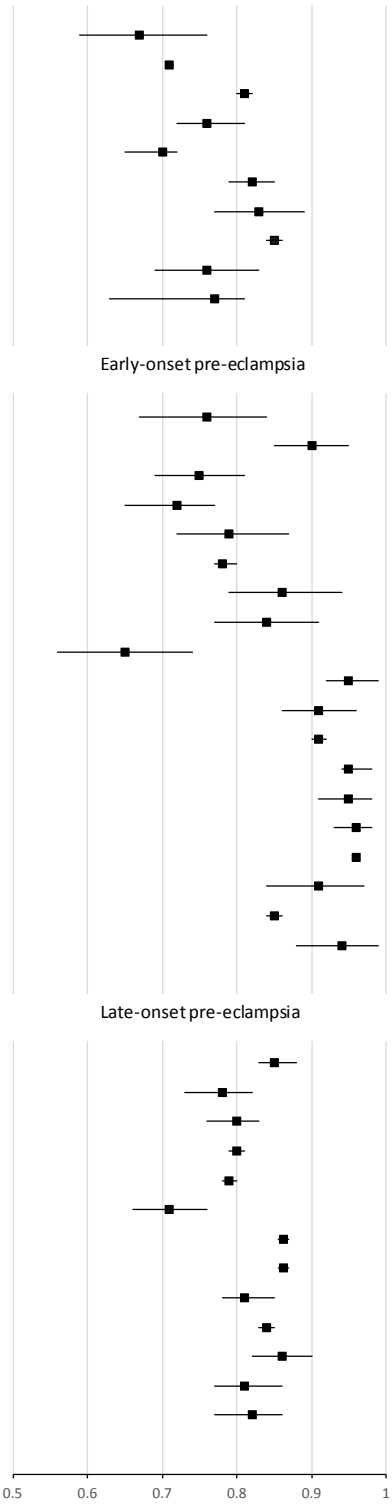

Figure 1. Performance of risk prediction models for pre-eclampsia reporting AUC and 95% CI.

AUC, area under the curve; BT, blood test; CI, confidence interval; D, Doppler; MC, maternal characterestics; NR, not reported.

*Number of pre-eclampsia events/total study population.

**Case-control or nested case-control study.

Author, year	n/N*	Model	Outcome	AUC (95% CI)
Model development studies, n = 7				
			Pre-eclampsia	
Plasencia et al. (2007)[39]	107/6015	MC		0.81 (0.80-0.82)
		MC+D		0.85 (0.84-0.86)
			Early-onset pre-eclampsia	
Myers et al. (2013)[40]	47/3529	MC		0.76 (0.67-0.84)
		MC+BT		0.84 (0.77-0.91)
Foidart et al. (2010)[27**]	30/270	MC		0.75 (0.69-0.81)
		MC+D+BT		0.95 (0.91-0.98)
Poon et al. (2010c)[28**]	26/402	MC		0.72 (0.65-0.77)
		MC+D+BT		0.96 (0.93-0.98)
Poon et al. (2010a)[29]	37/8366	MC		0.79 (0.72-0.87)
Poon et al. (2010b)[24***]		MC+D+BT		0.96 (0.956-0.964)
Poon et al. (2009e)[31***]		MC+D		0.95 (0.92-0.99)
Poon et al. (2009d)[32***]		MC+D		0.91 (0.86-0.96)
Plasencia et al. (2007)[39]	NR/6015	MC		0.78 (0.77-0.80)
		MC+D		0.91 (0.90-0.92)
			Late-onset pre-eclampsia	
Poon et al. (2010c)[28**]	90/402	MC		0.78 (0.73-0.82)
		MC+D+BT		0.86 (0.82-0.90)
Poon et al. (2010a)[29]	128/8366	MC		0.80 (0.76-0.83)
Poon et al. (2010b)[24***]		MC+D+BT		0.863 (0.855-0.87)
Poon et al. (2009e)[31***]		MC+D		0.863 (0.855-0.87)
Poon et al. (2009d)[32***]		MC+D		0.81 (0.78-0.85)
Plasencia et al. (2007)[39]	NR/6015	MC		0.80 (0.79-0.81)
		MC+D		0.84 (0.83-0.85)
Model validation studies, n = 2				
			Early-onset pre-eclampsia	
Park et al. (2013)[41]	12/3014	MC		0.76 (0.74-0.77)
		MC+D+BT		0.94 (0.93-0.95)
Herraiz et al. (2009)[43]	13/152	MC		0.74 (0.60-0.89)
		MC+D		0.78 (0.64-0.92)
			Late-onset pre-eclampsia	
Herraiz et al. (2009)[43]	7/152	MC		0.65 (0.49-0.80)
		MC+D		0.64 (0.48-0.80)

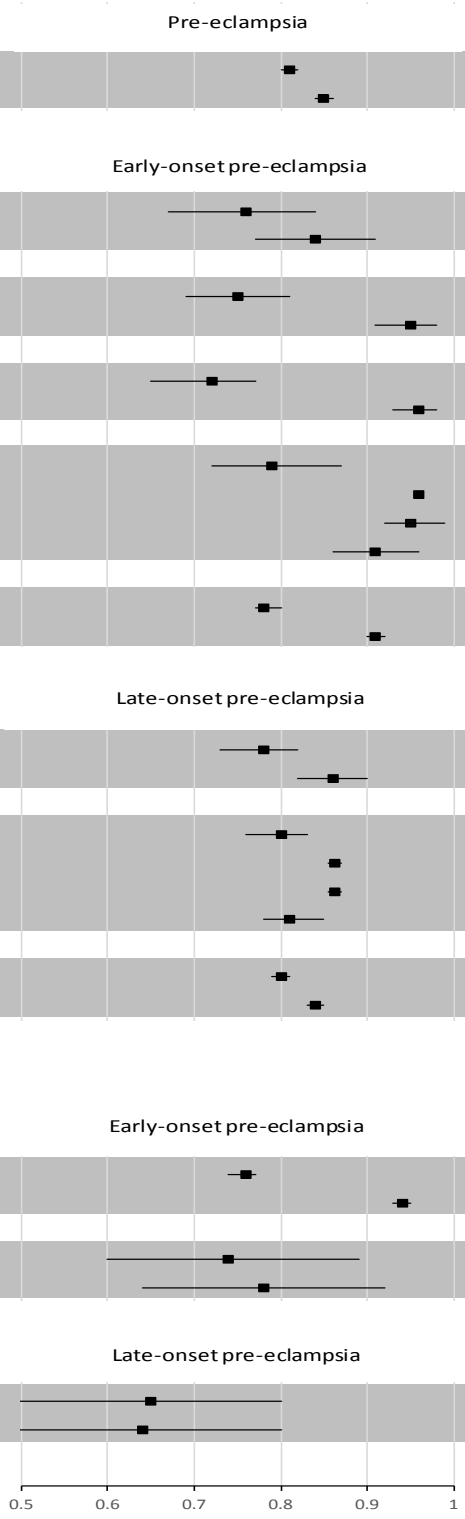

Figure 2. Comparison of performance of simple versus specialised models for pre-eclampsia for studies reporting model algorithm and AUC for both.

AUC, area under the curve; BT, blood test; CI, confidence interval; D, Doppler; MC, maternal characterestics; NR, not reported.

*Number of pre-eclampsia events/total study population.

**Case-control or nested case-control study.

***The study compared specialised models with simple models developed by Poon 2010a.[29]

Table 1. Predictors included in the best performing model from the 14 model development study populations

Author Year	Goetzinger et al. 2014 (12)	Caradeux et al. 2013 (13)	Direkvand-Moghadam et al. 2013 (14)	Keikkala et al. 2013 (15)	Kuc et al. 2013 (16)	Parra-Cordero et al. 2013 (17)	Scazzocchio et al. 2013 (18)	Di Lorenzo et al. 2012 (19)	Kuijk et al. 2011 (20)	North et al. 2011 (21)	Odibo et al. 2011 (22)	Goetzinger et al. 2010 (23)	Poon et al. 2010b (24)	Emonts et al. 2008 (25)
Outcome	PE	EO-PE	PE	PE	EO-PE*	EO-PE*	EO-PE*	EO-PE*,ǂ	EO-PE	PE	PE	PE	EO-PE*	PE
No. of predictors	6	10	3	4	9	4	7	13	5	12	4	5	8	14
Maternal factors														
Age		●			●			●		●				●
Parity		●		●	●		●	●		nulliparous			●	●
Smoking					●	●				●				
Race								●				●	●	
Family history of PE										●				
Past medical history														
Pre-eclampsia	●	●	●				●		all				●	
Hypertension	●	●	●				●	●	●		●	●	●	
Diabetes (I or II)	●											●		
Conception method													●	
Clinical examination														
Body mass index	●					●	●	●	●	●		●		●
Weight		●			●									
Systolic BP		●												●
Diastolic BP		●												●
MAP**		●		●	●		●			●			●	
*Other****		a	b		c		d	e	f	g				h
Uterine artery Doppler														
Bilateral UA notching	●							●						
UtA-PI**		●				●	●	●			●		●	
Blood tests														
PAPP-A**	●			●	●			●			●	●	●	
hCG**				●				●						
PlGF**					●	●		●						
PP-13**								●			●			
*Other****					c**				f					h

BP, blood pressure; EO-PE, early-onset pre-eclampsia; hCG, human chorionic gonadotrophin; MAP, mean arterial pressure; UA, uterine artery; UtA-PI, uterine artery pulsatility index, PAPP-A, pregnancy-associated plasma protein A; PE, pre-eclampsia; PlGF, placental growth factor; PP-13, placental protein 13.

*Study reports an additional different model for prediction of LO-PE (late-onset pre-eclampsia); **Some models require adjustment of additional factors to calculate log multiple of the median (log MoM) of this factor eg. Crown Rump Length (CRL); ***Other factors unique to a single model; ǂStudy reports additional different models for prediction of PE, EO-PE, LO-PE.

a- Preterm labour; b- Infertility; c- Height, A Disintegrin And Metalloprotease 12 (ADAM12), the study also reports models to predict EO-PE and LO-PE that uses clinical predictors alone; d- Chronic kidney disease; e- Past medical history of gestational DM, Sex of child; f- Gestational age at previous birth, Prior small-for-gestational-age, Fasting Blood Glucose (FBG). g- Vaginal bleeding ≥5days, High fruit intake, Alcohol consumption in first trimester, Maternal birth weight, One miscarriage ≤10 wk with same partner, ≥12 month to conceive, Family history of coronary heart disease; h- Gestation, Family history of hypertension, activated partial thromboplastin time (APTT), prothrombin time (PT), Activated factor VIII, Homocystein 4h, Free protein S, Vitamin B1, Relative plasma volume, the study also reports model that uses 7 clinical predictors alone.

Table 2. External validation of simple maternal factor risk models for pre-eclampsia; and comparative performance with National Institute of Health and Care Excellence (NICE) clinical decision rule

I. Comparison of model performance for development model study versus external validation study

Author **Year** **PE prevalence**	**Model predictors**	**Study size** **no. PE /no. patients**		**Discrimination** AUC (95% CI)		**Classification** Threshold for classifying sensitivity Sensitivity (Sn) % (95% CI) Specificity (Sp) % (95% CI)	
		Development	**Validation**	**Development**	**Validation**	**Development**	**Validation**
Development study Poon et al. 2010a (29) PE 2.0% ***Validation study*** Park et al. 2013 (41) PE 2.8%	*Early-onset pre-eclampsia* Race, Chronic HTN, Parity, Conception method	EO-PE 128/8366	EO-PE 12/3014	0.79 (0.72-0.87)	0.76 (0.74-0.77)	Threshold 10% FPR Sn 47% (23-65%) Sp 90% (fixed)	Threshold 10% FPR Sn 40% (10-76%) Sp 90% (fixed)
	Late-onset pre-eclampsia Age, FHx PE, Race, Parity , BMI	LO-PE 37/8366	LO-PE 71/3014	0.80 (0.76-0.83)	0.68 (0.66-0.69)	Threshold 10% FPR Sn 41% (33-50%) Sp 90% (fixed)	Threshold 10% FPR Sn 22% (12-32%) Sp 90% (fixed)
Development study Plasencia et al. 2007 (39) PE 107/6015 (1.8%) ***Validation study 1*** Herraiz et al. 2009 (43) PE 20/152 (13%) ***Validation study 2*** Farina et al. 2011 (42) LO-PE 39/554	*Early-onset pre-eclampsia* Race Parity +/- PHx PE	EO-PE NR	*Validation 1* EO-PE 13/152 *Validation 2* EO-PE NR		*Validation 1* 0.74 (0.60-0.89)	Threshold 10% FPR Sn 50% (95% CI NR) Sp 90% (fixed)	*Validation 1* Threshold 10% FPR Sn 29% (95% CI NR) Sp 90% (fixed)
	Late-onset pre-eclampsia Race FHx PE Parity +/- PHx PE BMI	LO-PE NR	*Validation 1* LO-PE 7/152 *Validation 2* LO-PE 39/554	0.80 (0.79-0.81)	*Validation 1* 0.65 (0.49-0.80) *Validation 2* 0.72 (0.62-0.82)	Threshold 10% FPR Sn 44% (95% CI NR) Sp 90% (fixed)	*Validation 1* Threshold 10% FPR Sn 23% (95% CI NR) Sp 90% (fixed) *Validation 2* Threshold 10% FPR Sn 54% (38-69%) Sp 90% (fixed)

II. Comparison of model performance for development study model versus NICE decision rule

Author **Year**	**PE** **no. events /no. patients**	**Model predictors**	**NICE Predictors**	**Classification** Threshold for classifying sensitivity Sensitivity % (95% CI) Specificity % (95% CI)	
				Study model	**NICE decision rule**
Poon et al. 2010a (29)	PE 165/8366 EO-PE 37 LO-PE 128	Parity, Race, PHx PE, PHx HTN, Conception method	*≥ 1 high risk factors:* PHx HDP CKD Autoimmune disease Diabetes Chronic HTN *≥ 2 moderate risk factors:* 1st pregnancy Age ≥40 years Pregnancy interval of >10 years BMI ≥35 kg/m^2 at 1st visit FHx PE Multiple pregnancy	EO-PE *From study text* Sn 37% (13-50%) Sp 95% (fixed) *From ROC curve* Sn 95% Sn 70% Sp 35% Sp 70% LO-PE *From study text* Sn 29% (21-38%) Sp 95% (fixed) *From ROC curve* Sn 97% Sn 70% Sp 35% Sp 70%	EO-PE Sn 89% (75-97%)* Sp 35% (34-36%)* LO-PE Sn 93% (87-97%)* Sp 36% (34-37%)* PE Sn 92% (87-96%)* Sp 36% (35-37%)*

AUC, area under the curve; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; EO-PE, early-onset pre-eclampsia; FHx, family history; FPR, false positive rate; HDP, hypertensive disease in pregnancy; HTN, hypertension; LO-PE, late-onset pre-eclampsia; NICE, National Institute for Health and Care Excellence; NR, not reported, PE, pre-eclampsia; PHx, past history of; ROC, receiver operating characteristic; Sn, sensitivity; Sp, specificity.
*Calculated from available data in table.

Supplementary Information

Appendix S1. Search strategy

For MEDLINE (set limited to human): 15-06-2014

1. Hypertension, Pregnancy-induced
2. Pre-Eclampsia
3. 1 or 2
4. risk factors/
5. risk/
6. risk assessment/
7. risk*
8. predict* rule*
9. 4 or 5 or 6 or 7 or 8
10. models, statistical/
11. nomograms/
12. logistic models/
13. model*
14. logistic*
15. regress*
16. combinat*
17. multivar*
18. algorithm*
19. Area Under Curve*
20. ROC Curve*
21. Receiver Operating Characteristic*
22. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 3 and 9 and 22

For PubMed: 15-06-2014

1. Hypertension, Pregnancy-induced
2. Pre-Eclampsia
3. 1 or 2
4. risk factors/
5. risk/
6. risk assessment/
7. risk*
8. predict* rule*
9. 4 or 5 or 6 or 7 or 8
10. models, statistical/
11. nomograms/
12. logistic models/
13. model*
14. logistic*

15. regress*
16. combinat*
17. multivar*
18. algorithm*
19. Area Under Curve*
20. ROC Curve*
21. Receiver Operating Characteristic*
22. Receiver Operat*
23. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 3 and 9 and 23
25. limit 24 to humans

For Embase: 18-06-2014

1. preeclampsia/exp or preeclampsia
2. maternal hypertension/exp or maternal hypertension
3. 1 or 2
4. risk/exp or risk
5. risk*:ab,ti
6. predict* and rule*:ab,ti
7. 4 or 5 or 6
8. statistical model/exp or statistical model
9. nomogram/exp or nomogram
10. model*:ab,ti
11. logistic*:ab,ti
12. regress*:ab,ti
13. combinat*:ab,ti
14. multivar*:ab,ti
15. algorithm*:ab,ti
16. area under the curve/exp or area under the curve
17. receiver operating characteristic/exp or receiver operating characteristic
18. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 3 and 7 and 18
20. 19 and human/de

Table S1. Characteristics of model development studies, *n* = 29 studies

Author Year	Study design Country Single/Multi centre, Setting Recruitment dates	N (n*)	Population		PE n (%)	Model method Validation method	Model type and outcome	Model output
			Selection criteria	Maternal characteristics**				
***Model development population*, *n* = 14 studies**								
Goetzinger et al. 2014 (12)	Retrospective cohort USA Single centre University Hospital clinic 2008-2012	1225 (1200) Development 578 Validation 622	1st trimester aneuploidy screening GA: 11-14 weeks Singleton	Maternal age: mean 31 y (SD 6) Nulliparous: 235/578 (41%)*** Multiple pregnancy: 0% PHx PE: 33/578 (6%)***	PE 88 (7.3%)	Multivariate logistic regression Internal validation	*Simple* NA *Specialised* PE	Risk score based on risk factor model weights Classify high risk of PE if score ≥6
Caradeux et al. 2013 (13)	Prospective cohort Chile Multicentre Hospital clinic Study dates: NR	627	1st trimester US screening GA: 11-14 weeks Singleton: NR	Maternal age: mean 28-29 y (SD 6 to 9) Nulliparous: 146 (23%)*** Multiple pregnancy: NR PHx PE: 15(2%)***	PE 29 (4.6%) EO-PE 9 (1.5%)	Multivariate logistic regression No internal & external validation	*Simple* NA *Specialised* EO-PE	Risk model Probability of EO-PE
Direkvand-Moghadam et al. 2013 (14)	Prospective cohort Iran Single centre Hospital obstetric unit 2010	610	Attended hospital obstetric unit GA: >20 week**** Singleton: NR	Maternal age: mean 28-29 y (SD 5) Nulliparous: NR Multiple pregnancy: NR PHx PE: 38 (6%)***	PE 58 (9.5%)	Multivariate logistic regression No internal & external validation	*Simple* PE *Specialised* NA	Risk model Probability of EO-PE
Keikkala et al. 2013 (15)	Nested case-control Finland Single centre University Hospital clinic 2008-2010	Base cohort 12615 Total 586 Cases 159 Controls 427	1st trimester screening for Down's syndrome GA: 8-13 weeks Singleton	Maternal age: mean 28-29 y (SD 5 to 6) Nulliparous (included): 301/586 (51%)*** Multiple pregnancy: 0% PHx PE: NR	Base cohort PE 273 (2.2%) No. cases PE 159 EO-PE 29	Multivariate logistic regression No internal & external validation	*Simple* NA *Specialised* PE, EO-PE	Risk model Probability of PE, EO-PE
Kuc et al. 2013 (16)	Nested case-control Netherlands Multicentre US clinics 2007-2009	667 Cases 167 Controls 500	1st trimester trisomy 21 screening GA: 9-13+6 weeks Singleton	Maternal age: median 33- 34 y (IQR 30 to 37) Nulliparous (included): 360/667 (54%)*** Multiple pregnancy: 0% PHx PE (included): 18/667 (3%)***	No. cases PE 167 EO-PE 68 LO-PE 99	Multivariate logistic regression No internal & external validation	*Simple* EO-PE, LO-PE *Specialised* EO-PE, LO-PE	Risk model Probability of EO-PE & LO-PE
Parra-Cordero et al. 2013 (17)	Nested case-control Chile No. of Centres: NR University Hospital clinic 2002-2010	Base cohort 5367 (2619) Total 359 Cases 70 Controls 289	1st trimester PE screening project GA: 11-13+6 weeks Singleton: NR	Maternal age: mean 29-30 y (SD* 6 to 7) Nulliparous (included): 172/359 (48%)*** Multiple pregnancy: NR PHx PE: NR	Base cohort PE 83 (3.2%) No. cases EO-PE 17 LO-PE 53	Multivariate logistic regression No internal & external validation	*Simple* NA *Specialised* EO-PE, LO-PE	Risk model Probability of EO-PE & LO-PE
Scazzocchio et al. 2013 (18)	Prospective cohort Spain Single centre Hospital clinic 2009-2011	5170	1sttrimester routine screening GA: 8-13+6 weeks Singleton	Maternal age: median 31-33 y (IQR 28 to 37) Nulliparous: 3055 (59%)*** Multiple pregnancy: 0% PHx PE: 43 (1%)***	PE 136 (2.6%) EO- PE 26 (0.5%) LO-PE 110 (2.1%)	Multivariate logistic regression No internal & external validation	*Simple* EO-PE *Specialised* EO-PE, LO-PE	Risk model Probability of EO-PE & LO-PE

Di Lorenzo et al. 2012 (19)	Prospective cohort Italy Single centre Hospital clinic 2007-2009	2170 (2118)	1st trimester aneuploidy screening GA: 11-13+6 weeks Singleton	Maternal age: mean 33-34 y (SD NR) Nulliparous: 1227 (58%)*** Multiple pregnancy: 0% PHx PE: NR	PE 25 (1.2%) EO-PE 12 (0.6%) LO-PE 13 (0.6%)	Multivariate logistic regression No internal & external validation	*Simple* NA *Specialised****** PE, EO-PE, LO-PE	Risk model Probability of PE, EO-PE & LO-PE
Kuijk et al. 2011 (20)	Retrospective cohort Netherlands Multicentre Hospital perinatal tertiary referral clinic 1993-2008	407	Past history of EO-PE in 1st pregnancy GA: 0 week (data collected after index EO-PE and prior to subsequent pregnancy) Singleton	Maternal age at 1st delivery: mean 29 y (SD 4) Nulliparous: 0% Multiple pregnancy: 0% PHxPE:100%	PE 28 (6.9%)	Multivariate logistic regression Internal validation	*Simple* NA *Specialised* Recurrence of EO-PE	Risk model Probability of recurrence of EO-PE and probability thresholds 4.6, 5.3, 5.4, 6.2%
North et al. 2011 (21)	Prospective cohort International Multicentre Hospitals, Obstetricians, GP, Midwives 2004-2008	3572 (3529)	Recruited to SCOPE study cohort to develop screening tests GA: 14-16 weeks Singleton	Maternal age: mean 27-28 y (SD 6) Nulliparous: 100% Multiple pregnancy: 0% PHx PE: 0%	PE 186 (5.3%)	Multivariate logistic regression Internal validation	*Simple* PE *Specialised* NA	Risk model Probability of PE
Odibo et al. 2011 (22)	Prospective cohort USA Single centre Hospital clinic 2009-2011	477 (452)	1sttrimester aneuploidy screening GA: 11-14 weeks Singleton	Maternal age: mean 30-32 y (SD 6) Nulliparous: 183 (40%)*** Multiple pregnancy: 0% PHx PE: NR	PE 42 (9%)	Multivariate logistic regression No internal & external validation	*Simple* NA *Specialised* PE	Risk model Probability of PE
Goetzinger et al. 2010 (23)	Retrospective cohort USA Single centre University Hospital clinic 2003-2009	4020 (3716)	1st trimester aneuploidy screening GA: 11-13+6 week -Singleton	Maternal age: mean 35 y (SD 4) Nulliparous: NR Multiple pregnancy: 0% PHx PE: NR	PE 293 (7.9%)	Multivariate logistic regression No internal & external validation	*Simple* NA *Specialised* PE	1. Risk model Probability of PE 2.Score system for prediction of PE based on number of risk factor
Poon et al. 2010b (24)	Prospective cohort UK Single centre Hospital clinic Mar 2006-Nov 2007	9149 (8366)	Routine first antenatal visit GA: 11-13+6 weeks Singleton	Maternal age: median 32-33 y (IQR 25 to 37) Nulliparous: 2674 (32%)*** Multiple pregnancy: 0% PHx PE: 241 (3%)***	PE 165 (2.0%) EO-PE 37 (0.4%) LO-PE 128 (1.5%)	Multivariate logistic regression External validation: by 2 studies	*Simple* EO-PE, LO-PE *Specialised* EO-PE, LO-PE	Risk model Probability of EO-PE & LO-PE
Emonts et al. 2008 (25)	Case-control Belgium Single centre Hospital clinic 1999-2002	151 Cases 101 Controls 50	Cases: hospitalized with severe PE Controls: normotensive, term delivery GA: NR Singleton: NR	Maternal age: mean 30 y (SD 5) Nulliparous: NR Multiple pregnancy: NR PHx PE: NR	PE 101 (%NR)	Multivariate logistic regression No internal & external validation	*Simple* PE *Specialised* PE	Risk model Probability of PE
***UK population*, *n* = 14 studies in addition to Poon 2010b (24) described above**								
Poon et al. 2011 (26)	Prospective cohort UK Single centre	9149 (8366)	Routine first antenatal visit GA:11-13+6 weeks	Maternal age: median 32-33 y (IQR 25-37) Nulliparous: 2674 (32%)***	PE 165 (2.0%) EO-PE	Multivariate logistic regression No internal &	*Simple* EO-PE, LO-PE *Specialised*	Risk model Probability of EO-PE & LO-PE

	Hospital clinic Mar 2006-Nov 2007		Singleton	Multiple pregnancy: 0% PHx PE: 241 (3%)***	37 (0.4%) LO-PE 128 (1.5%)	external validation	NA	
Foidart et al. 2010 (27)	Case-control UK Single centre Hospital clinic Mar 2006-Mar 2007	Base cohort 8234 Total 270 Cases 90 Controls 180	Routine first hospital visit in pregnancy GA: 11-13+6 weeks Singleton	Maternal age: median 32-33 y (IQR 25-37) Nulliparous (included): 141/270 (52%)*** Multiple pregnancy: 0% PHx PE (included): 21/270 (8%)***	Base cohort PE 147 (1.8%) No. cases PE 90 EO-PE 30 LO-PE 60	Multivariate logistic regression No internal & external validation	*Simple* EO-PE *Specialised* EO-PE	Risk model Probability of EO-PE
Poon et al. 2010c (28)	Case-control UK Single centre Hospital clinic Mar 2006-Nov 2007	Base cohort 9149 (8366) Total 402 Cases 201 Controls 201	Routine assessment of risk for chromosomal abnormalities GA: 11-13+6 weeks Singleton	Maternal age: median 32-33 y (IQR 26-39) Nulliparous (included): 139/402(35%)[3] Multiple pregnancy: 0% PHx PE (included): 32/402(8%)***	Base cohort PE 165 (2.0%) EO-PE 37 (0.4%) LO-PE 128 (1.5%) No. cases PE 116 EO-PE 26 LO-PE 90	Multivariate logistic regression No internal & external validation	*Simple* EO-PE, LO-PE *Specialised* EO-PE, LO-PE	Risk model Probability of EO-PE & LO-PE
Poon et al. 2010a (29)	Prospective cohort UK Single centre Hospital clinic Mar 2006-Nov 2007	9149 (8366)	Routine first antenatal visit GA: 11-13+6 weeks Singleton	Maternal age: median 32-33 y (IQR 25-37) Nulliparous: 2674 (32%)*** Multiple pregnancy: 0% PHx PE: 241 (3%)***	PE 165 (2.0%) EO-PE 37 (0.4%) LO-PE 128 (1.5%)	Multivariate logistic regression No internal & external validation	*Simple* EO-PE, LO-PE *Specialised* NA	Risk model Probability of EO-PE & LO-PE
Leal et al. 2009 (30)	Case- control UK Single centre Hospital clinic Study date: NR	1138 Cases 128 Controls 569	Routine assessment of risk for chromosomal abnormalities GA:11-13+6 weeks Singleton: NR	Maternal age: median 32-33 y (IQR 16-49) Nulliparous (included): 570/1138 (50%)*** Multiple pregnancy: NR PHx PE (included): 59/1138 (5%)***	No. cases PE 128	Multivariate logistic regression No internal & external validation	*Simple* NA *Specialised* PE	Risk model Probability of PE
Poon et al. 2009e (31)	Prospective cohort UK Single centre Hospital clinic Mar 2006-Nov 2007	9149 (8366)	Routine first antenatal visit GA: 11-13+6 weeks Singleton	Maternal age: median 32-33 y (IQR 25-37) Nulliparous: 2674 (32%)*** Multiple pregnancy: 0% PHx PE: 241 (3%)***	PE 165 (2.0%) EO-PE 37 (0.4%) LO-PE 128 (1.5%)	Multivariate logistic regression No internal & external validation	*Simple* EO-PE, LO-PE *Specialised* EO-PE, LO-PE	Risk model Probability of EO-PE & LO-PE
Poon et al. 2009d (32)	Prospective cohort UK Single centre Hospital clinic Mar 2006-Nov 2007	9149 (8366)	Routine first antenatal visit GA: 11-13+6 weeks Singleton	Maternal age: median 32-33 y (IQR 25-37) -Nulliparous: 2674 (32%)*** -Multiple pregnancy: 0% -PHx PE: 241 (3%)***	PE 165 (2.0%) EO-PE 37 (0.4%) LO-PE 128 (1.5%)	Multivariate logistic regression External validation: by 1 study	*Simple* EO-PE, LO-PE *Specialised* EO-PE, LO-PE	Risk model Probability of EO-PE & LO-PE
Poon et al.	Case-control	Total 1138	Routine assessment	Maternal age:	No. cases	Multivariate logistic	*Simple*	Risk model

2009c (33)	UK Single centre Hospital clinic Study dates: NR	Cases 569 Controls 569	of risk for chromosomal abnormalities GA: 11-13^{+6} weeks Singleton: NR	median 32-33 y (IQR 16-49) Nulliparous (included): 570/1138(50%)*** Multiple pregnancy: NR PHx PE (included): 59/1138 (5%)***	PE 128 EO-PE 29 LO-PE 99	regression No internal & external validation	NA *Specialised* EO-PE, LO-PE	Probability of EO-PE & LO-PE
Poon et al. 2009b (34)	Nested case-control UK Single centre Hospital clinic Mar 2006-Aug 2007	Base cohort 8481 (7797) Total 627 Cases 209 Controls 418	Routine first antenatal visit GA: 11-13 weeks Singleton	Maternal age: median 32-33 y (IQR 26-37) Nulliparous: 3715 (48%)*** Multiple pregnancy: 0% PHx PE: 222 (3%)***	Base cohort PE 157 (2%) EO-PE 34 (0.4%) LO-PE 123 (1.6%) No. cases PE 127 EO-PE 29 LO-PE 98	Multivariate logistic regression No internal & external validation	*Simple* NA *Specialised* EO-PE, LO-PE	Risk model Probability of EO-PE & LO-PE
Poon et al. 2009a (35)	Prospective cohort UK Single centre Hospital clinic Mar 2006-Jun 2007	8679 (8051)	Routine assessment of trisomy 21 risk GA: 11-13^{+6} weeks Singleton	Maternal age: median 32-32 y (IQR 16-49) Nulliparous: 3861 (48%)*** Multiplepreg.: 0% PHx PE: 233 (3%)***	PE 156 (1.9%) EO-PE 32 (0.4%) LO-PE 124 (1.5%)	Multivariate logistic regression External validation: by 1 study	*Simple* NA *Specialised* EO-PE, LO-PE	Risk model Probability of EO-PE & LO-PE
Akolekar et al. 2008 (36)	Case-control UK Centre: NR Hospital clinics Dates: NR	824 Cases 215 Controls 609	Routine assessment of risk for Trisomy 21 GA: 11- 13^{+6} weeks Singleton: NR	Maternal age: median 32-33 y (IQR 16-49) Nulliparous (included): 406/824 (49%)*** Multiple pregnancy: NR PHx PE (included): 44/824 (5%)***	Base cohort PE no. NR (1.8%) No. cases PE 127 EO-PE 29 LO-PE 98	Multivariate logistic regression No internal & external validation	*Simple* NA *Specialised* EO-PE, LO-PE	Risk model Probability of EO-PE & LO-PE
De Paco et al. 2008 (37)	Prospective cohort UK Single centre Hospital clinic 2006	4617 (4293)	Routine assessment of risk for chromosomal abnormalities GA: 11-13 $^{+6}$ weeks Singleton	Maternal age: median 31-33 y (IQR 16-49) Nulliparous: 2056 (48%)*** Multiple pregnancy: 0% PHx PE: 731 (17%)***	PE 83 (1.9%) PE without SGA 46 (1%)	Multivariate logistic regression No internal & external validation	*Simple* NA *Specialised* All PE, PE without SGA	Risk model Probability of all PE & PE without SGA
Poon et al. 2008 (38)	Prospective cohort UK Single centre Hospital clinic Mar 2006-Dec 2006	5590 (4619)	Routine assessment of risk for chromosomal abnormalities GA: 11-13^{+6} weeks Singleton	Maternal age: median 32 y (IQR 16-49) Nulliparous: 2177 (47%)*** Multiple pregnancy: 0% PHx PE: 131 (3%)***	PE 104 (2%)	Multivariate logistic regression No internal & external validation	*Simple* PE *Specialised* NA	Risk model Probability of PE
Plasencia et al. 2007 (39)	Prospective cohort UK Single centre Hospital clinic Study date: NR	6592 (6015)	1st trimester screening for chromosomal abnormalities GA: 11-13 $^{+6}$ weeks Singleton	Maternal age: mean 32-33 y (range 15-49) Nulliparous: 2821 (47%)*** Multiple pregnancy: 0% PHx PE: 181 (3%)***	PE 107 (1.8%)	Multiple regression analysis External validation: by 2 studies	*Simple* PE, EO-PE, LO-PE *Specialised* PE, EO-PE, LO-PE	Risk model Probability of PE, EO-PE & LO-PE
SCOPE population **, *n* = 1 study in addition to North et al 2011 (21) described above**								

Myers et al. 2013 (40)	Nested case-control International Multicentre Hospitals, Obstetricians, GP, Midwives 2004-2008	Base cohort 3572 (3529) Total 235 Cases 47 Controls 188	Recruited to SCOPE study cohort to develop screening tests GA: 14-16 weeks Singleton	Maternal age: mean 28 y (SD 5-6) Nulliparous: 100% Multiple pregnancy: 0% PHx PE: 0%	Base cohort PE 187 (5.3%) No. cases Preterm PE 47	Multivariate logistic regression Internal validation	*Simple* Preterm PE with delivery <37 week *Specialised* Preterm PE with delivery <37 week	Risk model Probability of preterm PE

EO-PE, early-onset pre-eclampsia; GA, gestational age; IQR, interquartile range; LO-PE, late-onset pre-eclampsia; NA, not applicable; NR, not reported; PE, pre-eclampsia; PHx, past history of; SCOPE, Screening for Pregnancy Endpoints; SD, standard deviation; SGA, small-for-gestational-age; UK, United Kingdom; US, ultrasound; USA, United States of America.

*Number of subjects included in analysis for development of final model.

**If mean age and SD is reported for multiple groups, the range of mean and SD between the groups is reported.

***Calculated from data presented in tables.

****Study population GA >20wk, however model developed that can be used before 17 weeks.

*****Model A included all maternal factors, both statistically significant and not, based on Nicolaides group's approach. Model B included statistically significant predictors only.

Table S2. List of predictors of pre-eclampsia risk prediction models

Author Year	Model predictors	
	Simple model	**Specialised model**
***Model development population, n* = 14**		
Goetzinger et al. 2014 (12)	NA	*PE* *MC* Chr. HTN, PHx PE, Pre-pregDM, BMI >25 *Uterine artery Doppler* Bilat. UA notching *Serum* PAPP-A
Caradeux et al. 2013 (13)	NA	*EO-PE* *MC* Age, Parity, PHx PE, PHx HTN, PHx preterm labor, Weight *BP* SBP, DBP, MAP *Uterine artery Doppler* UtA-PI*
Direkvand-Moghadam et al. 2013 (14)	*PE* *MC* PHx PE, PHx HTN, PHx Infertility	NA
Keikkala et al. 2013 (15)	NA	*PE & EO-PE* *MC* Parity *BP* MAP *Serum* PAPP-A*, hCG-h*
Kuc et al. 2013 (16)	*EO-PE* *MC* Age, Weight, Height, Parity, Smoking *LO-PE* *MC* Age, Weight, Parity	*EO-PE* *MC* Age, Weight, Height, Parity, Smoking *BP* MAP* *Serum* PAPP-A*, ADAM12*, PlGF* *LO-PE* *MC* Weight, Height, Parity *BP* MAP* *Serum* PAPP-A*, ADAM12*, PlGF*
Parra-Cordero et al. 2013 (17)	NA	*EO-PE* *MC* Smoking, BMI *Uterine artery Doppler* UtA-PI* *Serum* PlGF* *LO-PE* *MC* BMI *Uterine artery Doppler* UtA-PI* *Serum*

		PlGF*
Scazzocchio et al. 2013 (18)	*EO-PE* *MC* Chr. HTN, Hx Renal disease, Parity +/-PHxPE, BMI	*EO-PE* *MC* Chr. HTN, Hx Renal disease, Parity +/-PHxPE, BMI *BP* MAP* *Uterine artery Doppler* UtA-PI* *LO-PE* *MC* PHx PE, Chr. HTN, Hx DM, Hx Throm- bophilia, Parity, BMI *Serum* PAPP-A*
Di Lorenzo et al. 2012 (19)	NA	*Model A*** *PE* *MC* Age, BMI, Race, Parity, Smoking, GDM, Sex child, Chr. HTN *Uterine artery Doppler* UtA-PI*, Bilateral Notch12 *Serum* free b-hCG*, PAPP-A*, PP-13*, PlGF* *EO-PE* *MC* Age, BMI, Race, Parity, GDM, Sex child, Chr. HTN *Uterine artery Doppler* UtA-PI*, Bilateral Notch12 *Serum* free b-hCG*, PAPP-A*, PP-13*, PlGF* *LO-PE* *MC* Age, BMI, Parity, Smoking, GDM, Sex child *Uterine artery Doppler* UtA-PI*, Bilateral Notch12 *Serum* free b-hCG*, PAPP-A*, PP-13*, PlGF* *Model B*** *PE* *MC* Chr. HTN *Uterine artery Doppler* UtA-PI* *Serum* PlGF* *EO-PE* *MC* Chr. HTN *Serum* b-hCG*, PlGF*
Kuijk et al. 2011 (20)	NA	*Recurrence of EO-PE* *MC* GA at previous birth, Prior SGA, BMI, HTN *Blood test* FBG
North et al. 2011 (21)	*PE* *MC* Age, BMI***, FHx PE, FHx CHD, Maternal birth weight, PV bleeding >=5 days, PHx single miscarriage with the same partner, >=12 months to conceive, High intake of fruit, Cigarette /day, Alcohol use in trimester 1	NA

	BP MAP	
Odibo et al. 2011 (22)	NA	*PE* *MC* Hx Chr. HTN *Uterine artery Doppler* UtA-PI* *Serum* PP13*, PAPP-A*
Goetzinger et al. 2010 (23)	NA	*PE* *MC* Pre-preg DM, Chr.HTN, Race, BMI >25 *Serum* PAPP-A
Poon et al. 2010b (24)	*EO-PE* *MC* Race, Hx Chr. HTN, Parity +/-PHx PE, Conception method *LO-PE* *MC* Age, FHx PE, Race, Parity +/-PHx PE, BMI	*EO-PE* *MC* Race, Hx Chr. HTN, Parity +/-PHx PE, Conception method *BP* MAP* *Uterine artery Doppler* UtAL-PI* *Serum* PAPP-A* *LO-PE* *MC* Age, FHx PE, Race, Parity +/-PHx PE, BMI *BP* MAP* *Uterine artery Doppler* UtAL-PI*
Emonts et al. 2008 (25)	*PE* *MC* Age, Parity, Gestation, FHx HTN, BMI *BP* SBP, DBP	*PE* *MC* Age, Parity, Gestation, FHx HTN, BMI *BP* SBP, DBP *Serum* APTT, PT, Activated factor VIII, Homocyst-ein 4h, Free protein S, Vitamin B1 *PE* *MC* Age, Parity, Gestation, FHx HTN, BMI *BP* SBP, DBP *Serum* APTT, PT, Activated factor VIII, Homocyst-ein 4h, Free protein S, Vitamin B1, Relative plasma volume
***UK population*, *n* = 14 studies in addition to Poon 2010b (24) described above**		
Poon et al. 2011 (26)	*EO-PE* *MC* Race, Hx Chr. HTN, Parity +/-PHx PE, Conception method *BP* SBP OR, DBP OR MAP* *LO-PE* *MC* Age, FHx PE, Race, Parity +/-PHx PE, BMI *BP* SBP OR, DBP OR MAP*	NA
Foidart et al. 2010 (27)	*EO-PE* *MC* Race, Hx Chr. HTN, Parity +/-PHx PE, Conception	*EO-PE* *MC* Race, Hx Chr. HTN, Parity +/-PHx PE, Conception method

	method	*Uterine artery Doppler* UtAL-PI* *Serum* PlGF*, sEng*
Poon et al. 2010c (28)	*EO-PE* *MC* Race, Hx Chr. HTN, Parity +/-PHx PE, Conception method *LO-PE* *MC* Age, FHx PE, Race, Parity +/-PHx PE, BMI	*EO-PE* *MC* Race, Hx Chr. HTN, Parity +/-PHx PE, Conception method *BP* MAP* *Uterine artery Doppler* UtAL-PI* *Serum* PlGF* *LO-PE:* *MC* Age, FHx PE, Race, Parity +/-PHx PE, BMI *BP* MAP* *Uterine artery Doppler* UtAL-PI* *Serum* PlGF*, Activin-A*, P-selectin*
Poon et al. 2010a (29)	*EO-PE:* *MC* Race, Hx Chr. HTN, Parity +/-PHx PE, Conception method *LO-PE* *MC* Age, FHx PE, Race, Parity +/-PHx PE, BMI	NA
Leal et al. 2009 (30)	NA	*PE* *MC* FHx PE, Race, Parity +/- PHx PE, Hx Chr. HTN, BMI *Uterine artery Doppler* UtA-PI*
Poon et al. 2009e (31)	*EO-PE* *MC* Race, Hx Chr. HTN, Parity +/-PHx PE, Conception method *LO-PE* *MC* Age, FHx PE, Race, Parity +/-PHx PE, BMI	*EO-PE* *MC* Race, Hx Chr. HTN, Parity +/-PHx PE, Conception method *BP* MAP* *Uterine artery Doppler* UtAL-PI* *LO-PE* *MC* Age, FHx PE, Race, Parity +/-PHx PE, BMI *BP* MAP* *Uterine artery Doppler* UtAL-PI*
Poon et al. 2009d (32)	*EO-PE* *MC* Race, Hx Chr. HTN, Parity +/-PHx PE, Conception method *LO-PE* *MC* Age, FHx PE, Race, Parity +/-PHx PE, BMI	*EO-PE* *MC* Race, Hx Chr. HTN, Parity +/-PHx PE, Conception method *Uterine artery Doppler* UtAL-PI* (lowest OR mean OR highest) *LO-PE* *MC* Age, FHx PE, Race, Parity +/-PHx PE, BMI *Uterine artery Doppler* UtAL-PI* (lowest OR mean OR highest)
Poon et al. 2009c (33)	NA	*EO-PE* *MC* Hx Chr.HTN, Race

		Uterine artery Doppler UtA-PI* *Serum* PAPP-A* *LO-PE* *MC* FHx PE, Race, Parity +/- PHx PE, BMI *Uterine artery Doppler* UtA-PI* *Serum* MMP-9*
Poon et al. 2009b (34)	NA	*EO-PE* *MC* Parity +/-PHx PE, BMI *BP* MAP* *Uterine artery Doppler* UtA-PI* *Serum* PAPP-A*, PlGF* *LO-PE* *MC* Parity+/-PHx PE, Race, FHx PE (mother), BMI *BP* MAP* *Uterine artery Doppler* UtA PI* *Serum* PlGF*
Poon et al. 2009a (35)	NA	*EO-PE* *MC* Hx Chr. HTN, Race, Parity +/-PHx PE *Uterine artery Doppler* UtA PI* *Serum* PAPP-A* *LO-PE* *MC* FHx PE, Race, Parity +/-PHx PE BMI *Serum* PAPP-A*
Akolekar et al. 2008 (36)	NA	*EO-PE* *MC* Hx Chr. HTN, Race *Uterine artery Doppler* UtA-PI* *Serum* PlGF*, PAPP-A* *LO-PE* *MC* FHx PE (mother), Race, Parity +/- PHx PE, BMI *Uterine artery Doppler* UtA-PI* *Serum* PlGF*
De Paco et al. 2008 (37)	NA	*All PE & PE without SGA* *MC* Race, Parity+/-PHx PE, FHx PE, Weight (kg) *Echo* Cardiac output*
Poon et al.	*PE*	NA

2008 (38)	*MC* Race, FHx PE (mother), Parity+/-PHx PE, BMI *BP* MAP*	
Plasencia et al. 2007 (39)	*PE & LO-PE* *MC* Race, FHx PE, Parity+/-PHx PE, BMI *EO-PE* *MC* Race, Parity+/-PHx PE	*PE & LO-PE* *MC* Race, FHx PE, Parity+/-PHx PE, BMI *Uterine artery Doppler* UtA-PI* *EO-PE* *MC* Race, Parity+/-PHxPE *Uterine artery Doppler* UtA-PI*
SCOPE population **, *n* = 1 study in addition to North et al 2011 (21) described above**		
Myers et al. 2013 (40)	*PE with delivery <37 week* *MC* Fertility Rx, FHx PE *BP* MAP	*PE with delivery <37 week* *MC* Fertility Rx *BP* MAP *Serum* PlGF

ADAM12, A Disintegrin And Metalloprotease 12; APTT, activated partial thromboplastin time; b-hCG, beta human chorionic gonadotrophin; Bilat. UA notching, bilateral uterine artery notching; BMI=body mass index; BP, blood pressure; CHD, coronary heart disease; Chr., chronic; DBP, diastolic blood pressure; DM, diabetes mellitus; EO-PE, early-onset pre-eclampsia; FBG, Fasting Blood Glucose; FHx, family history of; fLI, free leptin index; GA, gestational age; GDM, gestational diabetes mellitus; hCG-h, proportion of hyperglycosylated human chorionic gonadotrophin (hCG) to hCG; HTN, hypertension; Hx, history of; LO-PE, late-onset pre-eclampsia; MAP, mean arterial pressure; MC, maternal characteristics; MMP-9, Matrix metalloproteinase-9; NA, not applicable; PAPP-A, pregnancy-associated plasma placentalprotein A; PE, pre-eclampsia; PHx, past history of; PlGF, placental growth factor; PP-13, placental protein 13; PT, prothrombin time; Rx, treatment; SBP, systolic blood pressure; SCOPE, Screening for Pregnancy Endpoints; sEng=Soluble endoglin; SGA, small-for-gestational-age; UA, Uterine artery; UK, United Kingdom; UtAL-PI, lowest uterine artery pulsatility index; UtA-PI, uterine artery pulsatility index.

*This variable was calculated after adjustment of other variables.

**-Model A included all maternal factors, both statistically significant and not, based on Nicolaides group's approach

-Model B included statistically significant predictors only.

***Categorized variable.

Table S3. Risk of bias assessment, *n* = 14 model development studies

Author Year	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Risk of Bias	External validation	Applicability
Goetzinger et al. 2014 (12)	*Study design:* Retrospective cohort *Patient sampling:* 11-14 weeks *Avoid inappropriate exclusions:* Yes	*Explicit predictor definition*: No *Blinding*: NR *Established high risk predictors considered*: Yes *Categorical variables with data driven threshold:* No *Continuous variables assessed for non-linear associations:* NA	*Explicit PE definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size:* Yes PE 88 events/6 variables *All enrollees included in analysis:* Yes	*Reports predictor selection method:* Yes *Accounts for over-fitting and optimism*: No *Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: Yes, goodness of fit, plot *Assessed discrimination*: Yes *Internal validation:* Yes	High	No	Low Requires blood test
Caradeux et al. 2013 (13)	*Study design:* Prospective cohort *Patient sampling:* 0-16 weeks *Avoid inappropriate exclusions:* Yes	*Explicit predictor definition:* No *Blinding:* NR *Established high risk predictors considered*: Yes *Categorical variables with data driven threshold:* No *Continuous variables assessed for non-linear associations:* Yes	*Explicit PE definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size:* No EO-PE 9 events/10 variables *All enrollees included in analysis:* Yes	*Reports predictor selection method:* No *Accounts for over-fitting and optimism*: No *Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: Yes, goodness of fit *Assessed discrimination*: Yes *Internal validation:* No	High	No	Low Requires uterine artery Doppler
Direkvand-Moghadam et al. 2013 (14)	*Study design:* Prospective cohort *Patient sampling:* >20 week *Avoid inappropriate exclusions:* Yes	*Explicit predictor definition:* No *Blinding:* NR *Established high risk predictors considered*: Yes *Categorical variables with data driven threshold:* No *Continuous variables assessed for non-linear associations:* NA	*Explicit PE definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size:* Yes PE 58 events/3 variables *All enrollees included in analysis:* Yes	*Reports predictor selection method:* Yes *Accounts for over-fitting and optimism*: No *Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: No *Assessed discrimination*: Yes *Internal validation:* No	High	No	Low Women >20 week Middle income country
Keikkala et al. 2013 (15)	*Study design*: Nested case-control *Patient sampling*: 8-13 weeks *Avoid inappropriate exclusions:* Yes	*Explicit predictor definition:* No *Blinding:* NR *Established high risk predictors considered*: Yes *Categorical variables with data driven threshold:* No *Continuous variables assessed for non-linear associations:* Yes	*Explicit PE definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size:* Yes PE 159 events/4 variables-yes EO-PE 29 events/4 variables-no *All enrollees included in analysis:* No	*Reports predictor selection method:* No *Accounts for over-fitting and optimism*: No *Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: No *Assessed discrimination*: Yes *Internal validation:* No	High	No	Low Requires blood test
Kuc et al. 2013 (16)	*Study design*: Nested case-control	*Explicit predictor definition:* Yes	*Explicit PE definition:* Yes	*Adequate sample size:* Yes EO-PE	*Reports predictor selection method:* Yes *Accounts for over-fitting and optimism*: Yes	High	No	Low Requires blood test

	Patient sampling: 9-13^{+6} weeks *Avoid inappropriate exclusions:* Yes	*Blinding:* NR *Established high risk predictors considered*: No *Categorical variables with data driven threshold:* No *Continuous variables assessed for non-linear associations:* Yes	*Blinded outcome assessment:* NR	simple 68 events/5 variables-yes special 68 events/9 variables-no LO-PE Simple 99 events/ 3 variables-yes special 99 events/7 variables-yes *All enrollees included in analysis:* Yes	*Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: No *Assessed discrimination*: Yes *Internal validation:* No			
Parra-Cordero et al. 2013 (17)	*Study design*: Nested case-control *Patient sampling*: 11-13^{+6} weeks *Avoid inappropriate exclusions*: No	*Explicit predictor definition:* Yes *Blinding: NR* *Established high risk predictors considered*: No *Categorical variables with data driven threshold:* No *Continuous variables assessed for non-linear associations:* Yes	*Explicit PE definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size:* Yes EO-PE 17 events/4 variables-no LO-PE 53 events/3 variable-yes *All enrollees included in analysis:* No	*Reports predictor selection method:* No *Accounts for over-fitting and optimism*: No *Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: No *Assessed discrimination*: Yes *Internal validation:* No	High	No	Low Requires blood test & uterine artery Doppler
Scazzocchio et al. 2013 (18)	*Study design*: Prospective cohort *Patient sampling*: 8-13^{+6} weeks *Avoid inappropriate exclusions:* Yes	*Explicit predictor definition:* No *Blinding*: NR *Established high risk predictors considered*: Yes *Categorical variables with data driven threshold:* No *Continuous variables assessed for non-linear associations:* Yes	*Explicit PE definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size:* Yes EO-PE Simple 26 events/5 variables-no Special 26 events/7 variables-no LO-PE Special 110 events/7 variables-yes *All enrollees included in analysis:* Yes	*Reports predictor selection method:* Yes *Accounts for over-fitting and optimism*: No *Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: Yes, nagelkerke R2 *Assessed discrimination*: Yes *Internal validation:* No	High	No	Low Requires blood test & uterine artery Doppler
Di Lorenzo et al. 2012 (19)	*Study design*: Prospective cohort *Patient sampling*: 11-13^{+6} weeks *Avoid inappropriate exclusions:* Yes	*Explicit predictor definition:* Yes *Blinding: NR* *Established high risk predictors considered*: Yes *Categorical variables with data driven threshold:* No *Continuous variables assessed for non-linear associations:* Yes	*Explicit PE definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size:* No Model A PE 25 events/14 variables-no EO-PE 12 events/13 variables-no LO-PE 13 events/12 variables-no Model B PE 25 events/3 variables-no EO-PE 12 events/3 variables-no *All enrollees included in analysis:* Yes	*Reports predictor selection method:* Yes *Accounts for over-fitting and optimism*: No *Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: No *Assessed discrimination*: Yes *Internal validation:* No	High	No	Low Requires blood test & uterine artery Doppler
Kuijk et al. 2011 (20)	*Study design*: Retrospective cohort *Patient sampling*: No *Avoid inappropriate exclusions:* Yes	*Explicit predictor definition:* Yes *Blinding*: *NR* *Established high risk predictors considered*: No *Categorical variables with data driven threshold:* No *Continuous variables assessed for non-linear*	*Explicit PE definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size*: No EO-PE 28 events/5 variables *All enrollees included in analysis:* Yes	*Reports predictor selection method:* Yes *Accounts for over-fitting and optimism*: Yes *Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: Yes, goodness of fit *Assessed discrimination*: Yes *Internal validation:* Yes	High	No	Low Requires blood test Applies to women with PHx PE

		associations: No						
North et al. 2011 (21)	*Study design*: Prospective cohort *Patient sampling*: 0-16 weeks *Avoid inappropriate exclusions:* Yes	*Explicit predictor definition:* Yes *Blinding*: NR *Established high risk predictors considered*: Yes *Categorical variables with data driven threshold:* No *Continuous variables assessed for non-linear associations:* NR	*Explicit PE Definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size:* Yes PE 186 events/12 variables *All enrollees included in analysis:* Yes	*Reports predictor selection method:* Yes *Accounts for over-fitting and optimism*: Yes *Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: Yes, plot *Assessed discrimination*: Yes *Internal validation:* Yes	Low	No	High
Odibo et al. 2011 (22)	*Study design*: Prospective cohort *Patient sampling*: 11-14 weeks *Avoid inappropriate exclusions:* Yes	*Explicit predictor definition:* Yes *Blinding*: NR *Established high risk predictors considered*: No *Categorical variables with data driven threshold:* No *Continuous variables assessed for non-linear associations:* Yes	*Explicit PE definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size:* Yes PE 42 events/ 4 variables *All enrollees included in analysis:* Yes	*Reports predictor selection method:* NR *Accounts for over-fitting and optimism*: No *Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: Yes, goodness of fit *Assessed discrimination*: Yes *Internal validation:* No	High	No	Low Requires blood test & uterine artery Doppler
Goetzinger et al. 2010 (23)	*Study design*: Retrospective cohort *Patient sampling*: 11-13^{+6} weeks *Avoid inappropriate exclusions:* No	*Explicit predictor definition:* No *Blinding*: NR *Established high risk predictors considered*: No *Categorical variables with data driven threshold:* Yes *Continuous variables assessed for non-linear associations:* Yes	*Explicit PE definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size:* Yes PE 293 events/ 5 variables *All enrollees included in analysis:* No	*Reports predictor selection method:* Yes *Accounts for over-fitting and optimism*: No *Score weights correspond to the regression coefficients*: No *Pre-specified risk group categories*: NA *Assessed calibration*: No *Assessed discrimination*: Yes *Internal validation:* No	High	No	Low Requires blood test
Poon et al. 2010b (24)	*Study design*: Prospective cohort *Patient sampling*: 11-13^{+6} weeks *Avoid inappropriate exclusions*: No	*Explicit predictor definition:* Yes *Blinding: NR* *Established high risk predictors considered*: Yes *Categorical variables with data driven threshold:* No *Continuous variables assessed for non-linear associations:* Yes	*Explicit PE definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size:* Yes EO-PE Simple 37 events/5 variables-no Special 37 events/8 variables-no LO-PE Simple 110 events/6 variables-yes Special 110 events/8 variables-yes *All enrollees included in analysis:* No	*Reports predictor selection method:* Yes *Accounts for over-fitting and optimism*: No *Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: No *Assessed discrimination*: Yes *Internal validation:* No	Low	Yes	Low Requires blood test & uterine artery Doppler
Emonts et al. 2008 (25)	*Study design*: Case-control *Patient sampling*: NR *Avoid inappropriate exclusions:* NR	*Explicit predictor definition*: No *Blinding*: NR *Established high risk predictors considered*: Yes *Categorical variables with*	*Explicit PE definition:* Yes *Blinded outcome assessment:* NR	*Adequate sample size:* No PE 101 events/14 variables *All enrollees included in analysis:* Yes	*Reports predictor selection method:* Yes *Accounts for over-fitting and optimism*: No *Score weights correspond to the regression coefficients*: Yes *Pre-specified risk group categories*: NA *Assessed calibration*: No	High	No	Low Requires blood test

		data driven threshold: No *Continuous variables assessed for non-linear associations:* No			*Assessed discrimination*: Yes *Internal validation:* No			

EO-PE, early-onset pre-eclampsia; LO-PE, late-onset pre-eclampsia; NA, not applicable; NR, not reported; PE, pre-eclampsia; PHx, past history of.

Table S4. Model performance and validation, *n* = 29 studies

Author Year	**PE no. events /no. patients**	**Discrimination** AUC (95% CI)		**Classification** Risk threshold Sensitivity% (95% CI) Specificity% (95% CI)		**Calibration**	**Validation method**
		Simple models	**Specialised models**	**Simple models**	**Specialised models**		
***Model development population*, *n* = 14 studies**							
Goetzinger et al. 2014 (12)	PE 88/1200	NA	PE* 0.76 (0.69-0.83)	NA	PE* risk score ≥ 6 37% (23-52%) 93% (91-95%)	1.Goodness of fit: Hosmer & Lemeshow test 2.Calibration plot	Internal validation: Split sample AUC 0.78 (0.69-0.86) Sn 26% (13-42%) Sp 95% (92-97%)
Caradeux et al. 2013 (13)	EO-PE 9/627	NA	EO-PE** 0.90 (95% CI NR)	NA	EO-PE** fixed at 5% FPR 63% (95% CI NR) 95% (95% CI NR)	Goodness of fit: Hosmer & Lemeshow test	NR
Direkvand-Moghadam et al. 2013 (14)	PE 58/610	PE 0.67 (0.59-0.76)	NA	PE Overall accuracy 91% (95% CI NR) Sn NR Sp NR	NA	NR	NR
Keikkala et al. 2013 (15)	PE 159/586 EO-PE 29	NA	PE*** 0.76 (0.72-0.81) EO-PE*** 0.86 (0.79-0.94)	NA	PE*** fixed at 10% FPR 39% (32-47%) 90% (fixed) EO-PE*** fixed at 10% FPR 69% (51-83%) 90% (fixed)	NR	NR
Kuc et al. 2013 (16)	PE 167/667 EO-PE 68/667 LO-PE 99/667	EO-PE NR LO-PE NR	EO-PE*** 0.88 (95% CI NR) LO-PE*** NR	EO-PE fixed at 10% FPR 64% (51-75%) 90% (fixed) LO-PE fixed at 10% FPR 45% (35-55%) 90% (fixed)	EO-PE*** fixed at 10% FPR 72% (59-83%) 90% (fixed) LO-PE*** fixed at 10% FPR 49% (38-60%) 90% (fixed)	NR	NR
Parra-Cordero et al. 2013 (17)	PE 83/2619 EO-PE 17/359 LO-PE 53/359	NA	EO-PE* NR LO-PE* NR	NA	EO-PE* fixed at 10% FPR 47% (95% CI NR) 90% (fixed) LO-PE* fixed at 10% FPR 29% (95% CI NR) 90% (fixed)	NR	NR
Scazzocchio et al. 2013 (18)	PE 136/5170 EO-PE 26/5170 LO-PE 110/5170	EO-PE NR	EO-PE** 0.95 (0.94-0.98) LO-PE*** 0.71 (0.66-0.76)	EO-PE fixed at 10% FPR 31% (95% CI NR) 90% (fixed)	EO-PE** fixed at 10% FPR 81%(95% CI NR) 90% (fixed) LO-PE*** fixed at 10% FPR 40%(95% CI NR) 90% (fixed)	Goodness-of-fit: Nagelkerke R	NR
Di Lorenzo et al. 2012 (19)	PE 25/2118 EO-PE 12/2118 LO-PE 13/2118	NA	Model B* EO-PE 0.89 (95% CI NR) Other models: NR	NA	Model A PE* fixed at 10% FPR 52% (95% CI NR) 90% (fixed) EO-PE* fixed at 10% FPR 67% (95% CI NR) 90% (fixed) LO-PE* fixed at 10% FPR 31% (95% CI NR)	NR	NR

					90% (fixed) Model B PE* fixed at 10% FPR 40% (95% CI NR) 90% (fixed) EO-PE*** fixed at 10% FPR 75% (95% CI NR) 90% (fixed)		
Kuijk et al. 2011 (20)	Recurrence EO-PE 28/407	NA	Recurrence EO-PE*** 0.65 (0.56-0.74)	NA	Recurrence EO-PE*** risk cut-off 6.2% 75% (55-89%)**** 54% (49-59%)****	Goodness of fit: Hosmer & Lemeshow test	Internal validation: Bootstrapping 200 samples shrinkage factor=0.74
North et al. 2011 (21)	PE 186/3529	PE 0.71 (0.706-0.714)§	NA	PE at 25% FPR 61% (54-68%) 75% (74-76%)	NA	Calibration plot	Internal validation: 10-fold cross validation AUC 0.71 (0.706-0.714)**** Sn 53% (48-58%) Sp 75% (74-76%)
Odibo et al. 2011 (22)	PE 42/452	NA	PE* 0.77 (0.63-0.81)	NA	PE* fixed at 20% FPR 60% (95% CI NR) 80% (fixed)	Goodness of fit	NR
Goetzinger et al. 2010 (23)	PE 293/3716	NA	PE*** 0.70 (0.65- 0.72)	NA	PE** score of ≥2 36% (31-43%) 87% (86-88%)	NR	NR
Poon et al. 2010b (24)	PE 165/8366 EO-PE 37/8366 LO-PE 128/8366	EO-PE 0.79 (0.72-0.87) LO-PE 0.80 (0.76-0.83)	EO-PE* 0.96 (0.956-0.964) LO-PE** 0.863 (0.855-0.87)	EO-PE fixed at 10% FPR 47% (23% to 65%) 90% (fixed) LO-PE fixed at 10% FPR 41% (33-50%) 90% (fixed)	EO-PE* fixed at 10% FPR 95% (82-99%) 90% (fixed) risk cut-off 1% Sn 87% Sp 93.5% risk cut-off 10% Sn 35% Sp 99.3% LO-PE** fixed at 10% FPR 57% (48-66%) 90% (fixed)	NR	External validation: by 2 studies
Validated by Park et al. 2013 (41)	PE 83/3014 EO- PE 12/3014 LO-PE 71/3014	EO-PE 0.76 (0.74-0.77) LO-PE 0.68 (0.66-0.69)	EO-PE* 0.93 (0.92 to 0.94)	EO-PE fixed at 10% FPR 40% (10-76%) 90% (fixed) LO-PE fixed at 10% FPR 22% (12- 32%) 90% (fixed)	EO-PE* fixed at 10% FPR 92% (62-99%) 90% (89.7-92%)	NR	NR
Validated by Farina et al. 2011 (42)	LO-PE 39/554	NA	LO-PE** 0.93 (0.88-0.98)	NA	LO-PE** fixed at 10% FPR 85% (73-96%) 90% (fixed)	NR	NR
Emonts et al. 2008 (25)	PE 101/151	PE NR	PE NR	PE risk estimate >0 67% (95% CI NR) 80% (95% CI NR)	PE*** (2 models) risk estimate >0 88% (95% CI NR) 88% (95% CI NR) risk estimate >0 88% (95% CI NR) 90% (95% CI NR)	NR	NR
***UK population*, *n* = 14 studies in addition to Poon 2010b (24) described above**							
Poon et al.	PE	EO-PE[A]	NA	EO-PE[A]	NA	NR	NR

2011 (26)	165/8366 EO-PE 37/8366 LO-PE 128/8366	0.90 (0.85-0.95) LO-PE[♣] 0.85 (0.83-0.88)		fixed at 10% FPR 76% (59-88%) 90% (fixed) LO-PE[♣] fixed at 10% FPR 52% (43-61%) 90% (fixed)			
Foidart et al. 2010 (27)	PE 90/270 EO-PE 30/270 LO-PE 60/270	EO-PE 0.75 (0.69-0.81)	EO-PE[*] 0.95 (0.91-0.98)	EO-PE fixed at 10% FPR 40% (23-59%) 90% (fixed)	EO-PE[*] fixed at 10% FPR 96% (81-99%) 90% (fixed)	NR	NR
Poon et al. 2010c (28)	PE 116/402 EO-PE 26/402 LO-PE 90/402	EO-PE 0.72 (0.65-0.77) LO-PE 0.78 (0.73-0.82)	EO-PE[*] 0.96 (0.93-0.98) LO-PE[*] 0.86 (0.82-0.90)	EO-PE fixed at 10% FPR 47% (13-79%) 90% (fixed) LO-PE fixed at 10% FPR 48% (24-68%) 90% (fixed)	EO-PE[*] fixed at 10% FPR 92% (75-99%) 90% (fixed) LO-PE[*] fixed at 10% FPR 66% (55-75%) 90% (fixed)	NR	NR
Poon et al. 2010a (29)	PE 165/8366 EO-PE 37/8366 LO-PE 128/8366	EO-PE 0.79 (0.72-0.87) LO-PE 0.80 (0.76-0.83)	NA	EO-PE fixed at 5% FPR 37% (13-50%) 95%(fixed) LO-PE fixed at 5% FPR 29% (22-38%) 95% (fixed)	NA	NR	NR
Leal et al. 2009 (30)	PE 128/1138	NA	PE[**] 0.82 (0.79-0.85)	NA	PE[**] fixed at 10% FPR 55% (95% CI NR) 90% (fixed)	NR	NR
Poon et al. 2009e (31)	PE 165/8366 EO-PE 37/8366 LO-PE 128/8366	EO-PE 0.79 (0.72-0.87) LO-PE 0.80 (0.76-0.83)	EO-PE[**] 0.95 (0.92-0.99) LO-PE[**] 0.863 (0.855-0.87)	EO-PE fixed at 10% FPR 47% (23-65%) 90% (fixed) LO-PE fixed at 10% FPR 41% (33-50%) 90% (fixed)	EO-PE[**] fixed at 10% FPR 89% (75-97%) 90% (fixed) LO-PE[**] fixed at 10% FPR 57% (48-66%) 90% (fixed)	NR	NR
Poon et al. 2009d (32)	PE 165/8366 EO-PE 37/8366 LO-PE 128/8366	EO-PE 0.79 (0.72-0.87) LO-PE 0.80 (0.76-0.83)	EO-PE[**,♣] 0.91 (0.86-0.96) LO-PE[**,♣] 0.81 (0.78-0.85)	EO-PE fixed at 10% FPR 47% (23-65%) 90% (fixed) LO-PE fixed at 10% FPR 41% (33-50%) 90% (fixed)	EO-PE[**,♣] fixed at 10% FPR 81% (65-92%) 90% (fixed) LO-PE[**,♣] fixed at 10% FPR 47% (38-56%) 90% (fixed)	NR	External validation: by 1 studies
Validated by Farina et al. 2011 (42)	LO-PE 39/554	NA	LO-PE[**] 0.75 (0.66-0.84)	NA	LO-PE[**] fixe at 10% FPR 44% (28-59%) 90% (fixed)	NR	NR
Poon et al. 2009c (33)	PE 128/1138 EO-PE 29/1138 LO-PE 99/1138	NA	EO-PE[*] 0.91 (0.84-0.97) LO-PE[*] 0.82 (0.77-0.86)	NA	EO-PE[*] fixed at 5% FPR 69% (95% CI NR) 95% (fixed) LO-PE[*] fixed at 5% FPR 34% (95% CI NR) 95% (fixed)	NR	NR
Poon et al. 2009b (34)	PE 127/627 EO-PE 29/627 LO-PE 98/627	NA	EO-PE[*] NR LO-PE[*] NR	NA	EO-PE[*] fixe at 5% FPR 93% (95%CI NR) 95% (fixed) LO-PE[*] fixe at 5% FPR 45% (95%CI NR)	NR	NR

					95% (fixed)		
Poon et al. 2009a (35)	PE 156/8051 EO-PE 32/8051 LO-PE 124/8051	NA	EO-PE* 0.85 (0.84-0.86) LO-PE*** 0.79 (0.78-0.80)	NA	EO-PE* fixe at 10% FPR 72% (95% CI NR) 90% (fixed) LO-PE*** fixed at 10% FPR 41% (95% CI NR) 90% (fixed)	NR	External validation: by 1 studies
Validated by Farina et al. 2011 (42)	LO-PE 39/554	NA	LO-PE*** 0.70 (0.60-0.79)	NA	LO-PE*** fixed at 10% FPR 35.9% (20.8-51) 90% (fixed)	NR	NR
Akolekar et al. 2008 (36)	PE 127/824 EO-PE 29/824 LO-PE 98/824	NA	EO-PE* 0.94 (0.88-0.99) LO-PE* 0.82 (0.77-0.86)	NA	EO-PE* fixed at 10% FPR 86% (68-96%) 90% (fixed) LO-PE* fixed at 10% FPR 49% (39-59%) 90% (fixed)	NR	NR
De Paco et al. 2008 (37)	PE 83/4293 PE without SGA 46/4293	NA	All PE** 0.81 (0.77-0.86) PE without SGA** 0.83 (0.77-0.89)	NA	All PE** fixed at 10% FPR 43% (33-55%) 90% (fixed) PE without SGA** fixed at 10% FPR 52% (37-67%) 90% (fixed)	NR	NR
Poon et al. 2008 (38)	PE 104/4619	PE 0.85 (95% CI NR)	NA	PE fixed 10% FPR 63% (95% CI NR) 90% (fixed)	NA	NR	NR
Plasencia 2007 (39)	PE 107/6015 EO-PE NR LO-PE NR	PE 0.81 (0.80-0.82) EO-PE 0.78 (0.77-0.80) LO-PE 0.80 (0.79-0.81)	PE** 0.85 (0.84-0.86) EO-PE** 0.91 (0.90-0.92) LO-PE** 0.84 (0.83-0.85)	PE fixed at 10% FPR 47% (95% CI NR) 90% (fixed) EO-PE fixed at 10% FPR 50% (95% CI NR) 90% (fixed) LO-PE fixed at 10% FPR 44% (95% CI NR) 90% (fixed)	PE** fixed at 10% FPR 62% (95% CI NR) 90% (fixed) EO-PE** fixed at 10% FPR 82% (95% CI NR) 90% (fixed) LO-PE** fixed at 10% FPR 52% (95% CI NR) 90% (fixed)	NR	External validation: by 2 studies
Validated by Farina 2011 (42)	LO-PE 39/554	LO-PE 0.72 (0.62-0.82)	NA	LO-PE fixed at 10% FPR 54% (38-69%) 90% (fixed)	NA	NR	NR
Validated by Herraiz 2009 (43)	PE 20/152 EO-PE 13/152 LO-PE 7/152	EO-PE 0.74 (0.60-0.89) LO-PE 0.65 (0.49-0.80)	EO-PE** 0.78 (0.64-0.92) LO-PE** 0.64 (0.48-0.80)	EO-PE fixed at 10% FPR 29% (95% CI NR) 90% (fixed) LO-PE fixed at 10% FPR 23% (95% CI NR) 90% (fixed)	EO-PE** fixed at 10% FPR 43%(95% CI NR) 90% (fixed) LO-PE** fixed at 10% FPR 23% (95% CI NR) 90% (fixed)	NR	NR
SCOPE population **, *n* = 1 study in addition to North et al 2011 (21) described above**							
Myers et al. 2013 (40)	EO-PE (Preterm PE) 47/3529	EO-PE (Preterm PE) 0.76 (0.67-0.84)	EO-PE (Preterm PE)*** 0.84 (0.77-0.91)	EO-PE (Preterm PE) fixed at 5% FPR 34% (22-48%) 95% (fixed)	EO-PE (Preterm PE)*** fixed at 5% FPR 45% (31-59%) 95% (fixed)	NR	Internal validation: 10-fold cross validation AUC 0.74 (0.735-0.744) Sn NR Sp NR

AUC, area under the curve; CI, confidence interval, EO-PE, early-onset pre-eclampsia; FPR, false positive rate; LO-PE, late-onset pre-eclampsia; NA, not applicable; NR, not reported; PE, pre-eclampsia; SCOPE, Screening for Pregnancy Endpoints; SGA, small-for-gestational-age; Sn, sensitivity; Sp, specificity; UK, United Kingdom.

~~A~~Report of best performing model

*Specialised model include maternal factors+uterine artery Doppler+blood test.
**Specialised model include maternal factors+uterine artery Doppler or Echo.
***Specialised model include maternal factors+blood test.
****Calculated from available data in tables.

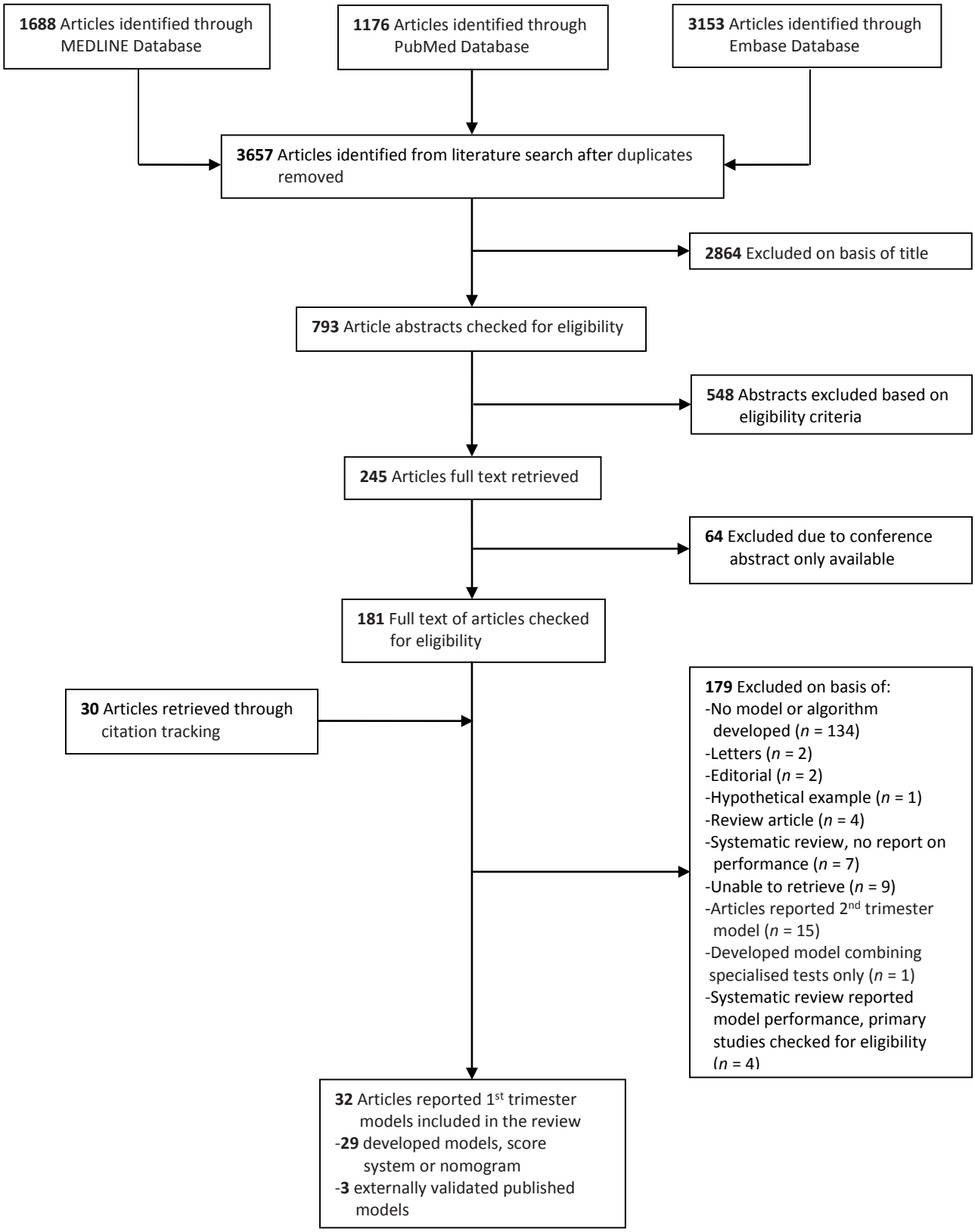

Figure S1. Quorum Flowchart.

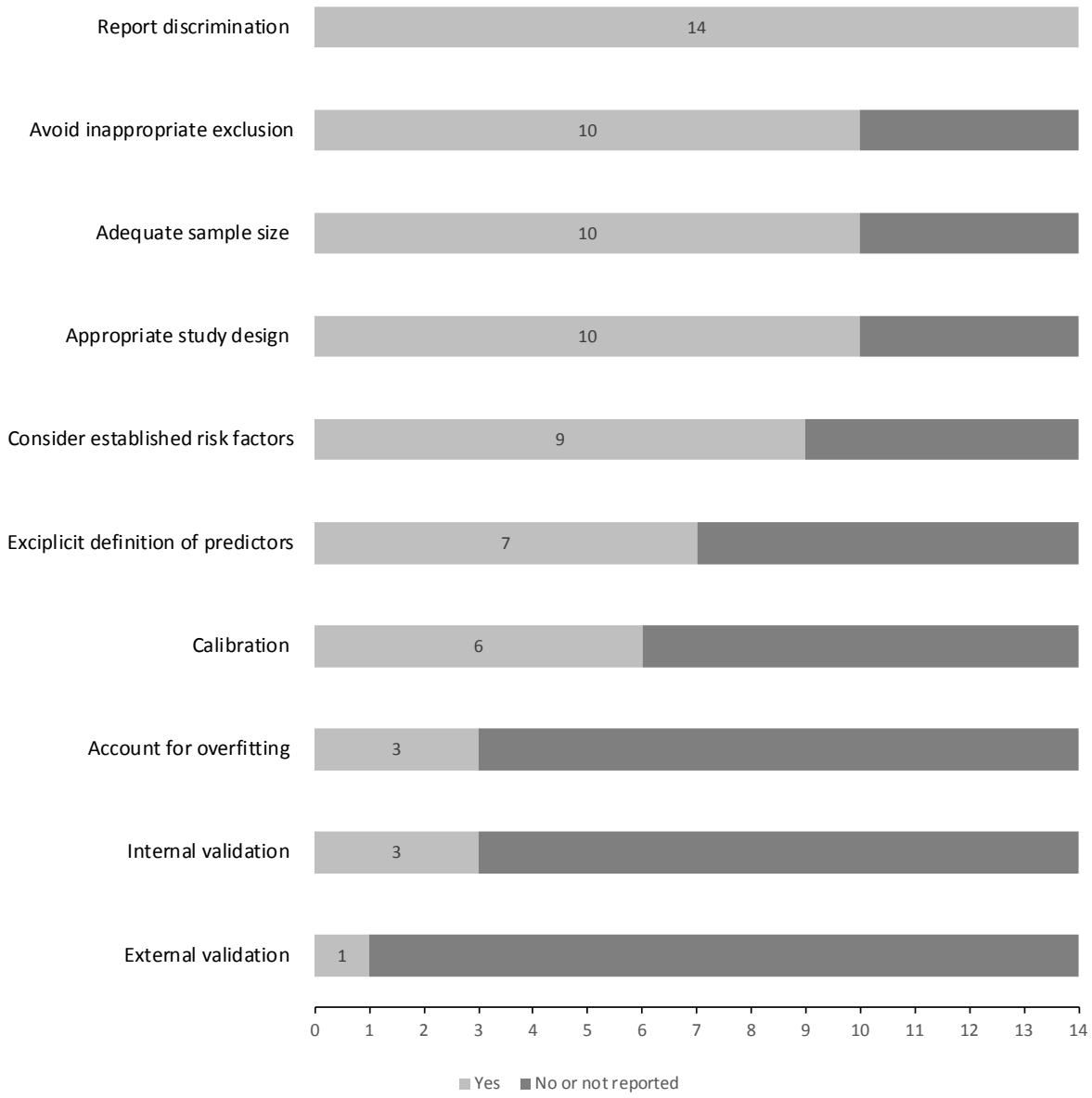

Figure S2. Risk of bias assessment of studies reporting risk prediction models for pre-eclampsia, *n* = 14 studies.