Pregnancy Hypertension 16 (2019) 48–66

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

Prediction models for preeclampsia: A systematic review

Annelien C. De Kat[a,b,*], Jane Hirst[a,b], Mark Woodward[a,b,c], Stephen Kennedy[b], Sanne A. Peters[a,b,c]

[a] The George Institute for Global Health, University of Oxford Le Gros Clark Building, South Parks Road, Oxford OX1 3QX, UK
[b] Nuffield Department of Women's & Reproductive Health, University of Oxford, Oxford, UK
[c] The George Institute for Global Health, University of New South Wales, Sydney, Australia

ABSTRACT

Background: Preeclampsia is a disease specific to pregnancy that can cause severe maternal and foetal morbidity and mortality. Early identification of women at higher risk for preeclampsia could potentially aid early prevention and treatment. Although a plethora of preeclampsia prediction models have been developed in recent years, individualised prediction of preeclampsia is rarely used in clinical practice.
Objectives: The objective of this systematic review was to provide an overview of studies on preeclampsia prediction.
Study design: Relevant research papers were identified through a MEDLINE search up to 1 January 2017. Prognostic studies on the prediction of preeclampsia or preeclampsia-related disorders were included. Quality screening was performed with the Quality in Prognostic Studies (QUIPS) tool.
Results: Sixty-eight prediction models from 70 studies with 425,125 participants were selected for further review. The number of participants varied and the gestational age at prediction varied widely across studies. The most frequently used predictors were medical history, body mass index, blood pressure, parity, uterine artery pulsatility index, and maternal age. The type of predictor (maternal characteristics, ultrasound markers and/or biomarkers) was not clearly associated with model discrimination. Few prediction studies were internally (4%) or externally (6%) validated.
Conclusions: To date, multiple and widely varying models for preeclampsia prediction have been developed, some yielding promising results. The high degree of between-study heterogeneity impedes selection of the best model, or an aggregated analysis of prognostic models. Before multivariable preeclampsia prediction can be clinically implemented universally, further validation and calibration of well-performing prediction models is needed.

1. Introduction

Globally, 10–15% of all maternal deaths are attributable to preeclampsia or eclampsia, a placentally derived disease of pregnancy [1,2]. Timely identification and management of preeclampsia can lead to significantly improved maternal and perinatal outcomes. However, even in settings with high-quality care, the severity and onset of the condition remain largely unpredictable, with high morbidity and mortality.

Risk prediction of preeclampsia and preeclampsia-related disorders has received much attention over the past two decades. Before 16 weeks' gestation, women at high risk of preeclampsia benefit from low-dose aspirin [3,4]. Moreover, increased vigilance for high-risk women throughout pregnancy can facilitate early identification and treatment, which should reduce the incidence of adverse outcomes. At the first antenatal visit, women are stratified into high or low-risk categories for the development of a range of pregnancy-related disorders, including preeclampsia, based on the presence of risk factors. However, individualised prediction models, especially for preeclampsia and its related disorders, are not currently available for use in clinical practice, despite various models having been developed.

To date, meta-analyses [5–9] have contributed to the literature for preeclampsia prediction and with single risk factors, and a 2016 review [10] provided a summary of prognostic models published up to July 2012. However, a comprehensive overview of the availability and predictive performance of multivariable predictive models for preeclampsia is lacking. To fill that knowledge gap, we conducted a systematic review as an extension to the 2016 paper. Moreover, as pregnancy is a dynamic process, we aimed to assess to what extent changes in risk factors during pregnancy have been taken into account in prediction models to date.

2. Methods

2.1. Search strategy

MEDLINE (PubMed) was searched on 10 January 2017 for published articles between 1 July 2012 and 10 January 2017. For reasons of consistency, the search terms published by Kleinrouweler et al. [10] were used, excluding terms for outcomes not associated with placenta-related pregnancy disorders. The outcomes were therefore "(abruption [tiab] OR growth restrict* OR preeclampsia [tiab] OR pre-eclampsia [tiab] OR pregnancy induced hypertension [tiab] OR HELLP [tiab] OR preterm deliver* [tiab] OR stillbirth OR "small-for-gestational-age" OR

* Corresponding author at: Julius Centre for Health Sciences and Primary Care, STR 6.131, P.O. Box 85500, 3508 GA Utrecht, The Netherlands.
E-mail address: a.c.dekat@umcutrecht.nl (A.C. De Kat).

https://doi.org/10.1016/j.preghy.2019.03.005
Received 15 November 2018; Accepted 11 March 2019
Available online 11 March 2019

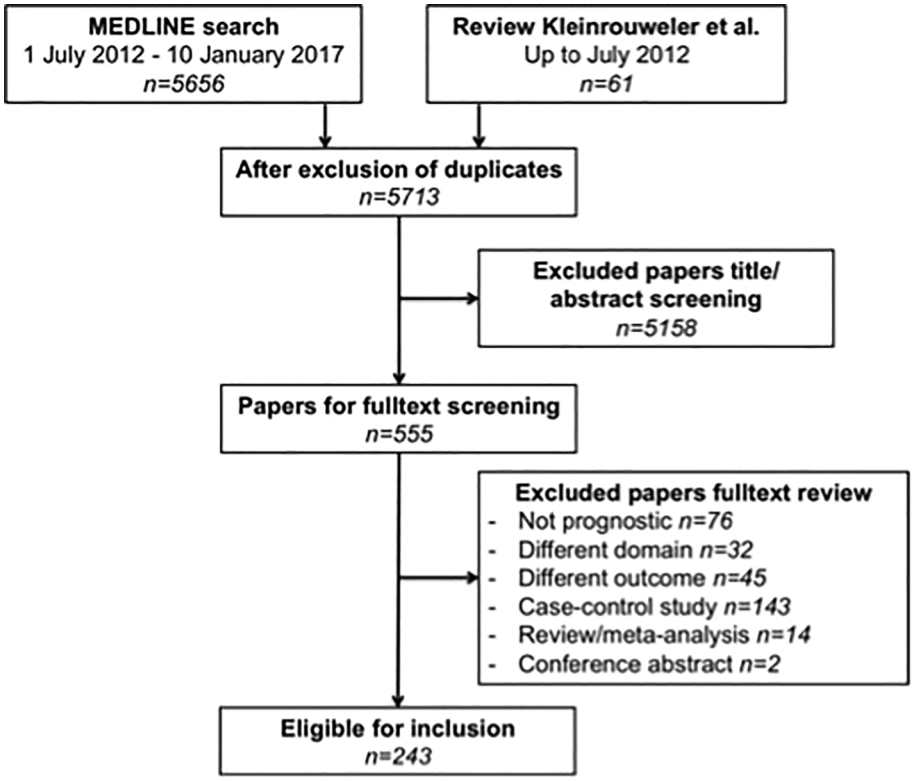

Fig. 1. Flow chart of literature screening process.

preterm birth [tiab] OR prematurity [tiab] OR "fetal death" [tiab] OR "perinatal mortality" [tiab])". See Appendix S1 for a detailed description of the search terms.

2.2. Study selection

Prognostic studies were included for the prediction of preeclampsia or preeclampsia-related disorders, e.g. HELLP (Hemolysis, ELevated liver enzymes, and Low Platelet count) syndrome, eclampsia, and pregnancy-induced hypertension, with at least one indicator of prediction model performance. The domain for the inference of the results was defined as pregnant women who could potentially develop preeclampsia or a preeclampsia-related disorder at a later time point in pregnancy. Studies assessing the outcome severity in women with current preeclampsia or hypertension were therefore excluded. In addition, studies restricted to women with pre-existing medical disorders, such as HIV/AIDS, antiphospholid syndrome or systemic lupus erythematosus, were excluded. If the method of participant selection was unclear, the corresponding author was contacted for clarification. Indicators of model performance included model discrimination, calibration and validation. The discrimination of a model is typically quantified using its receiver operating curve (ROC), which is a plot of sensitivity against one minus specificity across risk thresholds. The area under the ROC curve (AUC) is the probability of correctly identifying which of two individuals is more likely to have the outcome – a model with no prognostic value would have an AUC of 0.5. Model calibration indicates the degree to which the predicted and observed risks correspond to one another, typically quantified at the group level. Model validation is an assessment of whether the prediction model developed in one study population performs well in segments of the original population (also termed internal validation) or in a different population (also termed external validation). Included prediction models after full-text review were summarised based on the model performance listed above. AdK performed the paper screening and selection, in consultation with SP and SK.

2.3. Qualitative data synthesis

Data extraction was performed using a pre-specified extraction form. Study date, size, design, location and assessment of risk factor changes were recorded. Variables that were considered for prediction (candidate predictors) were recorded, as well as the variables that were included in the subsequent, 'final', prediction model (selected predictors). When multiple outcomes were considered in a single study, the prediction model with preeclampsia irrespective of severity or timing of gestation was presented as the main outcome for the purpose of comparability. The candidate and selected predictors were grouped according to the AUC, sensitivity/specificity or false positive/detection rate of the prediction model in order to see whether there was a global association of type of included predictor variables (such as serum markers or baseline characteristics) with model discrimination. Where available, the AUC of the final prediction models was recorded. Based on a previous review [10], the study populations and outcomes were expected to be too heterogeneous to perform an aggregated analysis. A meta-analysis was therefore not included in the pre-specified protocol.

2.4. Quality assessment

Studies that assessed the predictive capacity of a single prognostic factor, rather than assessing a combination of prognostic factors, were not included for quality assessment. Model development with a single prediction factor was aimed at assessing the association of a single variable with disease, while we aimed to include studies evaluating the best method to predict preeclampsia and preeclampsia-related disorders in a population. Studies in which the best prediction model had an AUC below 0.6 were furthermore not included for quality assessment, as a model with such poor discrimination between women who will and will not develop preeclampsia was deemed unlikely to be useful in clinical practice. The methodological quality of the remaining full-text papers was assessed using the Quality In Prognostic Studies (QUIPS) tool [11]. Studies were scored on risk of bias in the following

categories: study participation, study attrition, prognostic factor measurement, outcome measurement, and statistical analysis and reporting. 'Study confounding' is included in the QUIPS score, but is irrelevant in this context of risk prediction. Studies were selected for further analysis if they scored as 'low bias' on at least 3 of the 5 quality assessment categories.

3. Results

3.1. Systematic search

Fig. 1 shows a flow chart of the study selection process. Sixty-one papers were included for quality assessment from the previous review [10]. The updated systematic search yielded a further 5656 records. After full-text screening, the total number of included studies was 174. Following the quality assessment (Table S1), 70 studies with 68 prediction models including 425,125 women were selected for further review. From these 70, 21 studies were included from the Kleinrouweler review and 49 studies were included that had been published at a later date. The included studies are summarised in Tables 1–3. Most studies (76%) were based in Europe, USA or Australia. Study populations either comprised all pregnant women presenting for antenatal screening or a selection of women based on gestational age, parity, or presence of risk factors.

3.2. Outcome definition

Preeclampsia was relatively uniformly defined as a combination of de novo hypertension in pregnancy and proteinuria, with most studies adhering to the latest International Society for the Study of Hypertension in Pregnancy (ISSHP) consensus definition [12,13]. The definition changed slightly between 2001 and 2014, in the latter definition giving room to a diagnosis of preeclampsia without proteinuria in the presence of maternal organ dysfunction or uteroplacental dysfunction [13]. The greatest difference between studies arose in the definition of subgroups of timing and severity of disease. Sixty-five (87%) studies used 'all preeclampsia' as an outcome, 18 (26%) pregnancy-induced hypertension, 13 (19%) early-onset preeclampsia, 9 (13%) late-onset preeclampsia and 7 (10%) severe preeclampsia, including eclampsia and HELLP syndrome. Two studies solely considered severe preeclampsia [14,15].

3.3. Predictors

Table 1 lists the studies in which the final prediction models only included non-time-varying (i.e. parity or ethnicity) and time-varying (i.e. blood pressure) maternal characteristics. The prediction model in 2 (3%) studies only included non-time-varying maternal characteristics and 5 (7%) prediction models only included time-varying and non-time-varying maternal characteristics at baseline and/or throughout pregnancy. Twelve (17%) studies included maternal characteristics and ultrasound characteristics as predictor variables, of which 11 studies included both maternal and ultrasound characteristics in the final prediction model (Table 2). Maternal characteristics and biomarkers were assessed as candidate predictors in 15 (21%) studies (Table 2). From these, 10 studies included both variable types in the final model, 2 studies only included maternal characteristics and 3 studies only included biomarkers. Table 3 lists 35 (50%) studies that assessed maternal, ultrasound and biomarker characteristics as candidate predictors. Five studies included 1 predictor category in the final model, 8 studies included 2 categories and 22 studies included all three categories.

The most frequently used predictors were medical history (61% of models), body mass index (BMI) (59%), blood pressure (51%), parity (49%), uterine artery pulsatility index (UtA PI, 49%) measured using ultrasound, and maternal age (44%). In 91% of the models that included maternal baseline characteristics, blood pressure, or BMI as candidate predictors, these predictors were included in the final model.

3.4. Discrimination

Of all included models, the AUCs ranged from 0.61 [16] to 0.996 [17]. The study with the lowest AUC included 229 participants < 17 weeks' gestation, while the study with the highest AUC had 3529 participants between 22 and 25 weeks' gestation. The selected predictor variables in the final models seemed to be distributed independently of model AUC (Figs. 2–4). The AUCs of models with only maternal characteristics ranged between 0.77 and 0.89 (Table 1). The range of AUCs was 0.71–0.996 for models with the addition of ultrasound markers, and 0.61–0.90 for models with the addition of biomarkers (Table 2). The AUCs of models with included maternal characteristics, ultrasound markers and biomarkers as predictors ranged between 0.76 and 0.97. Where AUC was not reported as a measure of model discrimination, the detection rate was used in some cases. Models with a fixed 10% false positive rate exhibited a range of detection between 35 [18]-73%[19]. In other words, accepting a chance of 10% of incorrectly classifying someone at 'high risk', 73% of preeclampsia cases could potentially be detected using a model that included serum markers – placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) – and the mean arterial pressure at 35–37 week's gestation, compared to 35% with a set of maternal characteristics assessed between 9 and 13 weeks' gestation.

3.5. Timing of prediction

Most studies (87%) made a risk assessment at a set time point in pregnancy, sometimes coinciding with a clinically relevant event such as first trimester screening. Other studies (13%) assessed the predictive capacity of risk factors measured at multiple time points. In a study of 305 participants, changes in maximal capillary density (MCD) in the intervals 20–24 and 27–32 weeks' gestation were simultaneously included as significant predictors in the final prediction model, with an AUC of 0.94 [20]. Model performance with both measurements was not compared to a model with a single measurement at either time point. A larger study of 12,996 women included blood pressure measurements at various time points during pregnancy, leading to a prediction model at each time point [21]. The resulting AUCs increased with advancing gestational age. While this prediction model is illustrative of varying predictive performance with gestational age, it does not provide an updated individual risk throughout pregnancy, as prior blood pressure measurements were not included in the model. Overall, the trimester in which risk factors were assessed did not have a clear association with model performance (Figs. 2–4).

3.6. Validation and calibration

The majority of models were neither internally nor externally validated. Three studies divided their study population data into training and validation datasets [22–24]. There was high AUC concordance for predicting preeclampsia in the training and validation dataset in two studies: 0.83 in both training and validation datasets, [22] and 0.76 in training and 0.78 in the validation dataset [23]. The third study reported a somewhat larger difference, with an AUC of 0.73 in the training and 0.68 in the validation dataset [24]. Four papers externally validated different prediction models. In each case, the external validation was performed in a similar demographic and geographical setting to where the model was developed [16,21,25]. Two studies externally validated two prediction models that had been developed in a different patient setting [26,27]. One algorithm was developed in the UK and validated in a population from multiple European clinics (UK, Belgium, Spain, Italy and Greece) [27,28]. The validation study found similar indices of discrimination in the development and validation

Table 1
Characteristics of included studies: prediction models with maternal characteristics.

Study	Outcome	Population	Study design	Country, year	Study size	Candidate Predictors	Timing (weeks of gestation)	Dynamic changes?	Final model and model performance
Maternal characteristics									
De Paco et al. 2008 [33]	PE	Women attending routine care with singleton pregnancies	Prospective cohort	UK 2006	4617	**Maternal characteristics** Incl. age, ethnicity, smoking/ alcohol, medical history, parity, obstetric history, BMI Maternal cardiac output	11–14	No	Maternal weight, ethnicity, parity, history of PE, MoM of cardiac output AUC 0.81
Poon et al. 2008 [34]	PE DBP ≥90 on 2 occasions > 20 weeks with ≥300 mg/24hr or ≥2+ on dipstick (1988 definition ISSHP)	Singleton pregnancies, women attending routine screening	Prospective cohort	UK 2006	5193	**Maternal characteristics** Incl. age, ethnicity, smoking/ alcohol, medical history, obstetric history, family historyMAP	11–14	No	Maternal characteristics, MAP AUC 0.85
Poon et al 2010 [35]	PE (early/late) DBP ≥90 on 2 occasions > 0 weeks with ≥300 mg/24hr or ≥2+ on dipstick (1988 definition ISSHP)	Women with singleton pregnancies	Prospective cohort	UK 2006–2007	8366	**Maternal characteristics** Incl. age, ethnicity, smoking/ alcohol, medical history, obstetric history, family history	11–14	No	Race, history of hypertension, parity, prior PE, type of conception Early PE: AUC 0.79 Late PE: AUC 0.80
Wright et al 2012 [36]	PE ≥140/90 on at least 2 occasions with 3 g/24 h proteinuria or ++ on dipstick	Women attending first routine visit Singleton pregnancies delivering phenotypically normal live birth or stillbirth > 24 weeks	Prospective cohort	UK 2006–2010	58,884	**Maternal characteristics** Age, race, method of conception, smoking, medical history, obstetric history, family history	11–14	No	"Maternal factors", UtA PI, MAP 10% FPR: PE < 34 wks DR 90% PE < 37 wks DR 72% PE < 42 wks DR 57%
Wright et al 2015 [37]	PE ≥140/90 on at least 2 occasions with 3 g/24 h proteinuria or ++ on dipstick > 20 weeks	Women who attended routine first visit Singleton pregnancy, normal live birth or stillbirth > 24 weeks	Prospective cohort	UK 2006–2014	120,492	**Maternal characteristics** Age, race, method of conception, smoking, medical history, family history, obstetric history, BMI	11–13	No	Age, height, race, SLE/APS, IVF, prior PE, previous GA at delivery, chronic hypertension, DM, family history of PE (Competing risks model Update of prior model 5-fold cross-validation within cohort. Results stratified by parity and Afro-Caribbean origin.)
MacDonald-Wallis et al 2015 [21]	PE ≥140/90 with ≥1+ on dipstick on 2 occasions > 20 weeks	Population-based	Prospective cohort	UK ALSPAC: 1991–1992 SWS: 1998–2002	12996/3005 (training/ validation)	**Maternal characteristics** Age, parity, education, social class, ethnicity	< 18, 20, 25, 28, 31, 34, 26	No (each time point separately)	BMI, height, age ≥35, parity, smoking, essential hypertension, previous gestational hypertension, diabetes, previous gestational diabetes, non-white ethnicity, baseline MAP, BP At X weeks AUC 0.77–0.88
Guy et al 2017 [38]	PE Definition: ISSHP 2001	Women attending routine hospital visit	Prospective cohort	UK 2015	2764	**Maternal characteristics** BMI, hypertension, race, cardiac output, stroke volume, heart rate, cardiac power, thoracic fluid, ventricular ejection time, total peripheral resistance, MAP	35–37	No	Final model PE: "history", HR, MAP AUC 0.893

Table 2
Characteristics of included studies: prediction models with maternal characteristics and ultrasound markers or biomarkers.

Study	Outcome	Population	Study design	Country, year	Study size	Candidate Predictors	Timing (weeks of gestation)	Dynamic changes?	Final model and model performance
Maternal characteristics and ultrasound markers									
Arakaki et al 2015 [39]	PIH or PE ≥140/90 > 20 weeks on 2 occasions (with > 0.3 g/24 h proteinuria or protein/creatinin ratio > 0.30)	Singleton pregnancies with birth > 24 weeks and no fetal abnormalities	Prospective cohort	Japan 2011–2013	1362	**Maternal characteristics** Age, parity, BMI **Ultrasound** Placental volume, UtA Doppler	11–13	No	PIH < 34 weeks: placental volume, UtA PI AUC 0.832
Caradeux et al. 2013 [40]	PE ≥140/90 > 20 weeks on 2 occasions with > 300 mg/24hr or > 1+ on dipstick Early PE: < 34 weeks	Patients attending 1st trim ultrasound	Prospective cohort	Chile	627	**Maternal characteristics** Age, weight, height, race, smoking, parity, gravidity, priorPE, HT, DM, family history PE, BP, BMI **Ultrasound** UtA PI	11–14	No	Early PE: age, parity, prior PE, hypertension, weight, SBP, DBP, MAP, UtA PI, preterm labor history 5% FPR: 62.5% DR
Poon et al 2009 [41]	PE (early/late) DBP ≥90 on 2 occasions > 20 weeks with ≥300 mg/24hr or ≥2+ on dipstick (1988 definition ISSHP)	Women attending routine first visit	Prospective cohort	UK 2006–2007	8366	**Maternal characteristics** Incl. age, race, smoking, history, meds, parity, MAP **Ultrasound** UtA PI	11–14	No	Maternal risk factors, lowest UtA PI, MAP AUC early PE: 0.95 AUC late PE: 0.86
Gurgel Alves et al. 2014 [42]	PE > 20 weeks DBP ≥90 on 2 occasions with ≥300 mg/24 h or ≥2+ on dipstick	Women attending routine first-trimester screening	Prospective cohort	Brazil 2009–2011	550	**Maternal characteristics** Age, ethnicity, BMI, method of conception, smoking, alcohol, drugs, medical/obstetric/family history **Ultrasound** UtA PI, ophthalmic artery Doppler	11–14	No	Nulliparity, prior PE, family history of PE, UtA PI/ophthalmic artery first diastolic peak velocity AUC 0.83
Harrington et al. 1997 [43]	PE ≥140/90 with > 300 mg/24 h proteinuria	Women with singleton pregnancies	Prospective cohort	UK	626	**Maternal characteristics** Gestational age, race, parity, indication for referral, smoking, marital status **Ultrasound** UtA Doppler	12–16	No	Gestational age, bilateral notch, UtA velocity, UtA PI, UmA PI Sens 93% spec 85%
Kleinrouweler et al. 2013 [44]	PE ISSHP definition 2001	Nulliparous women who had a second-trimester UtA Doppler examination	IPD	Multicentre	6708	**Maternal characteristics** Country, age, BMI, smoking, ethnicity, alcohol, SBP **Ultrasound** UtA PI	2nd trimester	No	SBP, BMI, UtA RI, bilateral notch AUC 0.85
Praciano de Souza et al. 2016 [45]	PE DBP ≥90 on 2 occasions > 20 weeks in previously normotensive women with ≥300 mg/24 h proteinuria or ≥2+ on dipstick	Pregnant women who underwent a second trimester morphology scan	Prospective cohort	Australia 2011–2014	372	**Maternal characteristics** Age, ethnicity, BMI, conception method, smoking, alcohol, drugs, medical/obstetric/family history, MAP **Ultrasound** UtA PI, ophthalmic artery	18–23	No	BMI, prior PE, MAP, UtA PI, ethnicity, ophthalmic artery peak ratio AUC 0.71
Onwudiwe et al. 2008 [17]	PE (early < 34 weeks) BP ≥ 140/90 on 2 occasions with ≥300 mg/24 h or ≥2+ on dipstick > 20 weeks	Women attending second-trimester screening	Prospective cohort	UK 2006–2007	3529	**Maternal characteristics** Incl. age, ethnicity, smoking/ alcohol, medical history, obstetric history, family history MAP **Ultrasound** UtA PI	22–25	No	Early PE: maternal factors, MAP, UtA PI AUC 0.996

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Table 2 (*continued*)

Study	Outcome	Population	Study design	Country, year	Study size	Candidate Predictors	Timing (weeks of gestation)	Dynamic changes?	Final model and model performance
Papageorghiou et al. 2005 [46]	PE DBP ≥90 on 2 occasions in previously normotensive women with ≥300 mg/24 h proteinuria or ≥2+ on dipstick	Singleton pregnancies routine screening	Prospective cohort	Multicentre (10) 1999–2002	16,806	**Maternal characteristics** Incl. age, race, smoking, history, meds, parity **Ultrasound** UtA PI	22–24	No	Race, smoking, history of hypertension, parity, prior PE, UtA PI AUC 0.79
Yu et al 2005 [22]	PE ≥90 on 2 occasions in previously normotensive women with ≥300 mg/24 h proteinuria or ≥2+ on dipstick	Unselected low-risk women, singleton pregnancies	Prospective cohort	UK (7 centres) 1999–2004	15392/15392	**Maternal characteristics** Incl. age, race, height, weight, smoking, alcohol, history, obstetric history, family history **Ultrasound** UtA PI	22–24	No	History of PE, ethnicity, previous term live birth, smoker, bilateral notch, UtA PI AUC 0.83
Lai et al 2013 [47]	PE (intermediate/late) ≥140/90 on 2 occasions > 20 weeks with ≥300 mg/24 h proteinuria or ≥2+ on dipstick	Routine third trimester screening	Prospective cohort	UK 2011–2012	4855	**Maternal characteristics** Age, race, method of conception, smoking, medical/obstetric history, family history, parity, BP **Ultrasound** UtA PI, fetal biometry	30–33	No	Age, weight, height, Afro-Caribbean origin, UtA PI Intermediate PE: AUC 0.84 Late PE: AUC 0.79
Arakaki et al 2017 [48]	PIH or PE ≥140/90 on 2 occasions (with ≥0.3 g/24 h proteinuria or protein/creat ratio > 0.30 > 20 weeks)	Normotensive women who delivered ≥ 37 weeks	Prospective cohort	Japan 2012–2013	814	**Maternal characteristics** Age, BMI, SBP **Ultrasound** UmA PI and RI	36	No	UmA PI, SBP FPR 10% DR 44%
Maternal characteristics and biomarkers									
Van Kuijk et al. 2011 [49]	Recurrent early-onset PE De novo ≥140/90 > 20 weeks with de novo ≥300 mg/24 h proteinuria	Women with early-onset PE in prior pregnancy and with a following pregnancy	Prospective cohort	Nether-lands 1993–2008	407	**Maternal characteristics** Prior SGA, duration of index pregnancy, BMI, hypertension **Biomarkers** Fasting blood glucose	Preconception	No	Glucose, hypertension, GA at delivery, prior SGA, maternal BMI AUC 0.65
Van Kuijk 2014 [16]	PE recurrence ≥140/90 > 20 wks with ≥300 mg/24 h proteinuria "Maternal placental dysfunction"	GA < 17 wks, preceding pregnancy with EO-PE or HELLP	Prospective cohort	Nether-lands 2008–2012	229	External validation model above	< 17	No	External validation model above AUC 0.61
Myatt et al. 2012 [50]	PE Severe PE: HELLP and/or eclampsia ≥140/90 on 2 occasions with ≥0.3 g/24 h proteinuria or 2+ on dipstick or > 0.35 protein/creatinin ratio	Low-risk nulliparous women	Cohort nested within RCT	USA	2394	**Maternal characteristics** Age, BMI, family history, smoking and alcohol, no. of sex partners, WHR, blood pressure **Biomarkers (case-control study)** Blood count, ADAM12, PAPP-A, PP-13, sFlt-1, endoglin, PIGF	9–13	No	Race, SBP, BMI, education AUC 0.65
Schneuer et al. 2012 [51]	PE ≥140/90 > 20 weeks with proteinuria	Women with singleton pregnancy attending first trimester Down syndrome screening	Prospective cohort	Australia 2006	2989	**Maternal characteristics** Age, parity, smoking, weight, prior PE or GH **Biomarkers** PAPP-A, beta-hCG, PP13	10–14	No	Parity, weight, age, prior hypertension, β-hCG, PP13 AUC 0.72
Schneuer et al. 2013 [52]	PE "Proteinuric or non-proteinuric hypertension > 20 weeks"	Pregnant women attending first trimester Down screening	Prospective cohort	Australia 2006	2681	**Maternal characteristics** Age, weight, smoking, parity, ethnicity, prior hypertension/diabetes **Biomarkers** sFlt-1, PlGF, PAPP-A	1st trimester	No	PlGF, sFlt-1, PAPP-A, weight, smoking, parity, prior diabetes, prior hypertension, high BP during pregnancy, country of birth AUC 0.76

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Table 2 (*continued*)

Study	Outcome	Population	Study design	Country, year	Study size	Candidate Predictors	Timing (weeks of gestation)	Dynamic changes?	Final model and model performance
Goetzinger et al. 2010 [53]	PE > 140/90 on 2 occasions with ≥0.3 g/24 h proteinuria or ≥1+ on dipstick > 20 weeks	Women with singleton gestations (without aneuploidies)	Retrospective cohort	USA 2003–2009	3716	**Maternal characteristics** Incl. age, race, chronic hypertension, smoking/alcohol, BMI **Biomarkers** PAPP-A, beta-hcG	11–14	No	History of pre-gestational diabetes, maternal BMI > 25, African-American race, PAPP-A < 10th percentile AUC 0.69
Cohen et al. 2014 [54]	PE New onset hypertension (> 140/90 on 2 occasions) with coexistent proteinuria	All women who delivered in time period	Retrospective cohort (included women who delivered)	USA 2007–2010	2199	**Maternal characteristics** Height, weight, race, tobacco use, history of chronic hypertension, age, parity **Biomarkers** PAPP-A, msAFP, beta-hCG	10–13 15–22	No	PAPP-A, msAFP AUC 0.77
Kenny et al. 2014 [24]	PE ≥140/90 on 2 occasions and ≥300 mg/24 h or ≥2+ on dipstick or protein:creatinin ratio ≥30 mg/mmol	Nulliparous women with singleton pregnancies	Prospective cohort SCOPE Study	New Zealand, Australia, UK, Ireland 2004–2011	3747/1876 (training validation)	**Maternal characteristics** Age, ethnicity, marital status, SES, education, work, gravidity, obstetric history, smoking, BMI, BP **Biomarkers** Angiogenin, BMP, CRP, cystatin C, elafin, ICAM-1, IL-1Ra, leptin, leptin receptor, PlGF, TIMP-1	14–16 and 19–21 (ultrasound)	No	PlGF, MAP, BMI, high fruit intake, family history of PE AUC 0.73 training AUC 0.68 validation
Stamilio et al. 2000 [14]	Severe PE ≥160/110 with ≥5 g/24 h proteinuria or ≥3+ on dipstick, oliguria < 500 mL/24 h, cerebral/visual disturbances, epigastric pain & pulmonary edema/cyanosis	Singleton pregnancies	Retrospective cohort	USA 1995–1997	1998	**Maternal characteristics** Age, weight, race, (obstetric/family/medical) history, smoking **Biomarkers** hCG, AFP, E2/E3	15–20 (serum) 24–28 (MAP)	No	Previous PE, nulliparity, MAP, conjugated estradiol concentration AUC 0.75
Zhou et al. 2012 [55]	PE ≥140/90 on 2 occasions with ≥300 mg/24 h proteinuria or ≥1+ on dipstick > 20 weeks	Low risk pregnant women	Prospective cohort study	China 2009–2010	1015	**Maternal characteristics** Age, BMI **Biomarkers** TG, TC, HDL-c, LDL-c, ApoA1, ApoB, UA	20	No	TG, HDL-c, uric acid AUC 0.77
Ghojazadeh 2013 [56]	PE ≥140/90 with ≥300 mg/24 h proteinuria or ≥1+ dipstick	Nulliparous women, no comorbidities	Prospective cohort	Iran 2009–2011	739	**Maternal characteristics** Age, education, occupation, income, weight, height, parity, gravidity, disease history **Biomarkers** Ht	24–32	No	Age, education, BMI, gestational age, Ht, roll over test result (> 20 mmHg DBP increase) AUC 0.90
Andersen et al. 2016 [57]	PE GH > 140/90 on 2 occasions < 20 weeks with ≥0.3 g/24 h proteinuria or ≥1+ on dipstick	All pregnant women	Prospective cohort	Denmark 2010–2012	1909	**Maternal characteristics** Age, BMI, smoking, parity, parental country of origin **Biomarkers** sFlt-1, PlGF	20–34	No	PlGF AUC 0.755
Chaiworapongsa et al. 2013 [15]	Late PE, severe late PE ≥140/90 on 2 occasions with ≥300 mg/24 h proteinuria or ≥1+ dipstick twice or ≥2+ dipstick once Late PE: > 34 weeks Severe PE: ACOG criteria	Singleton gestation 6–22 weeks, no preterm labor or PE at time of enrollment, no fetal anomaly, no serious maternal disease	Prospective cohort	Chile 2003–2006	1269	**Maternal characteristics** Age, tobacco use, parity, PE history, BMI, storage time of lab specimen **Biomarkers** sVEGFR-1, sEng, PlGF	30–34	No	Severe late PE: age, BMI, parity, PE history, PlGF/sEng AUC 0.88

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Table 2 (*continued*)

Study	Outcome	Population	Study design	Country, year	Study size	Candidate Predictors	Timing (weeks of gestation)	Dynamic changes?	Final model and model performance
Masse et al. 1993 [58]	PE ACOG definition 1972. Incl. normal blood pressure 6 weeks post-partum	Nulliparous women without DM, cardiovascular disease or renal disease	Prospective cohort	Canada 1989–1991	1366	**Maternal characteristics** LMP, family history of PE or hypertension, height, weight, MAP **Biomarkers** Uric acid, total protein, albumin, transferrin, haptoglobin, ferritin, iron, sodium, potassium, calcium, magnesium, urea, creatinine, antithrombin III, progesterone, E3, microalbuminuria	15–24 25–34	No	15–24 weeks: SBP, MAP, microalbumin, progesterone, BMI 25–34 weeks: MAP, MCV, progesterone, weight change, transferrin, urine sodium, BMI AUC 0.809
Widmer et al. 2015 [59]	PE ≥ 140/90 on at least 2 occasions with protein/creatinin ratio ≥ 0.3, protein > 1 g/L, + + on dipstick	Women with risk factors for PE and delivered at a viable gestation	Prospective cohort	8 countries 2006–2009	5331	**Maternal characteristics** Age, BMI, parity, smoking, aspirin, BP, singleton **Biomarkers** sFlt-1, PlGF, sEng	< 20 23–27 32–35	No	Age, BMI, smoking, singleton, hypertension, history of hypertension, tx for hypertension 20 wks: + sEng AUC 0.74 27 wks: + PlGF 0.77 35 wks: + sEng 0.89

cohorts, although the confidence intervals in the validation study were larger despite a larger study population (9041 compared to 1058 participants) [27]. Although model discrimination was similar to that of the developed models in the second algorithm, the predictive performance for preeclampsia ≥ 34 weeks' gestation was poor (AUC 0.578) and the performance for predicting preterm preeclampsia could not be accurately assessed due to its low incidence (n = 5) [26]. In one study that externally validated a prediction model at 28 weeks' gestation, model calibration indicated a general overestimation of the risk of preeclampsia, leading to a re-calibrated model [21].

4. Discussion

In current clinical guidelines, antenatal screening for preeclampsia and related disorders only takes account of single risk factors, such as age and parity, that are independently associated with the risk of disease occurrence. In this systematic review of prediction models of placentally-derived pregnancy disorders, most models included medical history, BMI, blood pressure, parity, uterine artery pulsatility index (UtA PI) and maternal age; fewer models included additional biomarkers or emerging risk factors. The performance of the models did not seem to be associated with the choice of predictor variables. The current clinical relevance of these prediction models seems limited, as few were externally validated or calibrated. Furthermore, to date there is no prospective study that has assessed the accuracy of risk prediction with one or more selected algorithms, in comparison to the current single risk factor screening.

A recent multi-centre trial assessing the efficacy of aspirin treatment was the first to employ a preeclampsia risk prediction algorithm in a clinical setting to determine who would be eligible to receive aspirin prophylaxis or placebo [29]. The algorithm included maternal baseline characteristics, mean arterial pressure, UtA PI, and the serum markers PlGF and pregnancy-associated plasma protein A (PAPP-A). Women with a predicted risk of ≥ 1% were considered to be at high risk for preeclampsia and were therefore eligible for aspirin or placebo treatment. The resulting odds ratio (95% confidence interval) of preeclampsia for aspirin users was 0.38 (0.20–0.74) [29], compared to 0.90 (0.84–0.97) in a population identified as high-risk for preeclampsia with a single risk factor [30]. The larger treatment effect suggests that the use of a multifactorial prediction model could potentially refine the selection of women in need of increased vigilance and prophylaxis. However, the risk algorithm was employed with little evidence for its clinical utility. It therefore remains doubtful whether this method of patient selection can be extrapolated to a different population.

Besides predicting disease occurrence, there may be a clinical benefit in identifying women with preeclampsia who are most likely to have a severe outcome (such as eclampsia or organ failure). A selection of risk algorithms for the prediction of preeclampsia severity has already been identified and validated in several study populations [31,32]. The next step for the prediction of preeclampsia occurrence may be to test and compare multiple promising models in diverse populations in order to narrow down the options for subsequent testing in clinical practice, with more basic tools required in low-income settings.

Several aspects of this systematic review warrant discussion. The heterogeneity amongst the included studies is the main limiting factor in drawing a single conclusion on the benefits and reliability of preeclampsia prediction. Furthermore, the comparison of the various prediction models by model performance is subject to bias, as these values are strongly influenced by study-specific factors such as sample size and risk of preeclampsia in the population, which varied across studies. Studies that assessed the predictive performance of a single risk factor were not included, in order to focus solely on the results of model development. While this has ensured higher quality, comparing the efficacy of single factor versus multifactorial prediction algorithms is not possible, which may lead to an overoptimistic view of multivariable

Table 3
Characteristics of included studies: prediction models with maternal characteristics, ultrasound markers and biomarkers.

Study	Outcome	Population	Study design	Country, year	Study size	Candidate Predictors	Timing (weeks of gestation)	Dynamic changes?	Final model and model performance
Maternal characteristics, ultrasound and biomarkers									
Antonios et al. 2013 [20]	PE > 140/90 on 2 occasions with ≥300 mg/24 h, protein/creatinin > 30 mg/mmol or ≥2+ on dipstick	Singleton pregnancies without preexisting medical conditions (besides chronic hypertension)	Prospective cohort	UK	305	**Maternal characteristics** Age, weight, height, medical history, prior PE, family history of CVD, drug history, smoking, alcohol, recr drugs, BP **Ultrasound** UAD PI **Biomarkers** Electrolytes, urea, creatinine, uric acid, glucose, insulin, total cholesterol, triglycerides, full blood count **Other** MCD	11–16 (baseline) 20–24 27–32 34–38 +5–15	**Yes** MCD changes	SBP, DBP, pre-existing hypertension, prior PE, UtA PI, MCD change 20–24 weeks, MCD change 27–32 weeks AUC 0.94
Audibert et al. 2010 [60]	PE ≥140/90 mm Hg on 2 occasions at least 4 h apart and proteinuria ≥ 0.3 g/d after 20 weeks	Women presenting for trisomy 13 screening	Prospective cohort	Canada 2006–2008	1000	**Maternal characteristics** Age, history, ethnicity, medication **Ultrasound** Uterine artery Doppler **Biomarkers** PAPP-A, ADAM12, PIGF, beta-hCG, inhibin-A, PP13, M-PI, L-PI	11–13	No	"Maternal characteristics" + PIGF, inhibin A, PAPP-A, L-PI AUC 0.82
Austdal et al. 2015 [61]	PE ≥140/90 with ≥0.3 g/24 h on 2 occasions or ≥1+ on dipstick > 20 weeks	Nulliparous or PE/GH in a prior pregnancy	Prospective cohort	Norway 2010–2012	599	**Maternal characteristics** Age, BMI, smoking, medical/obstetric history, MAP **Ultrasound** UtA PI **Biomarkers** Urine and serum ^{1}H NMR spectra	11–13	No	Urine hippurate/ creatinin ratio, MAP, age, UtA PI AUC 0.778
Baschat et al. 2014 [62]	PE ≥140/90 on 2 occasions > 20 weeks with proteinuria	Women presenting for 1st trimester screening	Prospective cohort	USA 2007–2010	2441	**Maternal characteristics** Ethnicity, age, medical/obstetric history, BMI, BP **Ultrasound** UtA PI, notching **Biomarkers** PAPP-A, beta-hCG	1st trimester	No	Nulliparity, history of hypertension, history of prior PE, MAP, PAPP-A AUC 0.82
Chang et al. 2016 [63]	PE ≥140/90 on 2 occasions > 20 weeks Early PE: < 34 weeks FGR: BW < p10	Screening and delivery at study hospital, singleton pregnancy, natural conception Exclusion: delivery < 28 wks, smoking	Retrospective study of prospective cohort	China 2010–2011	4453	**Maternal characteristics** Age, BMI, parity, PE history, PE family history, autoimmune disease, MAP **Ultrasound** UtA Doppler **Biomarkers** PlGF, sEng, PP-13	11–13	No	Early onset PE with FGR: MAP, UtA Doppler, PAPP-A, PlGF AUC 0.76
Di Lorenzo et al. 2012 [64]	PE ACOG definition > 140/90 > 20 weeks in previously normotensive woman with > 0.3 g/24 h Early/late-onset 34 weeks	Pregnant women in "third level" hospital invited for ultrasound screening	Prospective cohort	Italy 2007–2009	2118	**Maternal characteristics** Age, BMI, race, parity, conception, smoking, DM, GDM, sex child, chronic hypertension **Ultrasound** Bilateral notch, UtA PI **Biomarkers** B-hCG, PAPP-A, PIGF, PP-13	11–14	No	Chronic hypertension, UtA PI, PIGF Model performance not described

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Table 3 (*continued*)

Study	Outcome	Population	Study design	Country, year	Study size	Candidate Predictors	Timing (weeks of gestation)	Dynamic changes?	Final model and model performance
Diguisto et al. 2017 [65]	PE ≥140/90 with > 0.3 g/24 h proteinuria in the absence of UTI > 20 weeks in previously normotensive women	High-risk pregnancies: chronic hypertension/DM/ nulliparity/age > 38/IVF/BMI > 25 kg/prior PE, SGA, or placental abruption	Prospective cohort	France 2007–2011	226	**Maternal characteristics** Age, BMI, medical/obstetric history, platelet therapy **Ultrasound** UtA PI/RI **Biomarkers** sFlt-1, PlGF	11–13	No	PlGF, low UtA PI, bilateral notch, antiplatelet therapy AUC 0.76
Goetzinger et al. 2013 [66]	PE > 140/90 on 2 occasions with ≥0.3 g/24 h proteinuria or ≥1+ on dipstick > 20 weeks	Women presenting for first-trimester aneuploidy screening	Prospective cohort	USA 2008–2010	578	**Maternal characteristics** Age, race, BMI, nulliparity, tobacco, chronic hypertension, DM **Ultrasound** UtA PI **Biomarkers** ADAM12, PAPP-A, beta-hCG	11–14	No	African American race, BMI, history of chronic hypertension, history of diabetes, ADAM12, PAPP-A, UtA PI AUC 0.79
Goetzinger et al. 2014 [23]	PE > 140/90 on 2 occasions with ≥0.3 g/24 h proteinuria or ≥1+ on dipstick > 20 weeks	Singleton pregnancies	Prospective cohort Development and validation	USA 2008–2012	578/622 (training/ validation)	**Maternal characteristics** Age, race, BMI, nulliparity, tobacco, chronic hypertension, DM **Ultrasound** UtA PI, bilateral notch **Biomarkers** ADAM12, PAPP-A, PP13, PlGF	11–14	No	Chronic hypertension, history of PE, pregestational diabetes, BMI > 30, PAPP-A < p10, UtA bilateral notch AUC 0.76 (Validation: AUC 0.78)
Gomaa et al. 2015 [67]	PE ≥140/90 with > 300 mg/24 h proteinuria or > 1+ on dipstick	Low-risk population: Singleton, primigravida, spontaneous conception, no history of infertility, no comorbidities	Prospective cohort	Egypt 2013	420	**Maternal characteristics** Age, weight, height, BMI, BP **Ultrasound** UtA PI **Biomarkers** Rh factor, TNF-a	11–13	No	TNF-a, UtA PI Sens 89%, spec 100%
Hannaford et al. 2015 [68]	PE ≥140/90 with ≥300 mg/24 h or ≥1+ on dipstick > 20 weeks	Singleton pregnancies without aneuploidy or anomalies	Prospective cohort	USA 2008–2012	570	**Maternal characteristics** Age, gravidity, parity, race, tobacco, BMI, chronic hypertension **Ultrasound** UtA Doppler, 3D ultrasound placenta **Biomarkers** PAPP-A	11–14	No	Placental bed VI alone AUC 0.88
Kanat-Pektas et al. 2014 [69]	PE ≥140/90 on 2 occasions and ≥300 mg/24 h or ≥2+ on dipstick proteinuria	Pregnant women without systemic disease or prior GHD	Prospective cohort	Turkey 2012	200	**Maternal characteristics** Age, weight, smoking, ethnicity, parity, BP **Ultrasound** NT **Biomarkers** β-hCG, PAPP-A, Hb, leukocytes, platelets, platelet volume	11–14	No	MPV and PAPP-A Sens 75% spec 64%
Khalil et al. 2012 [70]	PE ≥140/90 on 2 occasions and ≥300 mg/24 h or ≥2+ on dipstick or protein/ creatinin ≥30 mg/mmol or multisystem complication	Routine first trimester screening population in hospital	Prospective cohort study	UK 2009–2011	6947	**Maternal characteristics** Includes age, BMI, parity, smoking, etc **Ultrasound** Augmentation index, PWV, uterine artery PI **Biomarkers** PAPP-A	11–14	No	"Maternal history", "vascular-derived risk", UtA PI, PAPP-A AUC 0.85

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Table 3 (*continued*)

Study	Outcome	Population	Study design	Country, year	Study size	Candidate Predictors	Timing (weeks of gestation)	Dynamic changes?	Final model and model performance
Kumar et al. 2016 [71] *Predictors not in predictor summary for PE models*	GH Definition unclear	All patients attending prenatal care between 11 and 14 weeks	Prospective cohort	India 2012–2014	2042	**Maternal characteristics** Age, parity, height, weight, BMI, MAP **Ultrasound** Doppler **Biomarkers** β-hCG, PAPP-A	11–13	No	BMI, MAP, UtA PI, diastolic notch, PAPP-A AUC 0.81
Kumar et al. 2016 [72]	PE > 140/90 on 2 occasions with ≥300 mg/24 h proteinuria > 20 weeks	All women attending antenatal care between 11 and 14 weeks	Prospective cohort	India 2012–2015	3069	**Maternal characteristics** Age, parity, height, weight, BMI, MAP **Ultrasound** UtA PI and RI, diastolic notch **Biomarkers** PAPP-A, beta-hCG	11–13	No	Age, BMI, MAP, PAPP-A, UtA PI Sensitivity 73%, specificity 70%
Moon et al. 2015 [73]	PE > 140/90 on 2 occasions with ≥3.0 g/24 h protein or ≥1+ on dipstick > 20 weeks	Singleton pregnancies presenting for first trimester screening	Prospective cohort Note: high PE incidence (9 and 8%)	USA 2008–2011	1200	**Maternal characteristics** Parity, smoking, DM, race, BMI, MAP **Ultrasound** CRL, NT, UtA PI **Biomarkers** PAPP-A, ADAM12, PP13	11–14	No	Nulliparous: age, BMI, PAPP-A, ADAM12, MAP, diabetes, PP13, UtA PI AUC 0.88 Multiparous: age, PAPP-A, ADAM12, PP13, MAP, history of PE, UtA PI AUC 0.84
North et al. 2011 [74]	PE ≥140/90 on 2 occasions > 20 weeks with ≥300 mg/24 h or ≥30 mg/mmol protein/creatinin or ≥2+ on dipstick or any multisystem complication	Healthy nulliparous women < 15 weeks SCOPE	Prospective cohort study	New Zealand, Australia, UK, Ireland 2004–2008	3529	**Maternal characteristics (14–16 weeks)** Includes age, ethnicity, education, SES, gynaecological history, family history, diet, environmental risk factors, blood pressure, BMI **Ultrasound (19–21 weeks)** Fetal growth, Doppler of umbilical and uterine arteries **Biomarkers (14–16 wks)** Glucose, lipid concentrations Candidate predictors: 39 variables in analysis	14–16 interview and examination 19–21 ultrasound	No	"10 best models" → all possible models retaining 10 variables → key risk factors (excluding ultrasound!) + Doppler indices Final model: SBP, BMI, family history of PE, family history of CAD, maternal birth weight, vaginal bleeding > 5 days AUC 0.76
Odibo et al. 2011 [75]	PE (early < 34 weeks) ACOG definition 2002	Pregnant women for first-trimester screening	Prospective cohort	USA 2009–2011	452	**Maternal characteristics** Incl. race, BMI, chronic hypertension, pre-gestational diabetes **Ultrasound** Doppler indices **Biomarkers** PP-13, PAPP-A	11–14	No	Early PE: PP-13, PAPP-A, uterine artery PI, history of chronic hypertension AUC 0.77

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Table 3 (*continued*)

Study	Outcome	Population	Study design	Country, year	Study size	Candidate Predictors	Timing (weeks of gestation)	Dynamic changes?	Final model and model performance
O'Gorman et al. 2016 [28]	PE BP ≥140/90 on 2 occasions with ≥300 mg/24 h or ≥2+ on dipstick > 20 weeks	Women attending first routine visit, singleton with phenotypically normal birth > 24 weeks	Prospective cohort	UK 2010–2014	35,948	**Maternal characteristics** Age, BMI, race, medical/obstetric/family history, parity, smoking, MAP **Ultrasound** UtA PI **Biomarkers** PAPP-A, PlGF	11–13	No	"Maternal factors", UtA PI, MAP, PlGF PE < 37 weeks: AUC 0.91 PE ≥37 weeks: AUC 0.80
O'Gorman et al. 2017 [27]	PE BP ≥140/90 on 2 occasions with ≥300 mg/24 h or ≥2+ on dipstick > 20 weeks	Singleton pregnancy, mother > 18, delivery of phenotypically normal birth ≥24 weeks	Prospective cohort	UK, Spain, Belgium, Greece, Italy 2015	9041	External validation model above, no candidate predictors	11–13	No	External validation model above Final model: "maternal characteristics, MAP, PlGF, UtA PI PE < 37 weeks: AUC 0.92 PE ≥37 weeks: AUC 0.79
Park et al. 2013 [76]	PE (early/late) > 140/90 on 2 occasions with ≥300 mg/24 h or ≥30 mg protein/mmol creatinin	Women attending first trimester aneuploidy screening	Retrospective cohort	Australia 2010–2012	3099	**Maternal characteristics** Age, ethnicity, smoker, mode of conception, obstetric/medical/family history, BMI, BP **Ultrasound** UtA PI **Biomarkers** PAPP-A	11–13	No	Early PE: Maternal risk*, PAPP-A, UtA PI, MAP AUC 0.93 Late PE: Maternal risk, PAPP-A, MAP AUC 0.76 *African origin, history of chronic hypertension, parity, prior PE, conceived with ovulation induction
Park et al. 2014 [77]	PE (≥35 weeks) ≥140/90 and ≥300 mg/24 hr or ≥1+ on dipstick	Women at low risk of PE, singleton, < 40 yrs, no comorbidities, BMI < 25, early-onset PE excluded	Prospective cohort	Korea 2011	262	**Maternal characteristics** Parity, BMI **Ultrasound** UtA PI **Biomarkers** PAPP-A, sFlt-1, PlGF, inhibin-A, beta-hCG, E3, AFP	11–13 & 15–20 (PAPP-A) 24–27 & 34–37 (sFlt-1, PlGF) 20–24 (ultrasound)	No	PAPP-A, 2nd trim sFlt-1/PlGF ratio AUC 0.97
Pilalis et al 2007 [78]	PE ≥140/90 on 2 occasions with ≥300 mg/24 h proteinuria or ≥2+ on dipstick	All pregnant women with singleton pregnancy booking for delivery	Prospective cohort	Greece 2002–2004	878	**Maternal characteristics** Incl. age, race, BMI, parity, smoking, history **Ultrasound** UtA PI **Biomarkers** PAPP-A	11–14	No	UtA PI, history of PE or hypertension AUC 0.75

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Table 3 (*continued*)

Study	Outcome	Population	Study design	Country, year	Study size	Candidate Predictors	Timing (weeks of gestation)	Dynamic changes?	Final model and model performance
Poon et al 2009 [79]	PE DBP ≥90 on 2 occasions > 20 weeks with ≥300 mg/24 h or ≥2+ on dipstick (1988 definition ISSHP)	Women presenting for routine first-trimester screening	Prospective cohort	UK 2006–2007	8207	**Maternal characteristics** Incl. age, race, smoking, history, meds, parity **Ultrasound** Uterine artery PI **Biomarkers** PAPP-A	11–14	No	PAPP-A, parity, prior PE, race, UtA PI AUC 0.813
Scazzocchio et al. 2013 [80]	PE (early/late) ≥140/90 mm Hg on at least 2 occasions > 20 weeks with > 300 mg proteinuria in previously normotensive women	Singleton pregnancies	Prospective cohort	Spain 2009–2011	5170	**Maternal characteristics** Age, ethnicity, smoking, parity, BMI, medical/obstetric history, BP **Ultrasound** UtA Doppler **Biomarkers** PAPP-A, beta-hCG	11–13	No	Early PE: BMI, chronic hypertension, renal disease, prior PE, UtA PI, MAP AUC 0.96 Late PE: prior PE, chronic hypertension, diabetes, thrombophilic condition, multiparous, BMI, PAPP-A AUC 0.71
Scazzocchio et al. 2016 [25]	PE (early/late) > =140/90 mm Hg on at least 2 occasions > 20 weeks with > 300 mg proteinuria	Singleton pregnancies	Prospective cohort	Spain 2011–2013	4203	External validation of models above	11–13 weeks	No	External validation of models above Early PE: AUC 0.94 Late PE: AUC 0.72
Skrastad et al. 2014 [26]	PE requiring delivery < 42 weeks, < 37 weeks, ≥34 weeks ≥140/90 with ≥0.3 g/24 h proteinuria measured > 1 time > 20 weeks	Nulliparous women	Prospective cohort	Norway 2010–2012	585	**Maternal characteristics** Age, BMI, smoking, ethnicity, type of conception, MAP **Ultrasound** UtA PI **Biomarkers** PlGF, PAPP-A	11–13	No	"Maternal characteristics", MAP, UtA PI, PlGF, PAPP-A PE < 42 weeks: AUC 0.77 PE < 37 weeks: AUC 0.94
Skrastad et al. 2014 [81]	PE ≥140/90 and 0.3 g/23 h on 2 occasions	Nulliparous women	Prospective cohort	Norway 2010–2012	579	**Maternal characteristics** Age, BMI, MAP **Ultrasound** UtA PI **Biomarkers** PlGF, PAPP-A	11–13	No	Age, MAP, UtA PI AUC 0.74
Teixeira et al. 2014 [18]	PE New onset of hypertension (> 140/90) > 20 weeks in previously normotensive women with coexisting significant proteinuria (ACOG ref)	Singleton pregnancies (no chromosomal abnormalities, delivery > 24 wks)	Retrospective cohort	Portugal 2009–2013	4799	**Maternal characteristics** Age, ethnicity, method of conception, weight, smoking, medical/obstetric history **Ultrasound** NT, CRL **Biomarkers** PAPP-A, beta-hCG	9–13	No	Chronic hypertension, diabetes, caucasian, history of PE, age, weight smoker, multiparous, NT, CRL, PAPP-A, beta-hCG AUC 0.73
Youssef et al 2011 [82]	Late PE (> 34 weeks) ≥140/90 on 2 occasions > 20 weeks with ≥300 mg/24 h or ≥1+ on dipstick	Pregnant women attending care in tertiary hospital	Prospective cohort	Italy 2009–2010	528	**Maternal characteristics** Age, BMI, history, family history **Ultrasound** UtA PI **Biomarkers** PAPP-A, PIGF, sFlt-1, P-selectin, NGAL	11–14	No	PIGF, sFlt-1, NGAL AUC 0.82

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Table 3 (*continued*)

Study	Outcome	Population	Study design	Country, year	Study size	Candidate Predictors	Timing (weeks of gestation)	Dynamic changes?	Final model and model performance
Yucel et al. 2016 [83]	PE ≥140/90 on 2 occasions > 2-weeks in previously normotensive pregnancy with > 0.3 g/24 h proteinuria	Women presenting for aneuploidy screening	Prospective cohort	Turkey	602	**Maternal characteristics** Age, BMI, parity, smoking, history of PE **Ultrasound** UtA PI, placental volume **Biomarkers** PAPP-A	11–14	No	UtA PI, placental volume, PAPP-A (dichotomized) → if at least 2 parameters abnormal AUC 0.854
Diguisto et al. 2013 [84]	PE ≥140/90 with > 0.3 g/24 h proteinuria in the absence of UTI > 20 weeks in previously normotensive women	High-risk pregnancies: nullipara > 40, personal or family history of PE, stillbirth, abruption, IUGR, SGA, IVF, multiple gestation, chromosomal/ structural anomaly	Prospective cohort	France 2003–2008	237	**Maternal characteristics** Age, BMI, medical/obstetric history, platelet therapy **Ultrasound** UtA PI, bilateral notch **Biomarkers** PlGF, sFlt-1, sEndoglin, sFlt/PlGF, TC, HDL-c, TG, leptin	20–24	No	Age, nulliparity, bilateral notch, PlGF, sFlt-1, leptin, TG PE: AUC 0.795
Parra-Cordero et al. 2014 [85]	PE (early/intermediate/late) BP ≥ 140/90 with 300 mg/ 24 h proteinuria and resolution of hypertension and proteinuria after delivery	Singleton pregnancies that delivered at study hospital	Retrospective cohort	Chile 2004–2010	2002	**Maternal characteristics** Age, BMI, smoking, parity **Ultrasound** UtA PI **Biomarkers** OGTT	20–24	No	Early/intermediate PE: age, parity, UtA PI, OGTT 5% FPR 42% and 74% DR Late PE: BMI, UtA PI, OGTT 5% FPR 21% DR
Perales et al. 2016 [86] STEPS study	PE (early < 34 weeks) Newly occurring hypertension ≥140/90 with newly occurring proteinuria > 20 weeks	Women at risk for PE: prior PE/HELLP/IUGR, chronic hypertension, GH, kidney disease, DM-1, UtA PI > 1.45, thrombophilia, multiple pregnancy, age ≥ 40	Prospective cohort	Spain 2010–2013	729	**Maternal characteristics** Multiparity, prior PE, use of ART, MAP **Ultrasound** UtA PI **Biomarkers** sFlt-1, PlGF	19–20 23–24 27–28	No	Early PE: MAP, UtA PI, previous PE, sFlt-1/PlGF ratio AUC: 20 weeks: 0.91 24 weeks: 0.95 28 weeks: 0.95
Valino 2016 [87]	PE ISSHP definition 2001	Women attending routine hospital visit with available biomarker data and phenotypically normal birth ≥ 24 weeks	Prospective cohort	UK 2011–2014	8268	**Maternal characteristics** Age, race, method of conception, smoking, medical history, parity, BMI, MAP **Ultrasound** UtA PI, UA PI, MCA PI **Biomarkers** PlGF, sFlt-1	30–34	No	PE < 37 weeks: PlGf, sFlt-1, UTA PI, MAP AUC 0.992 PE > 37 weeks: PlGF, sFlt01, MCA PI, MAP AUC 0.81
Valino 2016 [19]	PE ISSHP definition 2001	Women with data available on all markers and delivery ≥24 weeks phenotypically normal baby	Prospective cohort	UK 2014	3953	**Maternal characteristics** Age, race, method of conception, smoking, medical history, parity, BMI, MAP **Ultrasound** UtA PI, UA PI, MCA PI **Biomarkers** PlGF, sFlt-1	35–37	No	MAP, sFlt-1, PlGF AUC 0.913

List of abbreviations by order of appearance
PE = preeclampsia
PIH = pregnancy-induced hypertension
MoM = multiple of mean
BMI = body mass index
MAP = mean arterial pressure
DBP = diastolic blood pressure
UtA PI = uterine artery pulsatility index
FPR = false positive rate

DR = detection rate
SLE = systemic lupus erythematosus
APS = antiphospholipid syndrome
IVF = in vitro fertilization
GA = gestational age
DM = diabetes mellitus
BP = blood pressure
HR = heart rate
UmA PI = umbilical artery pulsatility index
UtA RI = uterine artery refractory index
SBP = systolic blood pressure
SGA = small for gestational age
ADAM12 = metalloprotease 12
PAPP-A = pregnancy associated plasma protein A
PP13 = placental protein 13
hCG = human chorionic gonadotropin
sFlt-1 = soluble fms-like tyrosine kinase 1
PlGF = placental growth factors
msAFP = maternal serum alpha-fetoprotein screening
SES = socio-economic status
E2 = estradiol
E3 = estriol
BMP = bone morphogenetic protein
CRP = C-reactive protein
ICAM-1 = intercellular adhesion molecule 1
IL-1Ra = interleukin 1 receptor antagonist
TIMP-1 = tissue inhibitor of metalloprotease 1
TG = triglyceride
TC = total cholesterol
HDL-c = high-density lipid cholesterol
LDL-c = low-density lipid cholesterol
ApoA1 = apolipoprotein A1
ApoB = apolipoprotein B
Ht = hematocrit
sVEGFR-1 = soluble vascular endothelial growth factor 1
sEng = soluble endoglin
MCD = maximal capillary density
CVD = cardiovascular disease
NMR = nuclear magnetic resonance
TNF-a = tumor necrosis factor alpha
Hb = haemoglobin
MPV = mean platelet volume
CRL = crown rump length
NT = nuchal translucency
NGAL = neutrophil gelatinase-associated lipocalin
OGTT = oral glucose tolerance test
MCA = middle cerebral artery

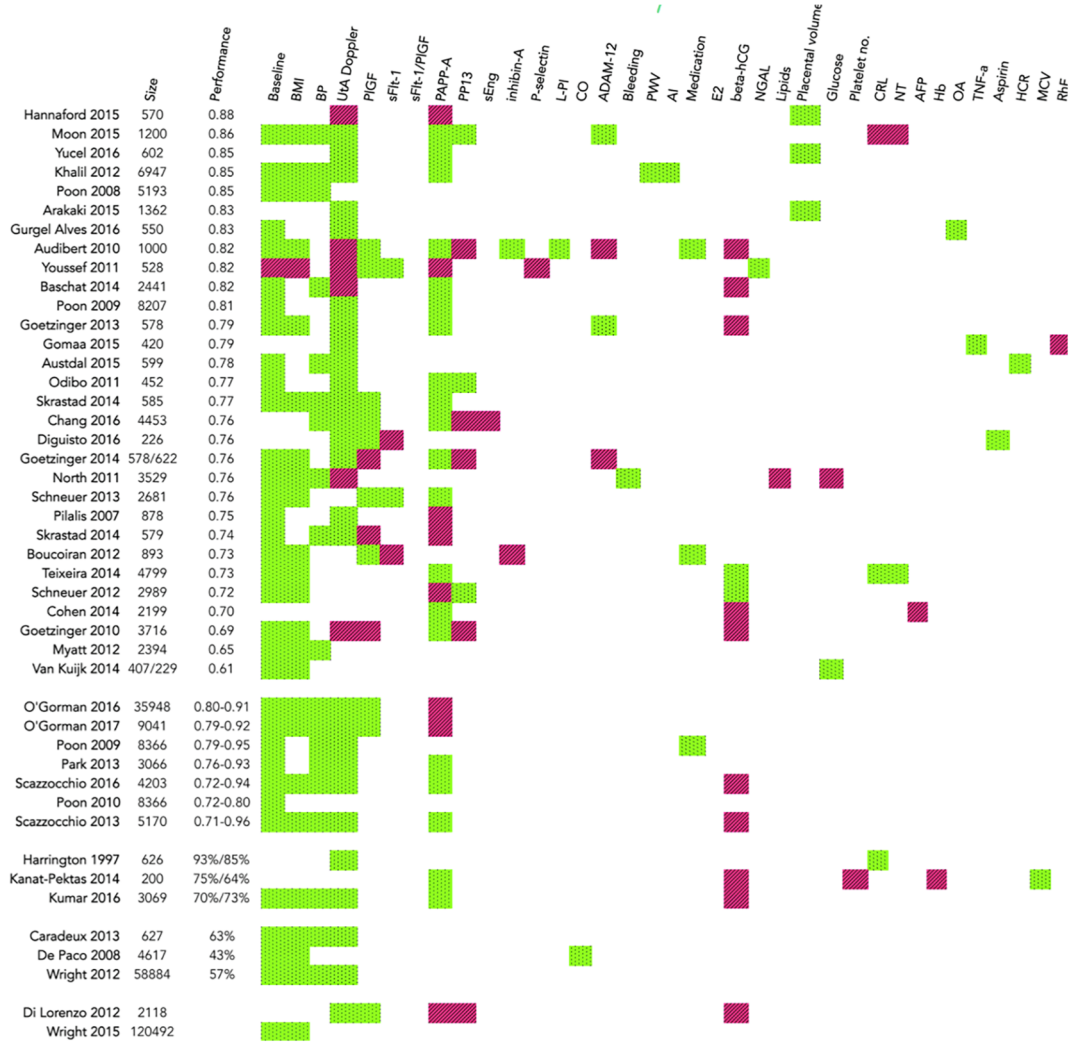

Fig. 2. First trimester predictor and prediction models overview. Top: Text size and text colours indicate the frequency in which the variable was used in the final prognostic models. Bottom: overview of candidate and selected predictors per study. Green and dotted boxes indicate predictors in final prediction model. Pink and striped boxes indicate candidate predictor. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

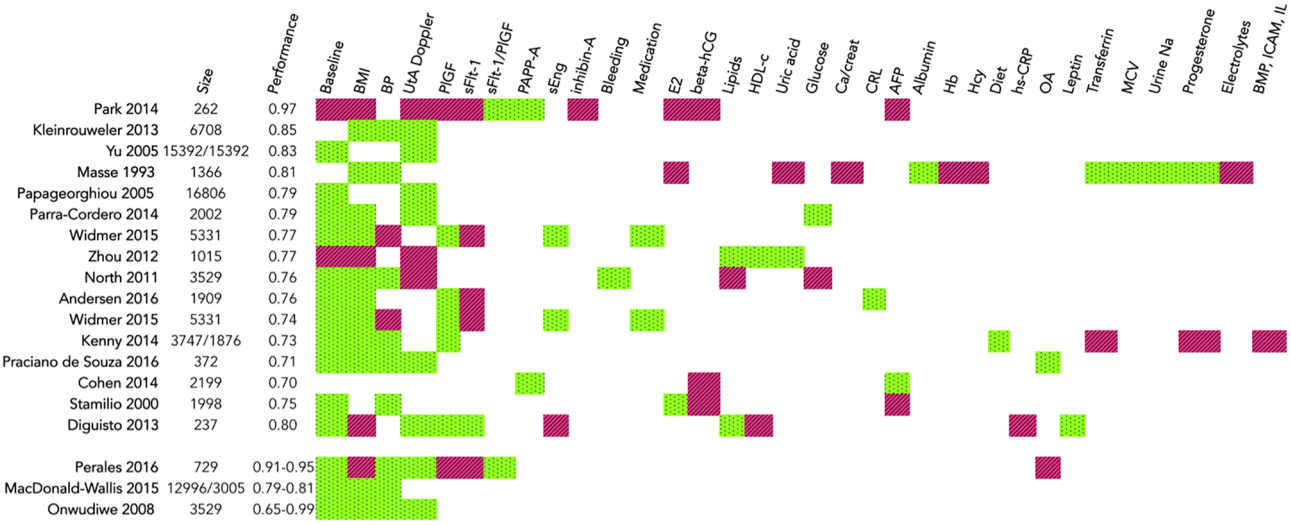

Fig. 3. Second trimester predictor and prediction models overview. Top: Text size and text colours indicate the frequency in which the variable was used in the final prognostic models. Bottom: overview of candidate and selected predictors per study. Green and dotted boxes indicate predictors in final prediction model. Pink and striped boxes indicate candidate predictor. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

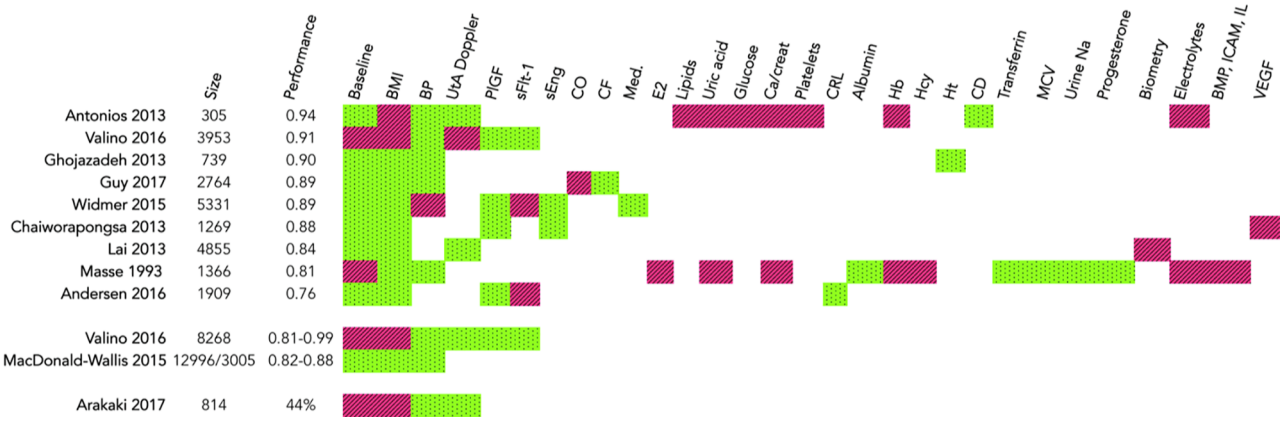

Fig. 4. Third trimester predictor and prediction models overview. Top: Text size and text colours indicate the frequency in which the variable was used in the final prognostic models. Bottom: overview of candidate and selected predictors per study. Green and dotted boxes indicate predictors in final prediction model. Pink and striped boxes indicate candidate predictor. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

prediction models. Lastly, the spectrum of placenta-related disorders of pregnancy is very broad and not limited to preeclampsia alone. Being able to predict fetal growth restriction, stillbirth and gestational diabetes, for example, would also have clinical benefits. Due to the sheer size of the available literature, it was not possible to include these outcomes in the current review.

In summary, with the large variety in preeclampsia prediction study designs and outcomes impeding model comparisons, it is not possible to identify the best-performing prediction algorithms or predictors. Moreover, the rarity of systematic model validation and calibration illustrates the current lack of a coordinated effort to implement preeclampsia prediction in clinical practice.

Disclosure of interests

The authors declare no conflict of interest

Contribution to authorship

SP and AdK were responsible for the conception of the systematic review. AdK performed the literature search, screening, data aggregation and drafted the manuscript. SP, JH, SK and MW contributed to the interpretation and presentation of the data. All authors edited and reviewed the manuscript and approved its final version.

Details of ethics approval

Not applicable for systematic review

Funding

This research was funded by the Ter Meulen Grant of the Royal Netherlands Academy of Arts and Sciences.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.03.005.

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