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Prediction of fetal and neonatal outcomes after preterm manifestations of placental insufficiency: systematic review of prediction models

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KEYWORDS: fetal growth restriction; fetal outcome; neonatal outcome; placental insufficiency; pre-eclampsia

CONTRIBUTION

What are the novel findings of this work?
Prediction models can support clinical decision-making and inform women and their partners regarding obstetric and neonatal management in complicated pregnancies. We identified 41 unique prediction models that have been derived for the prediction of fetal and neonatal outcomes in patients with preterm manifestations of placental insufficiency.

What are the clinical implications of this work?
At this time, none of the identified models is ready for clinical use owing to methodological shortcomings in model development and lack of external validation and prediction-model impact studies. Higher-quality models with external validation and prediction-model impact studies are needed to inform clinical decision-making based on prediction models.

ABSTRACT

Objectives *To identify all prediction models for fetal and neonatal outcomes in pregnancies with preterm manifestations of placental insufficiency (gestational hypertension, pre-eclampsia, HELLP syndrome or fetal growth restriction with its onset before 37 weeks' gestation) and to assess the quality of the models and their performance on external validation.*

Methods *A systematic literature search was performed in PubMed, Web of Science and EMBASE. Studies describing prediction models for fetal/neonatal mortality or significant neonatal morbidity in patients with preterm placental insufficiency disorders were included. Data extraction was performed using the CHARMS checklist. Risk of bias was assessed using PROBAST. Literature selection and data extraction were performed by two researchers independently.*

Results *Our literature search yielded 22 491 unique publications. Fourteen were included after full-text screening of 218 articles that remained after initial exclusions. The studies derived a total of 41 prediction models, including four models in the setting of pre-eclampsia or HELLP, two models in the setting of fetal growth restriction and/or pre-eclampsia and 35 models in the setting of fetal growth restriction. None of the models was validated externally, and internal validation was performed in only two studies. The final models contained mainly ultrasound (Doppler) markers as predictors of fetal/neonatal mortality and neonatal morbidity. Discriminative properties were reported for 27/41 models (c-statistic between 0.6 and 0.9). Only two studies presented a calibration plot. The risk of bias was assessed as unclear in one model and high for all other models, mainly owing to the use of inappropriate statistical methods.*

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Conclusions *We identified 41 prediction models for fetal and neonatal outcomes in pregnancies with preterm manifestations of placental insufficiency. All models were considered to be of low methodological quality, apart from one that had unclear methodological quality. Higher-quality models and external validation studies are needed to inform clinical decision-making based on prediction models.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Placental insufficiency comprises a spectrum of obstetric complications, including gestational hypertension, pre-eclampsia, HELLP syndrome and fetal growth restriction (FGR)[1]. Neonatal health is affected negatively by placental insufficiency, especially when clinical manifestations occur preterm (i.e. with onset before 37 weeks' gestation)[1]. For instance, neonatal mortality has been reported to be 4–10% after preterm delivery in mothers with pre-eclampsia and as high as 52% in pregnancies complicated by preterm FGR[2–4]. Poor neonatal prognosis is driven partly by the need for iatrogenic preterm birth to prevent further maternal morbidity or fetal mortality and partly by the disorder *per se*[5].

As a general management strategy, pregnancies with preterm manifestations of placental insufficiency are continued as long as the balance of fetal and maternal health risks does not sway the decision to expedite birth. In this phase of active maternal and/or fetal surveillance, patient-tailored prediction of fetal and neonatal outcomes is attractive from a clinical point of view to indicate intrauterine (maternal) transfer to a hospital with appropriate facilities, such as a neonatal intensive care unit[6]. Hence, prediction models that include available antenatal predictors of fetal and neonatal outcomes can facilitate clinical decision-making and counseling in pregnancies complicated by preterm manifestations of placental insufficiency.

Specific analytical steps are required from the development of a prediction model to its bedside use[7]. After development and internal validation, external validation of a prediction model should determine whether the performance remains adequate in other populations. Lastly, a prediction-model impact study should be undertaken, analyzing the effect of the use of the prediction model on fetal and neonatal outcomes in daily practice[8].

The aim of this systematic review was to identify all prediction models for fetal and neonatal (not maternal) outcomes in the setting of preterm manifestations of placental insufficiency. We searched for models that included antenatal predictors to facilitate clinical decision-making during pregnancy. Second, we aimed to appraise the quality of the models and their performance in external patient populations. Lastly, we aimed to pool their predictive performance measures in a meta-analysis.

METHODS

Data sources and searches

A literature search was performed on 26 February 2023 in EMBASE, Web of Science and PubMed. The search strings contained terms on placental insufficiency, prediction models and adverse fetal or neonatal outcomes (Appendix S1). No language or publication-date restrictions were applied. The protocol of this systematic review was registered with PROSPERO (https://www.crd.york.ac.uk/prospero/), an international prospective registry of systematic reviews (registration number: CRD42020178976).

Study selection

Studies developing or validating a prediction model on fetal or neonatal outcomes in the setting of preterm manifestations of placental insufficiency (gestational hypertension, pre-eclampsia, HELLP syndrome or FGR, with its onset before 37.0 weeks) were eligible for inclusion. Fetal and neonatal adverse outcomes were defined as any of the following: fetal/neonatal mortality or significant neonatal morbidity including but not limited to infant respiratory distress syndrome, severe bronchopulmonary dysplasia/chronic lung disease, moderate-to-severe hypoxic–ischemic encephalopathy, Grade III intraventricular hemorrhage or venous infarct (previously known as Grade IV intraventricular hemorrhage), cystic periventricular leukomalacia, necrotizing enterocolitis ≥ Grade 2 or retinopathy of prematurity requiring intervention.

Eligible studies were those that reported original data and were published in the form of a research letter, meeting abstract or full-text paper. Studies on term pregnancies, fetuses with congenital malformation or multiple gestations were excluded. We also excluded studies on prediction models containing neonatal outcome variables (such as Apgar score) as predictors, as these models did not fit with the timing of the research question. Study selection for inclusion was performed by two independent researchers (D.K. and C.V.) after duplicates had been removed. Discrepancies were resolved by consulting a third independent researcher (J.K.). Literature selection was conducted in two stages. The first stage included title and abstract screening, while the second phase included full-text perusal of the remaining articles. Corresponding authors were contacted in case of missing information relevant for inclusion, data extraction or quality assessment. Rayyan software (https://www.rayyan.ai) was used for screening.

Data extraction and quality assessment

Data extraction of included prediction models was performed by two independent researchers (D.K. and J.K.) using the Prediction model Risk Of Bias ASsessment Tool (PROBAST) and the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) using a standardized scoring form[7,9,10]. Discrepancies were resolved

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by consulting a third independent researcher (E.S.). CHARMS was used to extract information on study design, population characteristics, predictors and outcomes assessed by the prediction models, and statistical analysis, including handling of missing data, model-building strategies and model-performance measurements[9,10]. Relevant performance measures included but were not limited to the c-statistic (or area under the receiver-operating-characteristics curve), calibration measures (curve, slope, calibration-in-the-large), sensitivity, specificity, positive predictive value and negative predictive value, with corresponding 95% CIs.

PROBAST was used to assess the risk of bias of the included studies[7,10]. This tool was developed to assess the risk of bias and applicability issues in prediction-model studies using four domains: participants, predictors, outcome and analysis. Thereafter, an overall conclusion on the risk of bias and applicability can be drawn.

Data synthesis

We planned to perform a meta-analysis if at least two independent external validation studies provided information on the same performance measures of the same model.

RESULTS

The literature search yielded 22 491 unique results. After title and abstract screening, 218 full-text articles were screened, of which 14 were included (Figure 1). The studies that were excluded after full-text screening are listed in Table S1. All included studies were published as full-text papers. The 14 included studies developed a total of 41 individual prediction models[6,11–23]. All the studies were derivation studies, meaning that, within the study project, a new prediction model was developed and none of the included studies validated a pre-existing prediction model. Consequently, a meta-analysis of the prediction model performance measures was not possible. Characteristics of the included studies are reported in Table 1. One study was performed in Brazil[15] and one in South Africa[11]. The remaining studies were of European or North American origin. A summary of candidate predictors and predictors included in the final models is presented in Figure 2.

Prediction models within setting of pre-eclampsia or HELLP syndrome

Four studies were performed in women with pre-eclampsia or HELLP, describing four models. Detailed information on outcomes and models of each study is presented in Table S2.

The first study was conducted by Geerts and Odendaal[11] and included 113 prospectively enrolled patients diagnosed with pre-eclampsia between 24 and 34 weeks. The proportion of patients with concomitant FGR was not reported. The authors developed a model to predict a composite endpoint of neonatal morbidity, starting with 20 candidate predictors, which were reduced to seven predictors in the final model. A sensitivity of 79.0% and specificity of 88.2% were reported, without

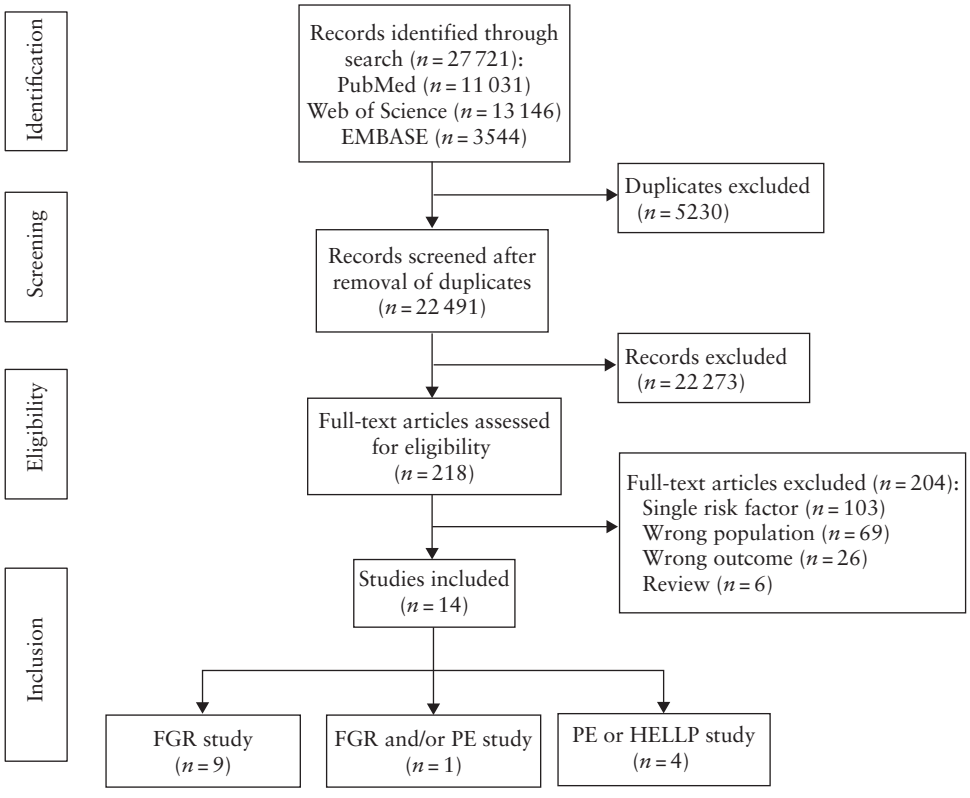

Figure 1 PRISMA flowchart summarizing study selection for systematic review. FGR, fetal growth restriction; PE, pre-eclampsia.

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Table 1 Characteristics of studies included in systematic review

Study	*Country*	*Placental insufficiency manifestation (definition)*	*Study design*	*Inclusion period*	*Type of prediction model study*	*Models* (n)	*Patients* (n)	*BW (g)**	*GA at birth (weeks)**
Baião (2020)[15]	Brazil	FGR (UA-PI > 2 SD; delivery at 24–33 weeks)	Retro, multicenter	2002–2016	Derivation	2	265	913 (315–1995)	Intact survivors, 30.1 (25–33); non-intact survivors, 27.5 (24–33)
Baschat (2003)[16]	USA and Germany	FGR (BW < p10 and UA-PI > 2 SD; delivery < 37 weeks)	Cohort, multicenter	1994–2001	Derivation	6	224	1090 (360–2010)	31 + 4 ± 3.6
Bilardo (2004)[17]	Netherlands, Germany and UK	FGR (AC < p5; delivery at 26–33 weeks)	Prosp, multicenter	NR	Derivation	3	70	Median, 810	NR
Bruin (2022)[23]	Netherlands	FGR (EFW < p10 and UA-PI > p95) and/or PE (2014 ISSHP criteria) (delivery or fetal demise < 32 weeks)	Retro, single center	2003–2015	Derivation	2	367	910 (750–1090)	29.6 (28.3–30.7)
Ganzevoort (2006)[14]	Netherlands	PE or HELLP syndrome (diagnosed at 24–34 weeks)	*Post-hoc* analysis of RCT, multicenter	2000–2003	Derivation	1	216	Median, 1266	Median, 31.5
Geerts (2007)[11]	South Africa	Severe PE (1988 ISSHP criteria; diagnosed at 24–34 weeks)	Prosp, single center	NR	Derivation	1	113	1412.3 ± 412.6	31 + 5 ± 2
Gómez-Arriaga (2014)[12]	Spain	PE (2001 ISSHP criteria; diagnosed < 34 weeks)	Prosp, single center	2007–2012	Derivation	1	51	1302 ± 600	30.3 ± 3.9
Hernandez-Andrade (2009)[18]	Spain and UK	FGR (EFW < p10 and UA-PI > p95; delivery at 24–34 weeks)	Prosp, multicenter	2006–2008	Derivation	1	97	956 [694–1170]	30 (28–32)
Mendoza (2021)[21]	Spain	FGR (EFW < p10; diagnosed between 20–32 weeks)	Prosp, single center	2017–2019	Derivation	2	173	2130 [1150–2620]	37.0 [32.0–38.0]
Odibo (2014)[19]	USA	FGR (EFW < p10 and UA-PI > p95; diagnosed at 26–37 weeks)	Prosp, single center	5-year period not specified	Derivation	1	66	1778.3 ± 678.7	34.1 ± 3.5
Rodríguez-Calvo (2023)[20]	Spain	FGR (UA-AEDF or EFW/AC < p3 or EFW/AC < p10 and UA-PI or UtA-PI > p95; diagnosed < 32 weeks)	Prosp, single center	2014–2020	Derivation	16	210	Median, 1065	Median, 30.5
Sharp (2019)[6]	UK	FGR (AC or EFW < p10 and UA-A/REDF; diagnosed at 22–30 weeks)	*Post-hoc* analysis of RCT, multicenter	2014–2016	Derivation and internal validation	3	105	590 [480–769]	28.3 [27–30]
Thangaratinam (2017)[13]	UK	PE or HELLP syndrome (diagnosed < 34 weeks)	Prosp, multicenter	2011–2014	Derivation and internal validation	1	945	NR	NR
Vergani (2005)[22]	Italy	FGR (AC < p10 with UA-A/REDF; diagnosed at 24–34 weeks)	Retro, single center	1995–2004	Derivation	1	39	Mean, 838	Mean, 29.3

Only first author is given for each study. Data are given as median (range), mean ± SD or median [interquartile range], unless stated otherwise. *Not all data types provided in all studies. AC, abdominal circumference; A/REDF, absent or reversed end-diastolic flow; AEDF, absent end-diastolic flow; BW, birth weight; EFW, estimated fetal weight; FGR, fetal growth restriction; GA, gestational age; ISSHP, International Society for the Study of Hypertension in Pregnancy; NR, not reported; p3/p5/p10/p95, 3rd/5th/10th/95th percentile; PE, pre-eclampsia; PI, pulsatility index; Prosp, prospective; RCT, randomized controlled trial; Retro, retrospective; UA, umbilical artery; UtA, uterine artery.

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information on the c-statistic or calibration properties of the model. No internal validation was reported.

The second study, by Gómez-Arriaga *et al.*[12], was a prospective single-center study. The authors derived a model to predict a composite outcome of perinatal mortality and morbidity in pregnancies complicated by pre-eclampsia before 34 weeks. The final model contained three predictors, including gestational age at the time of diagnosis, mean uterine artery pulsatility index and the soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PlGF) ratio. The model yielded a c-statistic of 0.89 (95% CI, 0.79–0.99). Calibration was not assessed and internal validation was not performed. Severe FGR (birth weight < 10th percentile and umbilical artery pulsatility index > 95th percentile) was reported in 19.6% of patients in this study.

The third study, by Thangaratinam *et al.*[13], was a prospective multicenter study (53 centers) that included 945 patients diagnosed with pre-eclampsia or HELLP syndrome before 34 weeks. The model predicted a combined outcome of perinatal or infant mortality/morbidity. The authors analyzed 25 candidate predictors, of which 15 were dropped in the model-building process. Uniform shrinkage factors were applied to all predictors in the final model to correct for overoptimism. A c-statistic of 0.76 (95% CI, 0.73–0.79) and a calibration slope of 0.77 (95% CI, 0.63–0.91) were reported for the final model, which was validated internally. The incidence of FGR within this study population was not reported.

The fourth study, by Ganzevoort *et al.*[14], was a *post-hoc* analysis of data from the Pre-eclampsia Eclampsia TRial Amsterdam (PETRA) trial, which was a two-center, open-label randomized controlled trial (RCT) studying the effect of plasma volume expansion compared with intravenous fluid restriction on maternal and fetal outcomes in women with preterm manifestations of placental insufficiency[24,25]. The PETRA trial included 216 patients diagnosed with pre-eclampsia or HELLP syndrome between 24 and 34 completed weeks. The authors developed a model to predict a composite endpoint of fetal and neonatal mortality and morbidity. Out of 17 candidate predictors, two were included in the final model (gestational age at inclusion and randomization arm; the latter was forced into the model). The model yielded a c-statistic of 0.91 (95% CI not reported). Calibration performance and internal validation were not reported. All patients had FGR (defined as estimated fetal weight < 10th percentile).

For three of four models, the full regression formula including intercept and predictor weights was presented in the publication[11–13].

Prediction models within setting of FGR

Nine studies derived a total of thirty-five prediction models for fetal or neonatal outcomes in pregnancies complicated by FGR. Detailed information on outcomes and models of each study is presented in Table S3.

Baião *et al.*[15] developed a model for neonatal morbidity and another model for overall mortality (i.e. stillbirth combined with neonatal mortality before discharge) for pregnancies complicated by FGR. Delivery was initiated between 24 and 33 weeks. A total of 115 cases developed neonatal morbidity, for which the authors evaluated 11 candidate predictors. The final model included two predictors, which were absent end-diastolic flow in the umbilical artery and reversed flow in the same vessel. Performance measures of the final model were not reported. For the outcome of overall mortality, which occurred in

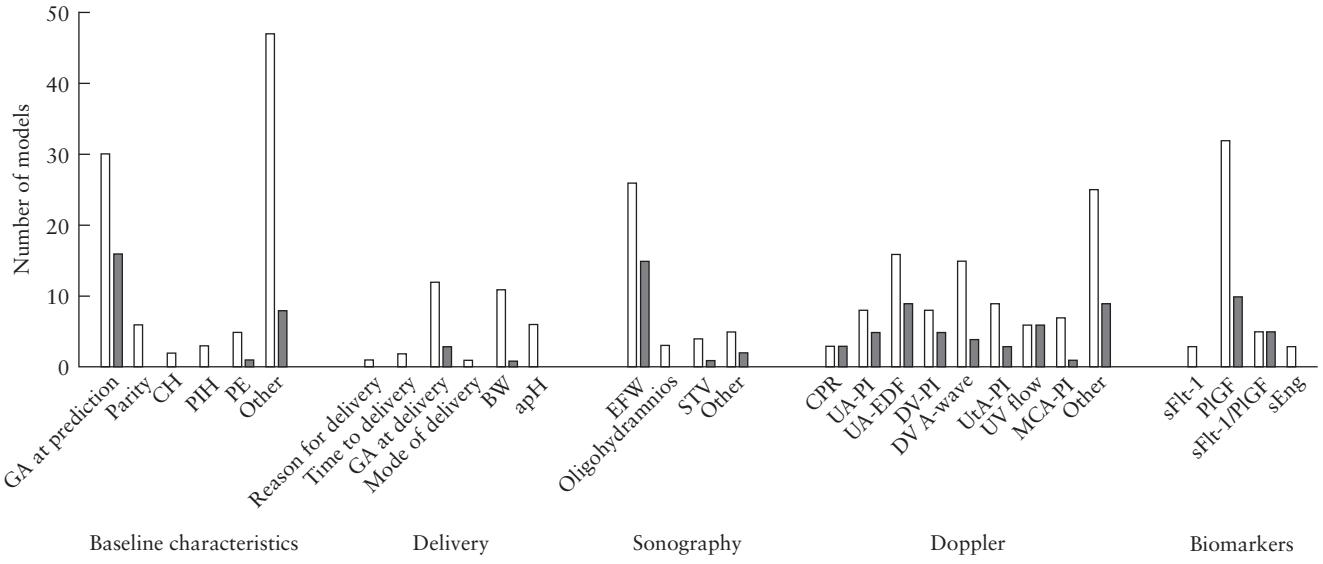

Figure 2 Number of models for which each predictor was considered (□) and included (■). apH, arterial umbilical cord pH; BW, birth weight; CH, chronic hypertension; CPR, cerebroplacental ratio; DV, ductus venosus; EDF, end-diastolic flow; EFW, estimated fetal weight; GA, gestational age; MCA, middle cerebral artery; PE, pre-eclampsia; PI, pulsatility index; PIH, pregnancy-induced hypertension; PlGF, placental growth factor; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase-1; STV, short-term variation; UA, umbilical artery; UtA, uterine artery; UV umbilical vein.

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45/265 fetuses or neonates, the same 11 candidate predictors were analyzed. The final model included the *Z*-score of estimated fetal weight and elevated pulsatility index of the ductus venosus. Performance measures of the model were not reported. The number of patients diagnosed with concomitant pre-eclampsia was not reported.

Baschat *et al.*[16] assessed which combination of fetal Doppler parameters achieved the best prediction of stillbirth and perinatal/neonatal mortality in 224 pregnancies complicated by FGR with delivery initiated before 37 weeks. All women underwent sonography 48 h prior to delivery, and Doppler values were used for modeling. The same set of candidate and final predictors were used for all three outcomes. For each outcome, two final models were derived, the first model including abnormal umbilical-vein flow (pulsatile instead of constant flow) and abnormal ductus-venosus flow (absent flow during the A-wave) patterns as final predictors (models A, C, E for each outcome, respectively, in Table S3). The second model for each outcome included the combination of absent or reversed end-diastolic umbilical artery flow and abnormal umbilical vein flow as final predictors (models B, D and F for each outcome, respectively, in Table S3). Test efficacy of the models was assessed using Bayesian analysis, the χ-square test, Fisher's exact test and multinomial logistic regression analysis, and ranged between 91% and 94%. Discrimination and calibration estimates were not reported. Mild pre-eclampsia was reported in 23.2% of patients and severe pre-eclampsia was reported in 4.5% (both not further defined).

Bilardo *et al.*[17] developed three prediction models, including two models for the combined endpoint of adverse perinatal outcome (perinatal death or intracerebral hemorrhage or bronchopulmonary dysplasia) and one model for adverse neonatal outcome (neonatal death, intracerebral hemorrhage or bronchopulmonary dysplasia). Seventy pregnancies complicated by preterm FGR were included. Pre-eclampsia was diagnosed in 48.6% of the study population. All three models included two final predictors: gestational age and ductus venosus pulsatility index, which were assessed at different time blocks (0–1, 2–7 and 8–14 days prior to delivery). Discrimination and calibration estimates were not assessed.

Hernandez-Andrade *et al.*[18] developed a prediction model for the endpoint of perinatal mortality. Within this FGR study population, 58.8% of pregnancies were complicated by pre-eclampsia. The authors included mainly fetal ultrasound markers and started with seven candidate predictors, which were reduced to three in the final model (gestational age at ultrasound examination < 28 weeks, absent or reversed A-wave of the ductus venosus and myocardial performance index $> 95^{th}$ percentile). The final model was simplified to a risk score, with the highest mortality rates in those with the highest score. No discrimination or calibration measures were reported.

The paper by Odibo *et al.*[19] describes the development of a prediction model for a combined endpoint of stillbirth, neonatal mortality and morbidity in 66 pregnancies resulting in 17 outcome events. They combined features of the biophysical fetal profile with a multivessel Doppler assessment, starting with a model with six candidate predictors, of which four were retained in the final model (pulsatility index of the middle cerebral artery $< 5^{th}$ percentile, peak systolic velocity of the middle cerebral artery, ductus venosus pulsatility index and cerebroplacental ratio). The model yielded a c-statistic of 0.73 (95% CI, 0.59–0.87). No calibration measures or internal validation steps were reported. The proportion of pregnancies complicated by pre-eclampsia was not reported.

Rodríguez-Calvo *et al.*[20] developed 16 prediction models, including eight models for the prediction of perinatal survival and eight for the prediction of a composite outcome of severe neonatal morbidity. A total of 210 pregnancies complicated by preterm FGR were included. They included five candidate predictors, which were estimated fetal weight, gestational age at diagnosis, PlGF level, PlGF-level multiples of the median and altered Doppler findings, defined as absent or reversed flow of the umbilical artery or middle cerebral artery pulsatility index $< 5^{th}$ percentile. Different combinations of two of these five candidate predictors were combined in the final models for both outcomes. The model containing PlGF multiples of the median and estimated fetal weight yielded the highest discriminative performance for the outcomes of perinatal survival and severe neonatal morbidity (c-statistic, 0.84 (95% CI, 0.75–0.92) and 0.73 (95% CI, 0.66–0.80), respectively). Calibration and internal validation were not reported. Concomitant pre-eclampsia was diagnosed in 49.7% of pregnancies with perinatal survival and in 66.7% of pregnancies resulting in neonatal mortality.

Sharp *et al.*[6] developed prediction models in a *post-hoc* analysis of the STRIDER UK trial, which was a multicenter RCT of sildenafil *vs* placebo for the treatment of severe early-onset FGR[26]. They developed six models including clinical features, sonographic measurements and angiogenic biomarkers. Their analysis was restricted to 78% of the cohort (105 patients) with complete information on the angiogenic markers sFlt-1 and PlGF. Of the six models that were developed, three were of interest for this systematic review based on the predicted outcome. The included models predicted overall survival, neonatal morbidity and stillbirth and initially included the same 17 candidate predictors. All final models were reduced using the Akaike information criterion in the forward stepwise selection process. The final models included estimated fetal weight for all three outcomes and the sFlt-1/PlGF-ratio for predicting overall survival and stillbirth. All other candidate predictors were removed. The models yielded varying discriminative values, with the c-statistic ranging from 0.70 to 0.90. Internal validation was performed by bootstrapping, resulting in a similar c-statistic for all three models compared with the original values. Calibration slopes ranged from 0.78 to 0.96 (for detailed information, see the appendix of Sharp *et al.*[6]). Concomitant pre-eclampsia was diagnosed in 17.1% of pregnancies within this population (not further defined).

The study of Mendoza *et al.*[21] was a prospective single-center study describing two models predicting a composite

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of adverse perinatal outcome. A total of 173 patients were included with an estimated fetal weight below the 10th percentile between 20 + 0 and 31 + 6 weeks. The number of patients with pre-eclampsia within this study was not reported. The first model consisted of seven candidate predictors and six final predictors (sFlt-1/PlGF ratio, umbilical artery pulsatility index above 95th percentile, umbilical artery absent or reversed end-diastolic flow, uterine artery pulsatility index above 95th percentile, estimated fetal weight and gestational age at diagnosis of FGR). For the second model, the sFlt-1/PlGF ratio was dropped in the model-building process, while all other predictors remained. The two models demonstrated similar discrimination, with a c-statistic of 0.87 (95% CI, 0.82–0.93) and 0.86 (95% CI, 0.80–0.91), respectively. Calibration and internal validation were not reported.

Vergani *et al.*[22] included 39 patients with a mean gestational age at diagnosis of 27.9 ± 2.6 weeks in the favorable-outcome (survival without severe morbidity) group and 26.4 ± 2.2 weeks in the adverse-outcome (perinatal mortality or severe morbidity) group. In total, 16 patients developed an adverse outcome. The authors selected 13 candidate predictors of the outcome, and their final model included the cerebroplacental ratio and estimated fetal weight at the last ultrasound scan before birth as predictors. Besides a Nagelkerke R^2 of 0.72, no other model performance measures were described. In this study, 10.3% of pregnancies were complicated by severe pre-eclampsia (not further defined).

For six out of 35 models, the full regression formula including intercept and predictor weights was presented in the publication[6,21,22].

Prediction models within setting of FGR and/or pre-eclampsia

The last study included in this systematic review was published by Bruin *et al.*[23] (Table S4). They included 367 patients with preterm FGR and/or pre-eclampsia, of whom 61 participated in the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE), a multicenter RCT in which delivery criteria in preterm FGR were assessed[27]. Within this combined set of 367 patients, two prediction models were developed, including advanced cardiotocography characteristics, which were phase-rectified signal averaging and short-term variation. The outcome of interest was a combined endpoint of low Apgar score, low arterial umbilical pH, need for resuscitation after birth by intubation or cardiac compressions or fetal death. In the study population, 98% of neonates were born with a birth weight below the 10th percentile, and 79% of pregnancies were complicated by pre-eclampsia. The two models demonstrated similar discriminative values, with a c-statistic of 0.64 (95% CI, 0.58–0.70) for the model including phase-rectified signal averaging and 0.67 (95% CI, 0.61–0.73) for the model including short-term variation. Both models were not validated internally. Calibration plots or full-regression formulae including intercepts and predictor weights were not presented.

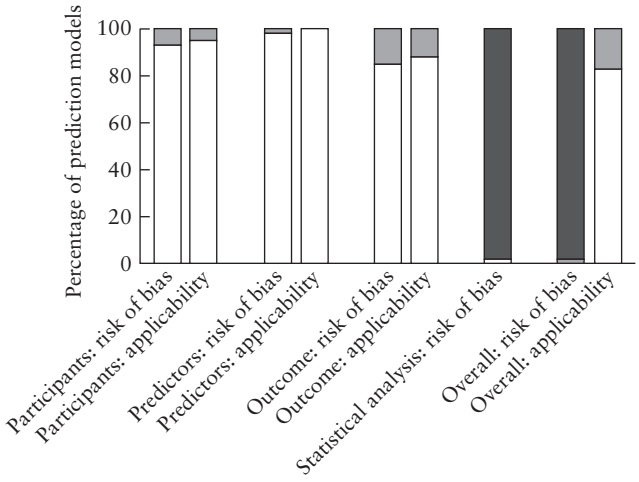

Figure 3 Risk of bias and applicability assessment of included models according to PROBAST tool. □, low risk; ▒, unclear risk; ■, high risk.

Risk of bias evaluation

Using PROBAST, applicability and the risk of bias were assessed at a model level. For the participants, predictors and outcome domains, the risk of bias and concerns regarding applicability were generally low (Figure 3). However, apart from the model described by Thangaratinam *et al.*[13], which had a low risk of bias in the statistical analysis domain, all other models were regarded as having a high risk of bias in this domain, mainly because of a low number of events per predictor variable, use of complete case analysis or unclear handling of missing data. Moreover, most models did not report on the criteria for selection of candidate predictors into the final model during the model-building process and lacked internal validation steps to control for overfitting and optimism. As a result, all studies were regarded as having a high risk of bias in the overall assessment, apart from the study of Thangaratinam *et al.*[13], for which the overall risk of bias was unclear (owing to an unclear risk of bias in the outcome domain). Out of 41 models, 34 demonstrated low concerns regarding applicability, while the remaining models were classified as unclear in this aspect.

DISCUSSION

This is the first systematic review on prediction models of fetal and neonatal outcomes in pregnancies with preterm manifestations of placental insufficiency. We identified 41 models, all of which lacked external validation. In general, prediction models can be used in clinical practice only when model derivation, external validation and prediction-model impact studies have been completed[8]. For the models identified in this systematic review, this process did not progress beyond model derivation. Moreover, their predictive performance was often difficult to assess because discrimination measures were under-reported and calibration was not evaluated in most studies. The development methods of most models were not in line with current standards.

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Consequently, overfitting of the models to the source data and subsequent overoptimistic performance estimates are likely. This is also reflected by the high risk of bias for almost all the included models.

Overall, the main conclusions of this systematic review are in line with the conclusions and recommendations of other systematic reviews on prediction-model studies across different topics and medical specialties[28–32]. The identified methodological shortcomings strongly emphasize the need for a better understanding of how to conduct and report this type of study. Tools and initiatives such as TRIPOD (Transparent Reporting of multivariable prediction models for Individual Prognosis Or Diagnosis, https://www.tripod-statement.org), PROBAST and CHARMS, which are publicly available, can provide research groups with key information on these important aspects[7,9,10,33].

The timing of application of the prediction models included in this systematic review is a concern that needs to be addressed. The intended clinical use of the models is to inform clinical monitoring and counseling about obstetric and neonatal management at the time of diagnosis or worsening of preterm pre-eclampsia or FGR. Unfortunately, almost all the models were built using ultrasound measurements taken at the timepoint closest to delivery, not at the time of diagnosis or counseling. Moreover, ideally, prediction models in the setting of placental insufficiency should be dynamic, not static. Dynamic models that can provide updated predictions on fetal and neonatal outcomes using repeat measurements during pregnancy would best reflect and support decision-making in the management of pregnancies complicated by preterm placental-insufficiency disorders.

Future research should focus on the external validation of existing models instead of the construction of new ones. The focus should be on improving their predictive performance, and future studies should preferably aim for a dynamic rather than static application in the evaluation of the model. Deriving new models will not result in new scientific knowledge, as the existing models already have a broad overlap in the lists of predictors included in their final models. Good candidate models for external validation studies based on their discriminative properties (area under the receiver-operating-characteristics curve) include the models published by Gómez-Arriaga *et al.*[12] and Sharp *et al.*[6]. However, preferably, the model by Gómez-Arriaga *et al.* should first be validated internally before entering the stage of external validation.

Another aspect worthy of discussion is the variability in disease, outcome and predictor definitions. Varying definitions result in clinical generalizability issues and hamper head-to-head comparisons of prediction models created for the same patient populations and outcomes. We also observed conflicting definitions of neonatal outcome, mainly for the combined outcome of neonatal morbidity. Future research should use endpoints based on core outcome sets, such as those derived by COMET (https://www.comet-initiative.org) or COSGROVE[34,35]. With regard to predictor definitions, although most models share common predictors in their final models, continuous variables, such as gestational age or estimated fetal weight, were dichotomized at varying cut-offs, based on the best fit to the studied population. This is unfortunate, as dichotomization tends to lead to loss of statistical power[36]. Moreover, the cut-offs used were not validated externally. As a result, prediction models containing dichotomized predictors in general have reduced predictive ability[37].

Incomplete reporting on the derivation process is another important issue for most studies included in this systematic review. For instance, handling of missing outcome or predictor variables and selection criteria for inclusion in the final model during multivariable analysis were not mentioned by most studies. In addition, important information on predictive properties of the models, such as calibration and discrimination measures, were under-reported[38]. Moreover, the final regression model equation, which is vital for external model validation and model updating, was described for only nine out of 41 models.

The strengths of this systematic review are underlined by the systematic and comprehensive search of the literature and the thorough data extraction using PROBAST and CHARMS by two independent researchers. Moreover, important analytical issues of the included studies were identified and are discussed in this study, and this knowledge could prevent similar methodological problems in future research. This systematic review was limited by the fact that external validation studies were lacking, and consequently a meta-analysis of performance measures of the models in external populations was not possible. Second, we restricted our literature search to prediction models derived or validated in patients with preterm placental insufficiency because prediction of fetal and neonatal outcomes is especially interesting in the preterm (and thus high-risk) period. Moreover, this systematic review focused on perinatal and neonatal outcomes, whereas in clinical practice, the timing of birth is based on fetal, neonatal and maternal outcomes. The prediction of maternal adverse events in pregnancies complicated by placental insufficiency is outside the scope of this systematic review but has been described in several studies, including those of Ganzevoort *et al.*[14] and Thangaratinam *et al.*[13], and was reviewed systematically by Ukah *et al.*[39].

To conclude, although this systematic review identified 41 prediction models for fetal and neonatal outcomes in pregnancies with preterm manifestations of placental insufficiency, none of them is ready for clinical use. Higher-quality models in terms of methodology in the derivation process and reporting of test characteristics followed by external validation and prediction-model impact studies are needed to allow clinical management based on prediction models in these high-risk pregnancies.

REFERENCES

1. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G, Ishaku S; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension* 2018; **72**: 24–43.

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2. Friedman SA, Schiff E, Kao L, Sibai BM. Neonatal outcome after preterm delivery for preeclampsia. *Am J Obstet Gynecol* 1995; **172**: 1785–1788.
3. Bossung V, Fortmann MI, Fusch C, Rausch T, Herting E, Swoboda I, Rody A, Härtel C, Göpel W, Humberg A. Neonatal outcome after preeclampsia and Hellp syndrome: a population-based cohort study in Germany. *Front Pediatr* 2020; **8**: 579293.
4. Lawin-O'Brien AR, Dall'Asta A, Knight C, Sankaran S, Scala C, Khalil A, Bhide A, Heggarty S, Rakow A, Pasupathy D, Papageorghiou AT, Lees CC. Short-term outcome of periviable small-for-gestational-age babies: is our counseling up to date? *Ultrasound Obstet Gynecol* 2016; **48**: 636–641.
5. Garite TJ, Combs CA, Maurel K, Das A, Huls K, Porreco R, Reisner D, Lu G, Bush M, Morris B, Bleich A; Obstetrix Collaborative Research Network. A multicenter prospective study of neonatal outcomes at less than 32 weeks associated with indications for maternal admission and delivery. *Am J Obstet Gynecol* 2017; **217**: 72.e1–72.e9.
6. Sharp A, Jackson R, Cornforth C, Harrold J, Turner MA, Kenny L, Baker PN, Johnstone ED, Khalil A, von Dadelszen P, Papageorghiou AT, Alfirevic Z. A prediction model for short-term neonatal outcomes in severe early-onset fetal growth restriction. *Eur J Obstet Gynecol Reprod Biol* 2019; **241**: 109–118.
7. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, Reitsma JB, Kleijnen J, Mallett S; PROBAST Group. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. *Ann Intern Med* 2019; **170**: 51–58.
8. Moons KGM, Kenge AP, Grobbee DE, Royston P, Vergouwe Y, Altman DG, Woodward M. Risk prediction models: II. External validation, model updating, and impact assessment. *Heart* 2012; **98**: 691–698.
9. Moons KGM, de Groot JA, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, Reitsma JB, Collins GS. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med* 2014; **11**: e1001744.
10. Moons KGM, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, Reitsma JB, Kleijnen J, Mallet S. PROBAST: A tool to assess risk of bias and applicability of prediction model studies: explanation and elaboration. *Ann Intern Med* 2019; **170**: W1–W33.
11. Geerts L, Odendaal HJ. Severe early onset pre-eclampsia: prognostic value of ultrasound and Doppler assessment. *J Perinatol* 2007; **27**: 335–342.
12. Gómez-Arriaga PI, Herraiz I, López-Jiménez EA, Escribano D, Denk B, Galindo A. Uterine artery Doppler and sFlt-1/PlGF ratio: prognostic value in early-onset pre-eclampsia. *Ultrasound Obstet Gynecol* 2014; **43**: 525–532.
13. Thangaratinam S, Allotey J, Marlin N, Mol BW, Von Dadelszen P, Ganzevoort W, Akkermans J, Ahmed A, Daniels J, Deeks J, Ismail K, Barnard AM, Dodds J, Kerry S, Moons C, Riley RD, Khan KS. Development and validation of Prediction models for Risks of complications in Early-onset Pre-eclampsia (PREP): a prospective cohort study. *Health Technol Assess* 2017; **21**: 1–100.
14. Ganzevoort W, Rep A, de Vries JIP, Bonsel GJ, Wolf H; PETRA investigators. Prediction of maternal complications and adverse infant outcome at admission for temporizing management of early-onset severe hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2006; **195**: 495–503.
15. Baião AER, de Carvalho PRN, Moreira MEL, de Sá RAM, Gomes SC Jr. Predictors of perinatal outcome in early-onset fetal growth restriction: A study from an emerging economy country. *Prenat Diagn* 2020; **40**: 373–379.
16. Baschat AA, Gembruch U, Weiner CP, Harman CR. Qualitative venous Doppler waveform analysis improves prediction of critical perinatal outcomes in premature growth-restricted fetuses. *Ultrasound Obstet Gynecol* 2003; **22**: 240–245.
17. Bilardo CM, Wolf H, Stigter RH, Ville Y, Baez E, Visser GHA, Hecher K. Relationship between monitoring parameters and perinatal outcome in severe, early intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2004; **23**: 119–125.
18. Hernandez-Andrade E, Crispi F, Benavides-Serralde JA, Plasencia W, Diesel HF, Eixarch E, Acosta-Rojas R, Figueras F, Nicolaides K, Gratacós E. Contribution of the myocardial performance index and aortic isthmus blood flow index to predicting mortality in preterm growth-restricted fetuses. *Ultrasound Obstet Gynecol* 2009; **34**: 430–436.
19. Odibo AO, Goetzinger KR, Cahill AG, Odibo L, Macones GA. Combined sonographic testing index and prediction of adverse outcome in preterm fetal growth restriction. *Am J Perinatol* 2014; **31**: 139–144.
20. Rodríguez-Calvo J, Villalaín C, Gómez-Arriaga PI, Quezada MS, Herraiz I, Galindo A. Prediction of perinatal survival in early-onset fetal growth restriction: role of placental growth factor. *Ultrasound Obstet Gynecol* 2023; **61**: 181–190.
21. Mendoza M, Hurtado I, Bonacina E, Garcia-Manau P, Serrano B, Tur H, Rodo C, Maiz N, Carreras E. Individual risk assessment for prenatal counseling in early-onset growth-restricted and small-for-gestational-age fetuses. *Acta Obstet Gynecol Scand* 2021; **100**: 504–512.
22. Vergani P, Roncaglia N, Locatelli A, Andreotti C, Crippa I, Pezzullo JC, Ghidini A. Antenatal predictors of neonatal outcome in fetal growth restriction with absent end-diastolic flow in the umbilical artery. *Am J Obstet Gynecol* 2005; **193**: 1213–1218.
23. Bruin CM, Lobmaier SM, Ganzevoort W, Müller A, Wolf H. Comparison of phase rectified signal averaging and short term variation in predicting perinatal outcome in early onset fetal growth restriction. *J Perinat Med* 2022; **51**: 634–640.
24. Ganzevoort W, Rep A, Bonsel GJ, De Vries JIP, Wolf H; PETRA investigators. A randomized trial of plasma volume expansion in hypertensive disorders of pregnancy: influence on the pulsatility indices of the fetal umbilical artery and middle cerebral artery. *Am J Obstet Gynecol* 2005; **192**: 233–239.
25. Ganzevoort W, Rep A, Bonsel GJ, Fetter WP, van Soderen L, De Vries JI, Wolf H; PETRA investigators. A randomised controlled trial comparing two temporising management strategies, one with and one without plasma volume expansion, for severe and early onset pre-eclampsia. *BJOG* 2005; **112**: 1358–1368.
26. Sharp A, Conforth C, Jackson R, Harrold J, Turner MA, Kenny LC, Baker PN, Johnstone ED, Khalil A, von Dadelszen P, Papageorghiou AT, Alfirevic Z; STRIDER group. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial. *Lancet Child Adolesc Health* 2018; **2**: 93–102.
27. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, Calvert S, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KTM, Thilaganathan B, Todros T, Valcamonico A, Visser GHA, Wolf H; TRUFFLE study group. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. *Lancet* 2015; **385**: 2162–2172.
28. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, Bonten MMJ, Dahly DL, Damen JAA, Debray TPA, de Jong VMT, de Vos M, Dhiman P, Haller MC, Harhay MO, Henckaerts L, Heus P, Kammer M, Kreuzberger N, Lohmann A, Luijken K, Ma J, Martin GP, McLernon DJ, Andaur Navarro CL, Reitsma JB, Sergeant JC, Shi C, Skoetz N, Smits LJM, Snell KIE, Sperrin M, Spijker R, Steyerberg EW, Takada T, Tzoulaki I, van Kuijk SMJ, van Bussel B, van der Horst ICC, van Royen FS, Verbakel JY, Wallisch C, Wilkinson J, Wolff R, Hooft L, Moons KGM, van Smeden M. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. *BMJ* 2020; **369**: m1328.
29. Damen JA, Hooft L, Schuit E, Debray TP, Collins GS, Tzoulaki I, Lassale CM, Siontis GC, Chiocchia V, Robberts C, Schlüssel MM, Gerry S, Black JA, Heus P, van der Schouw YT, Peelen LM, Moons KG. Prediction models for cardiovascular disease risk in the general population: systematic review. *BMJ* 2016; **353**: i2416.
30. Kleinrouweler CE, Cheong-See FM, Collins GS, Kwee A, Thangaratinam S, Khan KS, Mol BWJ, Pajkrt E, Moons KGM, Schuit E. Prognostic models in obstetrics: available, but far from applicable. *Am J Obstet Gynecol* 2016; **214**: 79–90.e36.
31. Bellou V, Belbasis L, Konstantinidis AK, Tzoulaki I, Evangelou E. Prognostic models for outcome prediction in patients with chronic obstructive pulmonary disease: systematic review and critical appraisal. *BMJ* 2019; **367**: l5358.
32. van Beek PE, Andriessen P, Onland W, Schuit E. Prognostic models predicting mortality in preterm infants: systematic review and meta-analysis. *Pediatrics* 2021; **147**: e2020020461.
33. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, Vickers AJ, Ransohoff DF, Collins GS. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015; **162**: W1–73.
34. Healy P, Gordijn SJ, Ganzevoort W, Beune IM, Baschat A, Khalil A, Kenny L, Bloomfield FH, Daly M, Kirkham J, Devane D, Papageorghiou AT. A Core Outcome Set for the prevention and treatment of fetal GROwth restriction: deVeloping Endpoints: the COSGROVE study. *Am J Obstet Gynecol* 2019; **221**: 339.e1–10.
35. Myatt L, Redman CW, Staff AC, Hansson S, Wilson ML, Laivuori H, Poston L, Robberts JM; Global Pregnancy CoLaboratory. Strategy for standardization of preeclampsia research study design. *Hypertension* 2014; **63**: 1293–1301.
36. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med* 2006; **25**: 127–141.
37. Collins GS, Ogundimu EO, Cook JA, Manach YL, Altman DG. Quantifying the impact of different approaches for handling continuous predictors on the performance of a prognostic model. *Stat Med* 2016; **35**: 4124–4135.
38. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, Pencina MJ, Kattan MW. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010; **21**: 128–138.
39. Ukah UV, De Silva DA, Payne B, Magee LA, Hutcheon JA, Brown H, Ansermino JM, Lee T, von Dadelszen P. Prediction of adverse maternal outcomes from pre-eclampsia and other hypertensive disorders of pregnancy: A systematic review. *Pregnancy Hypertens* 2018; **11**: 115–123.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Literature search

Table S1 List of excluded studies after full-text screening ($n = 204$)

Tables S2–S4 Prediction models in pregnancies complicated by pre-eclampsia or HELLP (Table S2), fetal growth restriction (Table S3) and fetal growth restriction and/or pre-eclampsia (Table S4)

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Predicción de resultados fetales y neonatales tras manifestaciones pretérmino de insuficiencia placentaria: revisión sistemática de modelos de predicción

RESUMEN

Objetivos. Identificar todos los modelos de predicción de resultados fetales y neonatales en embarazos con manifestaciones pretérmino de insuficiencia placentaria (hipertensión gestacional, preeclampsia, síndrome HELLP o restricción del crecimiento fetal con aparición antes de las 37 semanas de gestación) y evaluar la calidad de los modelos y su precisión en la validación externa.

Métodos. Se realizó una búsqueda sistemática de bibliografía en PubMed, Web of Science y EMBASE. Se incluyeron estudios que describían modelos de predicción de mortalidad fetal o neonatal, o morbilidad neonatal significativa, en pacientes con trastornos de insuficiencia placentaria pretérmino. La extracción de datos se llevó a cabo usando la lista de verificación CHARMS. El riesgo de sesgo se evaluó mediante PROBAST. La selección de la bibliografía y la extracción de los datos fueron realizadas por dos investigadores de forma independiente.

Resultados. La búsqueda bibliográfica produjo 22 491 publicaciones únicas. Tras el cribado del texto completo de los 218 artículos que quedaron tras las exclusiones iniciales, se incluyeron catorce. De los estudios se obtuvieron un total de 41 modelos de predicción, entre ellos cuatro modelos en el contexto de preeclampsia o HELLP, dos modelos en el contexto de restricción del crecimiento fetal y/o preeclampsia y 35 modelos en el contexto de restricción del crecimiento fetal. Ninguno de los modelos fue validado externamente, y la validación interna sólo se realizó en dos estudios. Los modelos finales contenían principalmente marcadores ecográficos (Doppler) como predictores de la mortalidad fetal/neonatal y la morbilidad neonatal. Se mencionaron propiedades discriminatorias para 27 de los 41 modelos (estadístico C entre 0,6 y 0,9). Sólo dos estudios presentaron un gráfico de calibración. El riesgo de sesgo se evaluó como poco claro en un modelo y alto en todos los demás, debido principalmente al uso de métodos estadísticos inadecuados.

Conclusiones. Se identificaron 41 modelos de predicción de resultados fetales y neonatales en embarazos con manifestaciones pretérmino de insuficiencia placentaria. Todos los modelos se consideraron de baja calidad metodológica, salvo uno cuya calidad metodológica estaba poco clara. Hacen falta modelos de mayor calidad y estudios de validación externa para fundamentar la toma de decisiones clínicas basadas en modelos de predicción.

预测产妇具有胎盘功能不全早产表现后胎儿和新生儿的结局：预测模型的系统综述

摘要

目的 确定所有预测具有胎盘功能不全早产表现（妊娠高血压、先兆子痫、HELLP 综合征或妊娠 37 周前发病的胎儿生长受限）的产妇的胎儿和新生儿结局的模型，并评估模型的质量及其外部验证的表现

方法 在 PubMed、Web of Science 和 EMBASE 中进行了系统的文献检索。其中包括对早产胎盘功能不全患者的胎儿/新生儿死亡率或新生儿重大发病率的预测模型进行了描述的研究。数据提取采用 CHARMS 核对表进行。使用 PROBAST 评估偏倚风险。文献选择和数据提取由两名研究人员独立完成。

结果 我们的文献检索共获得 22491 篇文献。在对初步排除后的 218 篇文章进行全文筛选后，有 14 篇纳入研究。这些研究共得出 41 个预测模型，包括 4 个先兆子痫或 HELLP 模型、2 个胎儿生长受限和/或先兆子痫模型以及 35 个胎儿生长受限模型。没有一个模型经过外部验证，只有两个研究进行了内部验证。最终的模型主要包含超声（多普勒）标记物，作为预测胎儿/新生儿死亡率和新生儿发病率的指标。41个模型中，27个具有判别特性（c 统计量介于 0.6 和 0.9 之间）。只有两项研究提供了校准曲线。其中一个模型的偏倚风险被评估为不明确，所有其他模型的偏倚风险都很高，这主要是由于使用了不恰当的统计方法。

结论 我们发现了 41 个预测具有胎盘功能不全早产表现产妇的胎儿和新生儿结局的模型。除了一个模型方法学质量不明确外，所有模型均被认为方法学质量较低。需要进行更高质量的模型和外部验证研究，以便为基于预测模型的临床决策提供依据。

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