Pregnancy Hypertension 11 (2018) 115–123

Contents lists available at ScienceDirect

Pregnancy Hypertension

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

Review article

Prediction of adverse maternal outcomes from pre-eclampsia and other hypertensive disorders of pregnancy: A systematic review

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ARTICLE INFO

Keywords:
Hypertensive disorders of pregnancy
Pre-eclampsia
Prognosis
Prediction
Maternal complications
Review

ABSTRACT

Background: The hypertensive disorders of pregnancy are a leading cause of maternal and perinatal mortality and morbidity. The ability to predict these complications using simple tests could aid in management and improve outcomes. We aimed to systematically review studies that reported on potential predictors of adverse maternal outcomes among women with a hypertensive disorder of pregnancy.

Methods: We searched MEDLINE, Embase and CINAHL (inception – December 2016) for studies of predictors of severe maternal complications among women with a hypertensive disorder of pregnancy. Studies were selected in a two-stage process by two independent reviewers, excluding those reporting only on adverse fetal outcomes. We extracted data on study and test(s) characteristics and outcomes. Accuracy of prediction was assessed using sensitivity, specificity, likelihood ratios and area under the receiver operating curve (AUROC). Strong evidence of prediction was taken to be a positive likelihood ratio > 10 or a negative likelihood ratio < 0.1, and for multivariable models, an AUROC ≥0.70. Bivariate random effects models were used to summarise performance when possible.

Results: Of 32 studies included, 28 presented only model development and four examined external validation. Tests included symptoms and signs, laboratory tests and biomarkers. No single test was a strong independent predictor of outcome. The most promising prediction was with multivariable models, especially when oxygen saturation, or chest pain/dyspnea were included.

Conclusion: Future studies should investigate combinations of tests in multivariable models (rather than single predictors) to improve identification of women at high risk of adverse outcomes in the setting of the hypertensive disorders of pregnancy.

1. Introduction

The hypertensive disorders of pregnancy (HDPs) complicate about 3–10% of pregnancies [1–3]. They are one of the major contributors to maternal and fetal mortality and morbidity globally, with approximately 30,000 maternal and 500,000 perinatal deaths attributed to the HDPs annually [2,4]. Maternal complications include eclampsia, stroke, and damage to the hepatic and renal organs [2,5]. Predicting the onset of these complications could aid in timely interventions such as increased surveillance, treatment of symptoms, transfer to higher care facility and delivery when necessary, which could reduce morbidity and mortality from the HDPs [6,7].

Maternal risk factors used as criteria for severity classification by some international clinical practice guidelines do not accurately identify women at high risk of developing maternal complications [8–11]. While many studies have reported associations between certain biomarkers and adverse outcomes [12–15], only a few studies have examined the accuracy of these tests in predicting adverse maternal outcomes; in other words, the accuracy of discriminating women who do experience serious morbidities versus those who do not at the individual level. The tests reported in these studies range from single markers to multiple markers combined in prediction models. Prediction models are increasingly used in clinical practice since they have the advantage of combining various factors to potentially provide more

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https://doi.org/10.1016/j.preghy.2017.11.006
Received 8 August 2017; Received in revised form 3 November 2017; Accepted 20 November 2017
Available online 21 November 2017
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accurate predictions [16]. Regardless of the prediction method used, there is a need for the results from these studies be summarised and compared to determine if they give meaningful and accurate information to assist clinicians in the management of the HDPs.

Several systematic reviews have assessed the predictive ability of individual variables such as uric acid, maternal symptoms, and liver function tests for maternal and fetal complications resulting specifically from pre-eclampsia [17–20]. To our knowledge, there have been no reviews assessing predictors for maternal complications resulting from all types of HDPs. This broader disease definition is important, as other HDPs still contribute substantially to the burden of the disease [2,10,21]. In addition, these reviews were conducted between 2006 and 2011 and since then the definition for HDPs, particularly pre-eclampsia, has evolved [3]. Furthermore, the studies included in these reviews solely assessed potential univariable predictors, thus the need to also review potential predictors combined in multivariable models. Therefore, we aimed to systematically review studies reporting the predictive ability, for both single and combined markers, of adverse maternal outcomes in women with HDPs.

2. Methods

2.1. Protocol and registration

A protocol for this review has been registered on PROSPERO (registration number: CRD42017054328).

2.2. Eligibility criteria

The population of interest was women with a HDP: pre-eclampsia, gestational hypertension, or chronic (pre-existing) hypertension, as defined by the study (with study definitions documented). The predictors of interest were any tests measured to predict adverse maternal outcomes from HDP. The adverse maternal outcomes considered were severe complications from the HDPs which had been agreed upon in a Delphi Consensus in the PIERS (Pre-eclampsia Integrated Estimates of RiSks study) (https://pre-empt.cfri.ca/monitoring/fullpiers) [7]; in addition, postpartum haemorrhage (PPH) and disseminated intravascular coagulation (DIC) were considered as these outcomes have been subsequently reported to be strongly linked with HDPs [21]. Detailed inclusion and exclusion criteria and full list of outcomes of interest are shown in Appendix S1.

2.3. Search and selection strategy

We searched MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO), and EBM Reviews (Ovid) Library databases from their inception to December 2016. We also searched Google Scholar and grey literature sources (such as University of British Columbia cIRcle, government websites, etc.) for other potential articles. Web of Science was used for citation tracking of review and eligible articles and the reference lists of studies selected for inclusion were scanned to capture any articles that were not identified through the electronic search. The search terms included both subject headings terms and key words related to the HDPs, with methodological filters to identify prognostic test studies for maternal complications (Appendix S2).

All retrieved articles were screened independently for eligibility by two reviewers (UVU and DAD), first by title and abstract and then, by reviewing the full articles. Final selections were compared and any conflicts resolved by discussion and/or by a third reviewer (BP).

The predictive measures used were sensitivity, specificity, likelihood ratios (LRs), and area under the receiver operating characteristic curve (AUROC). Studies that reported none of these predictive measures were included only if adequate data were provided to calculate these measures. We excluded studies reporting both maternal and fetal outcomes as a combined outcome except in cases where the test prediction performance for the maternal outcomes could be separated. We also excluded studies that included any of the HDPs as one of the outcomes.

2.4. Data extraction and assessment of study quality

For each eligible study, information on population characteristics, tests used as predictors, measures and accuracy of prediction were extracted by one reviewer (UVU) and reviewed by another (DAD). Methodological quality assessment of the included studies was carried out using the QUIPS (Quality in Prognostic Studies) tools [22], which have been validated and also used in similar studies [23]. The relevant study aspects that were scrutinized included methods of sampling and recruitment, adequate description of tests and outcomes, complete follow-up or handling of missing data explained, and sample size. In total, there were eight questions considered and one point was awarded for each assessment question that was met. In addition, studies reporting multivariable prediction models were assessed for internal and external validation. We considered studies with a total score of ≥ 7 as having a low risk of bias, 4–6 as medium risk of bias, and < 4 as high risk of bias.

2.5. Data synthesis

We constructed 2×2 tables for each included study cross-classifying test results and the occurrence of adverse maternal outcomes. Measures of predictive performance were sensitivity, specificity, LRs, predictive values, and AUROC. These measures were either retrieved directly from the studies or calculated from constructed from raw data and 2×2 tables. LRs were used to provide interpretations for clinical usefulness as a measure that is independent of disease prevalence; for positive LRs (LR+), an LR of 5–10 and > 10 were interpreted as having moderate and strong evidence to 'rule in' the disease respectively while for negative LRs (LR-), an LR of 0.1–0.2 and < 0.1 were interpreted as having moderate and strong evidence to 'rule out' the disease respectively [24]. An AUROC ≥ 0.70 was also considered to reflect good discriminatory ability for multivariable models [25]. Wherever possible, *meta*-analyses were conducted for similar tests predicting similar outcomes and having 3 or more 2×2 tables. Meta-analyses were performed using a bivariate *meta*-regression model, which uses a random effects approach, to calculate pooled estimates of the likelihood ratios [26–28].

All statistical analyses were performed using R version 3.1.3 (The R Project for Statistical Computing).

3. Results

3.1. Literature search and identification results

Fig. 1 summarizes article identification and selection. Of 2137 articles retrieved, we included 32 primary articles. Important exclusions presented an outcome that either included but were not restricted to women with a HDP (N = 6), presented combined maternal and fetal outcomes (N = 12), or studies for which a $2*2$ table could not be constructed in order to calculate the diagnostic tests characteristics of interest (N = 3) (see Appendix S3 for excluded references).

3.2. Characteristics of included studies

Characteristics of the included studies are presented in Appendix S4. In brief, included articles were published between 1988 and 2017. Eleven were multicentre and 21 from single centres. Most studies (30/32) were cohort in design, usually prospective (24/30); one was a randomized trial and another was a case-control study. The countries where data were collected included Australia (N = 8), the United Kingdom (N = 8), Canada (N = 7), New Zealand (N = 7), USA (N = 7),

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