OPHTHALMIC ARTERY DOPPLER PREDICTION OF PREECLAMPSIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Short title: Ophthalmic artery Doppler and preeclampsia

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ABSTRACT

Objective: To determine the accuracy of ophthalmic artery Doppler in pregnancy for the prediction of preeclampsia.

Methods: MEDLINE (1947–2017), EMBASE (1974–2017), CINAHL (inception-2017) and the Cochrane Library (inception-2017) were searched for relevant citations without language restrictions. Two reviewers independently selected studies that evaluated the accuracy of ophthalmic artery Doppler to predict the development of preeclampsia and performed data extraction to construct 2 × 2 tables. Individual patient data was obtained from the authors where available. A bivariate random-effects model was used for the quantitative synthesis of data.

Results: In total, 87 citations matched the search criteria. After exclusions, three studies (n=1119 pregnancies) were included for analysis. All included studies had clear descriptions of the index and reference tests, avoidance of verification bias and adequate follow-up. Individual patient data was obtained for all the included studies. The first diastolic peak velocity of ophthalmic artery Doppler at the cutoff of 23.3cm/s showed modest sensitivity (61.0%, 95% confidence interval: 44.2%-76.1%) and a specificity (73.2%, 95% confidence interval: 66.9%-78.7%) for the prediction of early-onset preeclampsia (area under the curve 0.68, confidence interval: 0.61-0.76). The first diastolic peak velocity had a much lower sensitivity for the prediction of late-onset preeclampsia (39.0%, 95% confidence interval: 20.6%-61.0%) with a similar specificity (73.2, 95% confidence interval: 66.9%-78.7%) and a lower area under the curve (0.58, confidence interval: 0.52-0.65). The pulsatility index of the ophthalmic artery didn't obtain a clinically useful sensitivity and specificity levels at any cutoff for early- or late-onset preeclampsia. A peak ratio above 0.65 showed a similar diagnostic accuracy compared to the first diastolic peak velocity with an area under the curve

of 0.67 (95% confidence interval: 0.58-0.77) for early onset disease and 0.57 (95% confidence interval: 0.51-0.63) for late onset disease.

Conclusions: Ophthalmic artery Doppler is a simple, accurate and objective technique with a stand-alone predictive value for the development of early-onset preeclampsia equivalent to that of uterine artery Doppler evaluation. The finding of a relationship between ophthalmic Doppler indices and preeclampsia cannot be a consequence of trophoblast invasion and may be related to hemodynamic adaptation to the pregnancy. This review justifies efforts to elucidate the effectiveness and the underlying mechanism whereby two seemingly unrelated maternal vessels can be used for the prediction of a disease considered a “placental disorder”.

INTRODUCTION

Preeclampsia is a major complication of pregnancy with the highest case-fatality ratio of any of the common pregnancy-related conditions.[1] In addition to related mortality and morbidity, preeclampsia contributes to the adverse long-term cardiovascular sequelae of affected women.[2, 3] Screening and prevention of preeclampsia are major health goals of maternal healthcare worldwide and large scale trials have shown the benefit of early pregnancy aspirin use in reducing preterm preeclampsia.[4] Prediction models for preeclampsia usually combine parameters of maternal characteristics, uterine artery Doppler and biochemical indices.[5] The rationale behind the use of uterine artery Doppler - the strongest predictor - lies in the placental origin hypothesis for the development of preeclampsia. The relationship between uterine artery Doppler indices and preeclampsia is explained by the inadequate invasion of trophoblast into spiral arteries, which in turn prevents the development of low impedance flow in uterine arteries. These changes can be detected before the development of overt clinical hypertension, hence enabling the use of uterine Doppler in predictive models for preeclampsia.

In addition to the uterine artery Doppler, several peripheral vessels Doppler indices have been investigated as a potential marker for the development of preeclampsia, among which is ophthalmic artery Doppler. Ophthalmic artery Doppler has the following advantages, first it is easy to measure with standard ultrasound equipment in daily obstetric setting, second, it is unaffected by adiposity, and thirdly the ophthalmic artery Doppler indices have constant reference ranges during throughout trimesters.[6] These factors make the ophthalmic artery Doppler a good candidate for use in predictive models to be employed in low resource settings with limited tech-

nical equipment or poor adherence to antenatal follow-up (Supplement A: details of the ultrasound examination, the acquisition, and interpretation of ophthalmic artery Doppler waveform). The main aim of this meta-analysis was to evaluate the predictive value of the ophthalmic artery Doppler, for preeclampsia. The results of this meta-analysis should help to determine the clinical utility of this technique and the need for further research in this area.

MATERIALS AND METHODS

Protocol, eligibility criteria, information sources, and search

This review was performed according to a protocol designed a priori and recommended for systematic reviews and meta-analysis.[7-9] MEDLINE (1947 - February 2017), EMBASE (1974 - February 2017), the Cochrane Library (since inception - February 2017) including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and The Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL (since inception - February 2017) were searched electronically on 28th February 2017 utilizing combinations of the relevant MeSH terms, keywords, and word variants for “preeclampsia”, “ophthalmic”, “Doppler”, “predict”, “pregnancy hypertension”, “gestational hypertension”. The search was restricted to the human studies. Reference lists of relevant articles and reviews were hand searched for additional reports. The SEDATE guidelines were followed. [9] The study was registered with the PROSPERO database (Registration number CRD42017060984).

Study selection, data collection and data items

Studies were assessed according to the following criteria: population, outcome, study design, type of preeclampsia and the gestational age at the assessment of the ophthalmic artery Doppler. Studies reporting the predictive accuracy of the ophthalmic artery Doppler for preeclampsia were included. All abstracts were independently reviewed by two authors (EK, AL). Agreement about potential relevance was reached by consensus, and full-text copies of those papers were obtained. The same two reviewers independently extracted data regarding study characteristics and the outcomes. Inconsistencies were discussed by the reviewers and consensus reached. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. Prospective and retrospective case-control and cohort studies were included. Case series, case reports, conference abstracts, and editorials were excluded. Studies, where the data on outcomes could be extracted, were included.

Risk of bias, summary measures and synthesis of the results

Quality assessment of the included studies was performed using the QUADAS-2 tool.[10] Data on the true positive, true negative, false positive, and false negative rates with corresponding participant numbers were extracted from each included study to form 2x2 tables. The Doppler indices used for the prediction and if applicable, the parameters of the combined model for prediction, were extracted. The analysis of the extracted data was performed with RStudio (Version 1.0.136, RStudio, Inc.) using the “mada”, “meta” and “glmmML” packages. [11] A random effects model with Hedg-

es' g was used to obtain bias corrected standardized mean differences between preeclampsia cases and controls. Standardized mean differences were chosen over mean differences due to the unfamiliar nature of the investigated parameters to the most practicing obstetricians. A slight loss of statistical power is expected with the use of standardized mean differences but the statistical significance of results rarely changes due to used methodology. [12] A SMD of 0.2 represents a "small" effect, an SMD of 0.5 represents a "medium effect" and an SMD of 0.8 or more represents a "large" effect. The variance between the studies was tested using the I squared statistics. When the individual patient data was available, logistic regression was employed to generate receiver characteristics curves and obtain optimal cut-offs for each parameter. In a second step, a bivariate analysis was employed using predetermined cut-offs to obtain sensitivity and specificity values and generate summary receiver operating characteristics curves. [13] The publication bias was not explored due to inadequate power of funnel plots asymmetry (i.e. Egger test) when the number of included studies is low.[14-16]

RESULTS

Study selection, characteristics and risk of bias

In total, 87 citations matched the search criteria. After evaluating the abstracts and removing duplicate results, five studies were retrieved for detailed investigation (Table 1). Among five studies [17-21], one study was excluded from the final analysis due to overlapping populations [20] and one study was excluded from the final analysis due to significant risk of selection bias [18]. Three studies involving a total of 1119 women were included in the final analysis (Figure 1). [17,19,21] All three studies used internationally accepted criteria for the diagnosis of preeclampsia. [22] Methodological charac-

teristics of the included studies are shown in Table 1. In two studies included in the review, the ophthalmic artery Doppler was performed in the first trimester, while it was performed in the second trimester in the third study (Table 1). Two studies included women of undetermined risk for preeclampsia, whereas one study included women perceived to be at high risk for preeclampsia. The definition of early onset disease also varied across studies as two studies opted to define early-onset disease with gestational age at delivery and the third one chose to define early-onset disease with laboratory characteristics. A summary of the quality evaluation of the included studies according to QUADAS-2 is presented in Table 2. The individual patient data of all the included studies were obtained from the authors.

Synthesis of results

First, a quantitative synthesis of ophthalmic artery Doppler indices for comparing the means were undertaken to identify best candidates for the predictive accuracy synthesis. The first diastolic peak velocity (SMD -0.36, 95% CI: -0.55 to -0.16, I^2: 82.6%), peak ratio (SMD -0.33, 95% CI: -0.53 to -0.14, I^2: 0%) and peak systolic velocity (SMD -0.34, 95% CI: -0.59 to -0.10, I^2: 0%) had significant standardized mean differences between cases and controls (Table 3). The resistance index (SMD 0.26, 95% CI: -0.05 to 0.44, I^2: 0%) and pulsatility index (SMD 0.18, 95% CI: -0.02 to 0.38, I^2: 0%) on the other hand didn't show significant standardized mean difference between case and controls. The first diastolic peak velocity, peak ratio and pulsatility index were chosen for the quantitative synthesis of the predictive accuracy. The resistance index and peak systolic velocity were discarded as the number of studies reporting this outcome were low.

The synthesis of first diastolic peak velocity data has shown that the parameter (>23.3cm/s) has modest accuracy for the prediction of early-onset preeclampsia with a sensitivity of 61.0% (95% CI 44.2-76.1) and a specificity of 73.2% (95% CI 66.9-78.7) (area under the curve 0.68, 95% CI: 0.61-0.76) (Table 4). The predictive accuracy of the first diastolic peak velocity was weak for late-onset preeclampsia (AUC: 0.58, 95% CI: 0.52-0.65) (Table 4). The peak ratio showed a predictive accuracy similar to the first diastolic peak velocity for early (AUC: 0.67, 95% CI 0.58-0.77) and late-onset preeclampsia (AUC: 0.57, 95% CI 0.52-0.63) (Table 4). The pulsatility index on the other hand didn't reach clinically useful sensitivity and specificity values for any given cut-off value. The pulsatility index below 2.4 had a sensitivity of 24.8% (95% CI: 12.0-44.2) and a specificity of 71.6% (95% CI: 61.5-79.9) for the prediction of early-onset preeclampsia (AUC: 0.54, 95% CI: 0.45-0.64). The summary receiver operating characteristics curves were generated using a bivariate model for early and late preeclampsia separately. The first diastolic peak velocity offered the best predictive accuracy for early-onset preeclampsia (Figure 2), but no parameter reached a clinically meaningful accuracy level for the prediction of late-onset preeclampsia (Supplementary Figure A).

COMMENT

Main findings

The prediction of preeclampsia is a major focus of current obstetric research. Uterine artery Doppler is the most commonly used variable in validated predictive models, due to its importance and weighting relative to other predictive indices for preeclampsia.[5,23,25] The findings of this meta-analysis suggest that the ophthalmic artery Doppler indices measured in either the first or second trimester, have a signifi-

cant association with the subsequent development of early-onset preeclampsia. The magnitude of the effect was constant across the studies and the stand-alone accuracy of the ophthalmic artery Doppler indices was similar to those for uterine artery Doppler for early-onset disease.[23]

Study strengths and limitations

This is the first meta-analysis on the use of ophthalmic artery Doppler in the prediction of preeclampsia. We performed a comprehensive search by including four major databases with no language restrictions. Despite a low number of obtained studies, there were a reasonable number of women included in the final analysis (n=1119). Studies were performed at variable gestational age ranges, but importantly, the ophthalmic artery Doppler indices do not vary with advancing gestation.[6,24,25] However, we should note that these studies were mostly performed after 20 weeks of gestation. Also, only two of the included studies were performed on low risk populations contributing to the significant methodological heterogeneity between studies. None of the included studies reported information about the reproducibility of ophthalmic artery Doppler indices. The definition of early-onset preeclampsia varied across studies as well, but the prevalence of the early-onset preeclampsia was within known norms in all included studies. The bivariate models were chosen over univariate methods despite the former being low powered when the number of included studies is low. [12] However, it is not unheard of bivariate methods being used with low number of studies [26] and we had access to individual patient data of all the included studies allowing us to check whether the estimated results were skewed. Despite employing a thorough methodology, this meta-analysis is limited by the low number of studies with methodological heterogeneity. We should caution against the general-

ization of these results as all the included studies were performed in South America. Therefore, further studies in different populations are needed to ascertain the generalizability of their findings.

Comparison with existing literature

Effective early pregnancy screening for preeclampsia is a desired objective given increasing evidence for the effectiveness of low-dose aspirin in ameliorating adverse disease outcomes. [4,27] Most effective and validated screening models rely on uterine artery Doppler assessment because it has the highest diagnostic odds ratios for preeclampsia compared to other biomarkers. Maternal demographic characteristics and other biomarkers such as placental growth factor (PlGF) and mean arterial blood pressure are often included to improve screening accuracy.[28] According to a recent meta-analysis by Velauthar *et al.*, first trimester uterine artery Doppler has sensitivity and specificity of 47.8% (95% CI: 39.0-56.8) and 92.1% (95% CI: 88.6-94.6), respectively for the development of preeclampsia, which are not dissimilar to that of ophthalmic artery Doppler with sensitivity of 61.0% (95% CI 44.2-76.1) and specificity of 73.2% (95% CI 66.9-78.7) using the first diastolic peak velocity, suggesting that the ophthalmic artery Doppler assessment may be as effective as uterine artery Doppler assessment in screening for preeclampsia.[23] Furthermore, ocular Doppler has been shown to be an accurate, objective and promising technique that, unlike uterine artery Doppler assessment, does not suffer from the methodological issues related to the space-occupying effect of a gravid uterus and/or maternal obesity.[6] Ocular Doppler assessments are also more amenable to use in an office setting rather than requiring a scheduled exam with an ultrasound technician. The latter is of particular

relevance when considering the increasing utility of repeat and third trimester measurement of maternal hemodynamic assessment in later pregnancy in screening and diagnosis of preeclampsia.[29,30] There is no study combining serum biomarkers with ophthalmic artery Doppler for the prediction of preeclampsia. However, given similar performance to uterine artery Doppler screening, it might be safe to expect equal effectiveness in combined Doppler/biochemical screening for preeclampsia.

Research implications

Defective trophoblast development and impaired maternal spiral artery conversion are considered to be fundamental etiological factors for the development of preeclampsia. [31,32] Predictive models for preeclampsia, for the most part, use markers that are considered to be surrogates for placentation and placental function, such as PlGF and uterine artery Doppler. [33-38] The finding that ophthalmic artery Doppler may be as effective as uterine artery Doppler in the prediction of preeclampsia questions this paradigm as the former evaluation reflects maternal hemodynamic adaptation in pregnancy and cannot be related to trophoblast development. It is important to note that preeclampsia is associated with reduced cardiac index, increased vascular resistance and impaired myocardial relaxation which precede the overt clinical hypertension by several months. [39] Women with early-onset preeclampsia show more pronounced effects on the cardiovascular system [40] which may be related to the detected ophthalmic artery changes. Uterine artery waveform changes reflective of normal placentation have also been paradoxically reported with abdominal implantation of the placenta, consistent with the ophthalmic artery Doppler findings of this study. [41,42] A recent meta-analysis of villous and vascular placental lesions in normal pregnancy and preeclampsia has also shown that these histological findings are nei-

ther sensitive nor specific to preeclampsia, lending further support to the hypothesis that these placental lesions are in fact a consequence rather than the cause of preeclampsia. [43] An alternative hypothesis is that late-onset preeclampsia - the most prevalent form of the disorder - is unrelated to abnormal placentation and due to unspecified 'maternal' factors. [44-46] Although this explains the lack of placental findings in preeclampsia cases, the hypothesis remains consistent with maternal cardiovascular origins for preeclampsia. [47]

Conclusions

Ophthalmic artery Doppler is a simple, accurate and objective technique for assessing maternal hemodynamic circulation that may have utility in a resource-restricted setting. This meta-analysis confirms that ophthalmic artery Doppler has stand-alone predictive value for the development of early-onset preeclampsia, which is equivalent to that of the uterine artery Doppler evaluation. It is possible that the utility of uterine and ophthalmic artery Doppler evaluation in screening for preeclampsia is founded on the relationship of these indices to maternal hemodynamic adaptation to pregnancy rather than trophoblast invasion and maternal spiral artery conversion. The review findings justify efforts to elucidate the underlying mechanism by which two seemingly unrelated maternal vessels can be used for prediction of a disease commonly hailed as a placental disorder.

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Figure legends

Figure 1. Study selection flow diagram.

Figure 2. Summary receiver operating characteristics curves of Doppler parameters for the prediction of early-onset preeclampsia.

Supplementary Figure A. Summary receiver operating characteristics curves of Doppler parameters for the prediction of late-onset preeclampsia.

Table 1. Summary of the studies which reported the predictive accuracy of the ophthalmic artery Doppler for preeclampsia

Study	Diagnostic parameters	Screening time	Description of population	Period of recruitment	Study Center	Preeclampsia prevalence in study population
Gurgel-Alves 2014 [16]	S/D, PI, RI, PD1, PSV, PR	11 to 14 weeks' gestation	General obstetric population of undetermined risk for preeclampsia.	2009-2011	Fortaleza General Hospital, Brazil	31/440 (7%)
De Aquino 2014 [17]	RI	24 to 28 weeks' gestation	Women with a risk factor for developing preeclampsia (obesity, history of preeclampsia, diabetes mellitus)	Undetermined	Federal University of Minas-gerais, Brazil	14/73 (19.1%)
Matias 2014 [18]	PSV, EDV, MV, PMDV, RI, PI, PR	20 to 28 weeks' gestation	Pregnant women at high risk for developing preeclampsia (age, history of PE, primipaternity or new father, multiple gestation, hypertension, diabetes, obesity)	2010-2012	Bahia Perinatology Institute, Brazil	40/347(11.5%)
Gurgel-Alves 2016 [19]	PI, PD1, PR	11 to 14 weeks' gestation	General obstetric population of undetermined risk for preeclampsia.	2009-2011	Fortaleza General Hospital, Brazil	12/477(2.4%)
De Souza 2016 [20]	PI, PD1, PR	18 to 23 weeks' gestation	General obstetric population of undetermined risk for preeclampsia.	2011-2014	Fortaleza General Hospital, Brazil	40/349 (11.5%)

EDV: End-diastolic velocity, MV: Mean velocity, PD1: First diastolic peak velocity-1, PI: Pulsatility index, PMDV, Peak meso-diastolic velocity, PR: Peak ratio, RI: Resistive index

Table 2. QUADAS-2 domains of the studies which reported the predictive accuracy of the ophthalmic artery Doppler for preeclampsia.

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Gurgel-Alves 2014 [16]	☺	☺	☺	☺	☺	☺	☺
De Aquino 2014 [17]	☹	☺	☺	☹	☹	☺	☺
Matias 2014 [18]	?	☺	☺	☺	☺	☺	☺
Gurgel-Alves 2016 [19]	☺	☺	☺	☺	☺	☺	☺
De Souza 2016 [20]	☺	☺	☺	☺	?	☺	☺

☺: Low risk, ☹: High risk,? Undetermined risk

Table 3. Ophthalmic artery Doppler indices for the diagnosis of preeclampsia

Parameter	No. of studies and reference no.	No. of preeclampsia cases and controls	Standardized mean difference (95% CI) *	I-squared
PD-1	3 [16,18,20]	111/1008	-0.36 (-0.55 to -0.16)	82.6% (P=0.003)
Pulsatility index	3 [16,18,20]	111/1008	0.18 (-0.02 to 0.38)	0% (P=0.933)
Peak ratio	3 [16,18,20]	111/1008	-0.33 (-0.53 to -0.14)	0% (P=0.416)
Resistive index	2 [16,18]	71/699	0.26 (-0.05 to 0.44)	0% (P=0.670)
Peak systolic velocity	2 [16,18]	71/699	-0.34 (-0.59 to -0.10)	0% (P=0.589)

CI: confidence interval, PD-1: first diastolic peak velocity-1

* Meta-analysis using a random effects model with Hedges' g for bias corrected standardized mean differences.

Table 4. Accuracy of ophthalmic artery Doppler indices for the prediction of early and late onset preeclampsia

	Early-onset preeclampsia				
Parameter and cut-off	Sensitivity (95% CI)*	Specificity (95% CI) *	AUC (95% CI) †	Positive LR ‡	Negative LR ‡
PD-1 (>23.3 cm/s)	61.0% (44.2-76.1)	73.2% (66.9-78.7)	0.68 (0.61-0.76)	2.44 (1.77-3.35)	0.54 (0.35-0.82)
Pulsatility index (<2.4)	24.8% (12.0-44.2)	71.6% (61.5-79.9)	0.54 (0.45-0.64)	0.88 (0.51-1.50)	1.05 (0.86-1.29)
Peak ratio (>0.65)	51.3% (31.4-70.9)	82.3% (71.3-89.7)	0.67 (0.58-0.77)	3.27 (1.93-5.53)	0.64 (0.46-0.88)
	Late-onset preeclampsia				
Parameter and cut-off	Sensitivity (95% CI)*	Specificity (95% CI) *	AUC (95% CI) †	Positive LR ‡	Negative LR ‡
PD-1 (>23.3 cm/s)	39.0% (20.6-61.0)	73.2% (66.9-78.7)	0.58 (0.52-0.65)	1.44 (0.67-3.07)	0.87 (0.64-1.20)
Pulsatility index (<2.4)	21.6% (12.7-34.5)	71.6% (61.5-79.9)	0.57 (0.50-0.64)	0.77 (0.49-1.20)	1.08 (0.95-1.21)
Peak ratio (>0.65)	19.4% (11.9-30.1)	82.3% (71.3-89.7)	0.57 (0.51-0.63)	1.12 (0.61-2.06)	0.99 (0.85-1.15)

AUC: area under the curve, CI: confidence interval, LR: likelihood ratio, PD-1: first diastolic peak velocity-1

* Data from a bivariate random effects model.

† Data from a generalized linear model with fixed group effects for clustering using pooled individual patient data.

‡ Data from a univariate random effects model