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First-trimester maternal ophthalmic artery Doppler analysis for prediction of pre-eclampsia

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KEYWORDS: Doppler sonography; first-trimester screening; ophthalmic artery; pregnancy; uterine artery Doppler

ABSTRACT

Objective *To determine the performance of a multiparametric test comprising maternal risk factors, uterine artery Doppler and ophthalmic artery Doppler in the first trimester of pregnancy for the prediction of pre-eclampsia (PE).*

Methods *This prospective observational cohort study recruited patients in the first trimester of pregnancy. Maternal uterine artery and ophthalmic artery Doppler assessments were performed in 440 singleton pregnancies at 11–14 weeks of gestation. Additional history was obtained through participant questionnaires, and follow-up occurred to discharge postdelivery. The normotensive and pre-eclamptic groups were compared using parametric (Student's t-test) and non-parametric (Mann–Whitney U-test) tests. Univariable and multivariable logistic regression analyses were performed to determine which biophysical factors, and which of the factors among the maternal characteristics and medical and obstetric history, had a significant contribution to the prediction of PE in a multiparametric model.*

Results *Thirty-one (7%) patients developed PE, including nine (2%) who required delivery before 34 weeks (early PE) and 22 (5%) with late PE. There were statistically significant differences in uterine artery pulsatility index (UtA-PI) and ophthalmic artery first diastolic peak (PD1) mean values between the PE and control groups. In a multiparametric model, both UtA-PI and PD1 achieved a 67% detection rate for early PE, although when combined, the detection rate only increased to 68%.*

Conclusions *The efficiency of ophthalmic artery PD1 in the first trimester as a predictive marker for the later development of PE was approximately equal to that described for uterine artery Doppler. Although these findings do not support the replacement of uterine artery Doppler analysis in multiparametric predictive models for PE, they do provide novel insights into first-trimester maternal systemic vascular changes that precede the clinical development of this condition. Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Pre-eclampsia (PE) – new-onset hypertension and proteinuria – affects about 2–8% of pregnancies and is a leading cause of maternal and perinatal mortality and morbidity[1]. Recent evidence suggests that PE can be subdivided into early- and late-onset forms[2,3], each having a distinct underlying pathophysiological origin[4,5]. Early-onset PE (that requiring delivery < 34 weeks' gestation) is commonly associated with intrauterine growth restriction (IUGR) and adverse maternal and perinatal outcomes[6,7]. In contrast, late-onset PE (delivery ≥ 34 weeks) is often associated with milder maternal disease and the perinatal outcomes are usually favorable. Although the etiology of PE remains incompletely understood, the most accepted hypothesis is that it is a placental function disorder arising from defective remodeling of the uterine spiral arteries in early gestation, particularly in those pregnancies destined to develop early-onset PE[8]. Late-onset PE appears to have a closer association with maternal constitutional factors and cardiovascular risk[9].

First-trimester prediction of PE would allow for initiation of prophylactic therapies and institution of appropriate clinical surveillance, thereby potentially improving outcomes[10]. No single predictive test has demonstrated sufficient specificity and sensitivity to be of clinical utility, leading to the development of

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multiparametric testing regimens that commonly incorporate maternal factors, uterine artery Doppler, mean arterial pressure (MAP) and various biochemical markers. Such tests perform particularly well in the detection of early-onset PE[11–14]. Maternal cardiac output and middle cerebral artery (MCA) Doppler indices have also demonstrated modest predictive value for PE[15,16].

The neurological complications of severe PE, primarily mediated through a loss of autoregulation in the maternal cerebrovasculature, are responsible for a significant proportion of the morbidity and mortality arising from this disease[17]. Alterations in cerebral blood flow have been shown to predate the clinical development of PE by some weeks: for example, the resistance index (RI) and pulsatility index (PI) in the maternal MCA are lower in women who go on to develop PE[18,19]. In light of their functional, embryological and anatomical similarities with intracranial vessels, Doppler assessment of orbital vessels can provide insights into the small-caliber cerebral vasculature that cannot be imaged in a transcranial manner[20]. Studies of the maternal ophthalmic artery in women with PE have generally shown decreased RI and PI, combined with increased blood-flow velocity, suggesting decreased vascular resistance[21–24]. Whether changes occur in this vessel before the development of PE, thereby permitting its prediction, has not yet been determined.

The aim of this study was to determine the performance of a multiparametric test comprising maternal risk factors, uterine artery Doppler and ophthalmic artery Doppler in the first trimester of pregnancy for the prediction of PE.

METHODS

This prospective observational cohort study recruited patients attending the Maternal-Fetal Medicine Service of Fortaleza General Hospital in northeastern Brazil for routine first-trimester Down syndrome screening between August 2009 and February 2011. Participants were drawn from the general obstetric population at this center, and were of undetermined risk for PE. All patients signed an informed consent form approved by the local Research Ethics Committee, which had also approved the overall study. The participants' epidemiological characteristics and Doppler indices were entered into a database. Patients were followed up to delivery, and information concerning the evolution of pregnancy and its maternal and perinatal outcomes was obtained from hospital records.

Baseline characteristics of participants were obtained from their medical record and by use of a questionnaire that included the following: age, ethnicity (Native Brazilian, Caucasian, other), current body mass index (BMI), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), smoking during pregnancy (any number of cigarettes per day), alcohol intake during pregnancy (any volume), use of drugs during pregnancy, and medical history (chronic hypertension, diabetes mellitus, family history of PE in the mother or sister of the woman (Fam-PE), and obstetric history, including parity and history of PE in a previous pregnancy (Previous PE)).

Participants underwent a fetal ultrasound scan to measure the crown–rump length (CRL) and to confirm gestational age (GA), in addition to routine measurement of nuchal translucency. GA was established on the basis of menstrual dates and was confirmed by this ultrasound; if there was a difference of more than 7 days, then the ultrasound date was used.

Patients with a singleton pregnancy recruited in the first trimester who subsequently delivered a phenotypically normal stillbirth or live birth, at or after 24 weeks' gestation, were included in this study. The exclusion criteria were: multiple gestation; pregnancies with major fetal abnormalities and those ending in miscarriage or fetal death before 24 weeks; birth weights below the 10th percentile without concomitant PE; pregnancies affected by gestational hypertension; and loss to follow up.

Participants remained at rest for 10 min prior to the ultrasound examinations, which were all performed using a Voluson 730 (GE Healthcare Ultrasound, Milwaukee, WI, USA). A 6–12-MHz linear probe was used for the ophthalmic artery assessment, and a 3.5-MHz convex transducer was used for transabdominal sonography. To assess the uterine artery, women were placed in a supine position and a transabdominal ultrasound was performed to obtain a sagittal image of the uterus at the level of the internal cervical os. The transducer was gently inclined from one side to the other, while color Doppler flow mapping was used to identify the uterine arteries bilaterally. Pulsed Doppler was then used to obtain velocity waveforms from the ascending branch of the uterine artery at the point closest to the internal os. When three similar consecutive waveforms were obtained, the PI was measured and the mean was calculated using the values obtained for the left and right arteries.

The ophthalmic artery was assessed with the patient in the same supine position, with her eyes closed. Following application of conduction gel, the transducer was placed transversely over the upper eyelid. In keeping with the technique established by other researchers, only the right ophthalmic artery was assessed[25]. The examiner performed movements in a craniocaudal direction, without exerting too much pressure, to avoid inducing alterations in the observed parameters. The ophthalmic artery was insonated at approximately 15 mm from the optic disc, medial to the optic nerve. Following identification of the artery, at least six uniform waves were recorded using pulsed wave Doppler (Figure 1a). A sample angle of less than 20° was required, using a 50-Hz filter, with a pulse repetition frequency of 125 kHz and sample volume of 2 mm. The parameters analyzed were the PI, RI, peak systolic velocity (PSV), first diastolic peak velocity (PD1) and the peak ratio (PR) (Figure 1b). The PR was defined as the ratio between the PD1 and the PSV[26].

Pre-eclampsia was defined in accordance with criteria determined by the International Society for the Study of Hypertension in Pregnancy (ISSHP)[27]: hypertension developing after 20 weeks of gestation with a diastolic

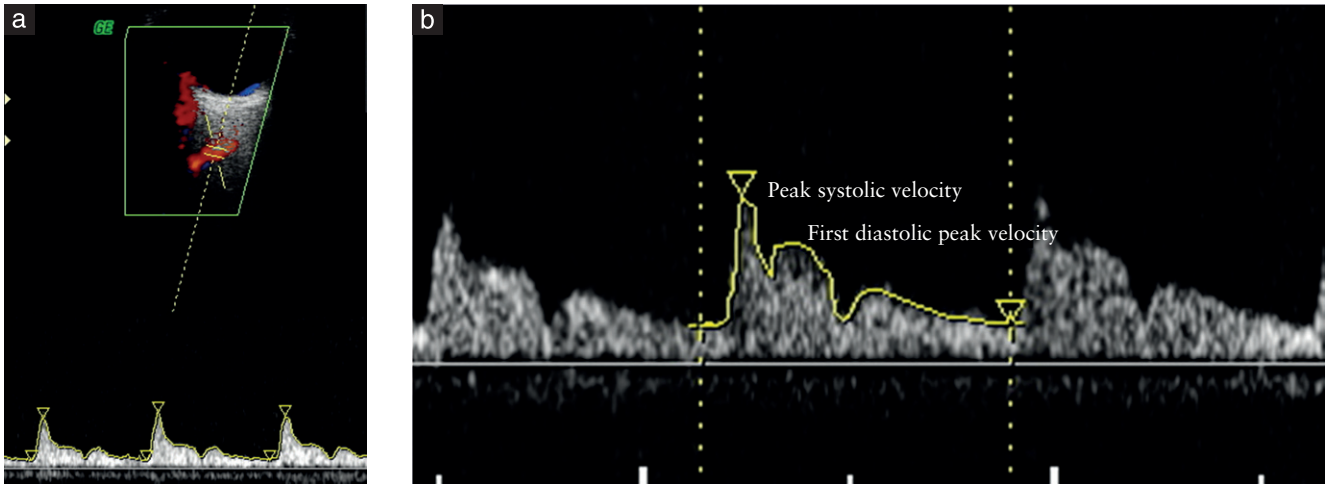

Figure 1 Ophthalmic artery Doppler interrogation (a) and waveform (b).

Table 1 Demographic characteristics

		Pre-eclampsia		
Characteristic	*Controls (n = 409)*	*All (n = 31)*	*Late (n = 22)*	*Early (n = 9)*
Maternal age (years)	26.1 ± 6.7	26.0 ± 6.1	24.0 ± 5.6	30.5 ± 5.1*†
Ethnicity				
Caucasian	94 (23.0)	5 (16.1)	3 (13.6)	2 (22.2)
Native Brazilian	303 (74.1)	26 (83.9)	19 (86.4)	7 (77.8)
Other	12 (2.9)	0 (0)	0 (0)	0 (0)
Parity				
Nulliparous	201 (49.1)	18 (58.1)	15 (68.2)	3 (33.3)
Para 1	115 (28.1)	9 (29.0)	5 (22.7)	4 (44.4)
Para 2 or 3	82 (20.0)	4 (12.9)	2 (9.1)	2 (22.2)
Para ≥ 4	11 (2.7)	0 (0)	0 (0)	0 (0)
Previous PE	24 (5.9)	10 (32.2)‡	5 (22.7)	5 (55.6)‡
Family history of PE	60 (14.7)	11 (35.5)*	7 (31.8)	4 (44.4)‡
Cigarette smoker	25 (6.1)	0 (0)	0 (0)	0 (0)
Alcohol consumption	46 (11.2)	3 (9.7)	2 (9.1)	1 (11.1)
BMI (kg/m^2)	25.0 ± 4.6	28.2 ± 4.6‡	27.2 ± 4.4	30.1 ± 4.6
High BMI (>30)	56 (13.7)	12 (38.7)‡	5 (22.7)	7 (77.8)‡
Chronic hypertension	9 (2.2)	3 (9.7)	2 (9.1)	1 (11.1)
Pre-existing diabetes	12 (2.9)	0 (0)	0 (0)	0 (0)

Values are expressed as mean ± SD or *n* (%). Comparisons by chi-square test and Fisher's exact test for categorical variables and by Mann–Whitney *U*-test with post-hoc Bonferroni correction for continuous variables. All PE and early PE *vs* control group: *$P = 0.01$; ‡$P < 0.001$. Early PE *vs* late PE: †$P = 0.01$. BMI, body mass index; Previous PE, parous with previous pre-eclampsia.

blood pressure of 90 mmHg or more on at least two occasions, 4 h apart, and proteinuria of 300 mg or more in 24 h, or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h urine collection is available.

Statistical analysis

The measured uterine artery PI (UtA-PI) was converted to multiples of the median (MoM) and corrected for fetal CRL, maternal age, weight, smoking, parity and ethnicity. Comparisons between pre-eclamptic and normotensive participants were conducted using appropriate parametric (Student's *t*-test) and non-parametric (Mann–Whitney *U*-test) tests. Univariable and multivariable logistic regression analysis was used to determine which factors among the maternal characteristics and biophysical factors had a significant association with the later development of PE. The performance of these factors was determined by receiver–operating characteristics (ROC) curves, and through calculation of sensitivity, specificity, likelihood ratios (LRs) and predictive values. All calculations were performed using the STATA 10 statistical program (Stata Corp., College Station, TX, USA).

RESULTS

The study cohort initially consisted of 550 consecutive, singleton pregnancies with a live fetus between 11 and 14 weeks' gestation. Forty-five (8.2%) cases were lost

Table 2 Biophysical factors in the first trimester of pregnancy according to maternal outcome

Variable	*Controls* (n = *409*)	*Pre-eclampsia*		
		All (n = *31*)	*Late* (n = *22*)	*Early* (n = *9*)
CRL (mm)	62.65 ± 12.93	64.78 ± 9.93	64.86 ± 10.1	64.76 ± 9.79
Uterine artery				
PI	1.53 ± 0.54	1.67 ± 0.5	1.60 ± 0.5	1.85 ± 0.3
PI MoM	0.92 ± 0.49	1.02 ± 0.29	0.96 ± 0.3	1.14 ± 0.22
PI centile¶	37.46 ± 30.04	50.35 ± 31.77*	43.44 ± 33.5	67.26 ± 31.77†§
Ophthalmic artery				
S/D	5.63 ± 2.46	5.44 ± 3.07	5.55 ± 3.50	5.20 ± 1.70
PI	2.06 ± 0.57	1.97 ± 0.6	1.92 ± 0.6	2.11 ± 0.6
RI	0.81 ± 0.12	0.78 ± 0.06	0.78 ± 0.70	0.79 ± 0.60
PD1 (cm/s)	21.13 ± 7.76	24.56 ± 12.22†	24.77 ± 13.6‡	24.03 ± 8.2
PSV (cm/s)	36.34 ± 12.08	39.69 ± 13.9	40.65 ± 15.9	37.35 ± 7.1
PR	0.58 ± 0.11	0.60 ± 0.14	0.59 ± 0.15	0.63 ± 0.13

Values are expressed as mean ± SD. Comparisons by Mann–Whitney *U*-test with post-hoc Bonferroni correction, as follows: all PE and early PE *vs* unaffected group: *$P < 0.001$; †$P = 0.01$; late PE *vs* unaffected group: ‡$P = 0.03$; early PE *vs* late PE: §$P = 0.01$. ¶Based on data from reference 14. CRL, crown–rump length; MoM, multiples of the median; PD1, first diastolic peak velocity; PE, pre-eclampsia; PI, pulsatility index; PR, peak ratio; PSV, peak systolic velocity; RI, resistance index; S/D, systolic/diastolic blood velocity.

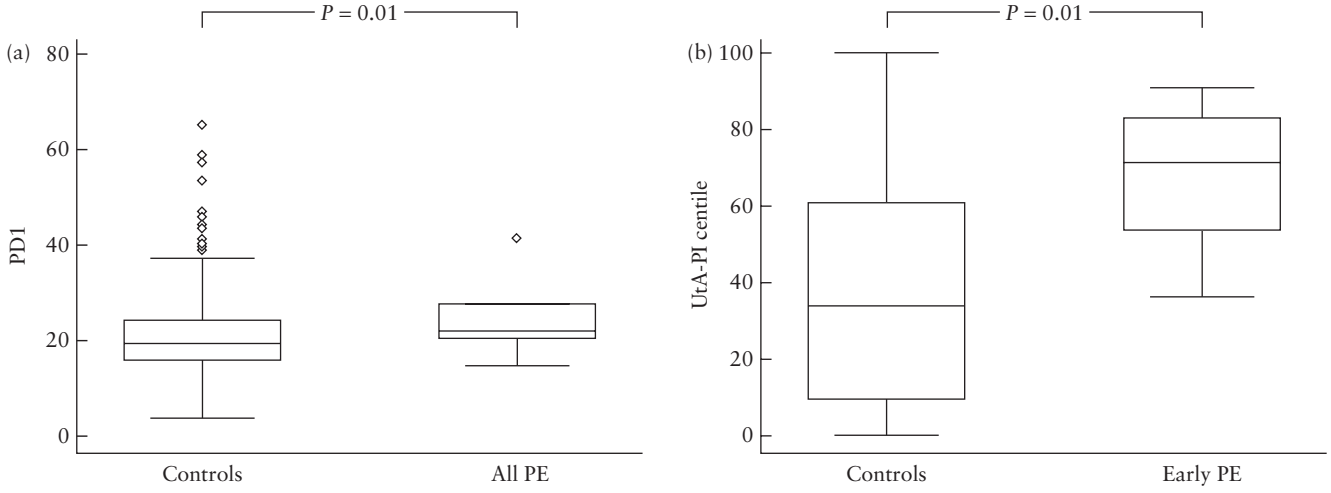

Figure 2 Box plots comparing: (a) first diastolic peak velocity (PD1) between controls and both types of pre-eclampsia (All PE); (b) mean uterine artery pulsatility index (UtA-PI) centile between controls and the early PE group. Boxes and internal lines represent lower and upper quartiles and median, respectively, whiskers show range and diamonds show outliers.

to follow up, and thus excluded. Also excluded were 12 (2.2%) normotensive women who delivered neonates with birth weights below the 10th percentile, 47 (8.5%) who developed gestational hypertension (GH) and six (1.0%) whose pregnancies resulted in fetal death or miscarriage before 24 weeks of gestation. In the remaining 440 women, 31 (7.0%) developed PE, including nine who required delivery before 34 weeks (early PE) and 22 with late PE. We have published previously findings from the 409 healthy controls, as a reference range of maternal ophthalmic artery Doppler parameters[28].

The baseline characteristics of the 31 patients affected by PE and 409 controls are summarized in Table 1. Previous PE, family history of PE and BMI > 30 showed statistically significant differences between the PE and control groups. The mean maternal age was statistically significantly higher in the early-PE group when compared with both the late-PE group and the control group ($P = 0.01$ for both) (Table 1).

There were statistically significant differences in mean UtA-PI and mean PD1 values between PE and control groups (Table 2, Figure 2). The highest mean ± SD for PD1 was observed in the late PE group (24.77 ± 13.6), and was statistically significantly higher than that of the control group (21.13 ± 7.76) ($P = 0.03$).

An adjusted logistic regression model for the prediction of PE was developed, comprising three categorical variables (nulliparity, previous PE and family history of PE) and three continuous variables (BMI, UtA-PI and PD1). The *a-priori* risk of PE was calculated by the formula: odds — (1 + odds), where odds is e^Y, derived from the multiple logistic regression analysis of the maternal characteristics and biophysical parameters. The logarithmic model was: PE = −5.6904 + 0.9983 × [previous PE] × 0.5345 [if patient's mother or sister had PE] × 0.8150 [nulliparous] × 0.0924 [BMI] + 0.0403 [DP1] × 0.0112 [UtA-PI]. All coefficients were observed to be positive,

Table 3 Comparison of the performance of screening for pre-eclampsia (PE) according to maternal risk factors, uterine artery pulsatility index (UtA-PI) and ophthalmic artery first diastolic peak velocity (PD1)

	AUC (95% CI)			*DR (%) for 10% FPR*		
Variable	*All PE*	*Late PE*	*Early PE*	*All PE*	*Late PE*	*Early PE*
Maternal history	0.75 (0.66–0.83)	0.75 (0.66–0.83)	0.72 (0.62–0.81)	43	40	59
BMI	0.69 (0.59–0.78)	0.64 (0.58–0.75)	0.79 (0.63–0.95)	25	22	33
Maternal factors	0.81 (0.73–0.90)	0.79 (0.73–0.90)	0.86 (0.73–0.98)	45	50	63
UtA-PI	0.61 (0.51–0.72)	0.54 (0.41–0.67)	0.77 (0.67–0.87)	16	13	22
PD1	0.56 (0.45–0.66)	0.53 (0.40–0.66)	0.61 (0.42–0.79)	19	22	11
Maternal factors + UtA-PI	0.83 (0.75–0.90)	0.80 (0.71–0.90)	0.86 (0.74–0.99)	58	45	67
Maternal factors + PD1	0.83 (0.75–0.90)	0.81 (0.72–0.89)	0.86 (0.73–0.98)	48	36	67
Maternal factors + UtA-PI + PD1	0.83 (0.76–0.91)	0.81 (0.73–0.91)	0.86 (0.74–0.99)	54	40	68

AUC, area under the receiver–operating characteristics curve; BMI, body mass index; DR, detection rate; FPR, false-positive rate.

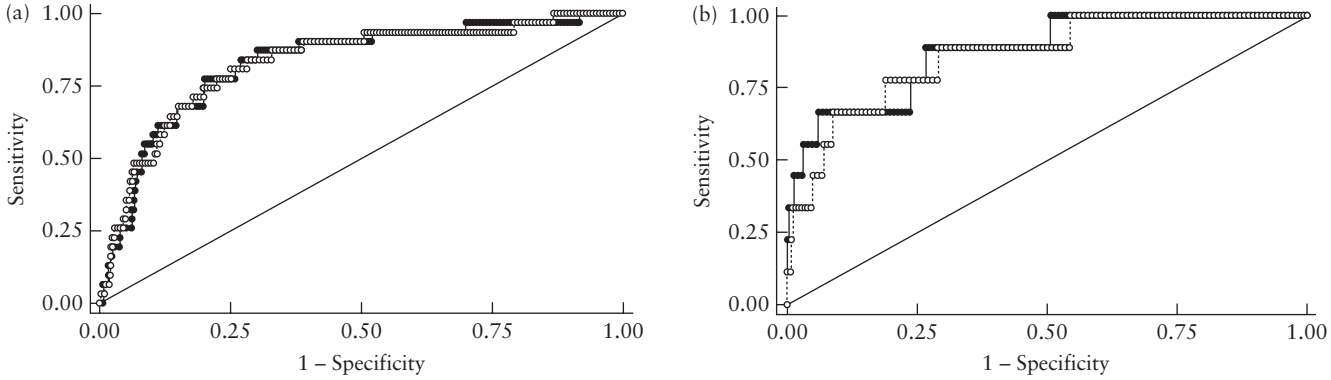

Figure 3 Receiver–operating characteristics (ROC) curves of ophthalmic artery first diastolic peak velocity (PD1) + maternal factors (···○···) and uterine artery pulsatility index (UtA-PI) + maternal factors (—●—) for the prediction of all pre-eclampsia (PE) (a) and early PE (b). In (a), area under the ROC curve (AUC) = 0.8301 for UtA-PI + maternal factors and 0.8294 for PD1 + maternal factors ($P = 0.97$). In (b), AUC = 0.8746 for UtA-PI + maternal factors and 0.8603 for PD1 + maternal factors ($P = 0.21$).

and all the variables contributed to an increase in the probability of PE.

Univariate logistic regression analysis revealed that the estimated detection rates of PE from screening based on UtA-PI and PD1 alone were 16% and 19%, respectively, at a fixed false-positive rate of 10%. However, the multiple regression analysis demonstrated that models combining maternal factors with UtA-PI and PD1 provided significantly improved prediction of PE, with the former achieving a detection rate of 58% and the latter a detection rate of 48%. The highest detection rates in these models were for the outcome of early PE, at 67% with UtA-PI or PD1, and 68% when combined. Among the outcomes studied, late PE had the lowest detection rates, with the addition of UtA-PI and PD1 to maternal factors in fact lowering the detection rate achieved by maternal factors alone (Table 3). The areas under the ROC curves did not demonstrate statistically significant differences for screening by maternal factors with UtA-PI and maternal factors with PD1 in the prediction of PE ($P = 0.97$) and early PE ($P = 0.21$) (Figure 3).

For the prediction of PE, the positive predictive values of models incorporating PD1 with maternal factors and UtA-PI with maternal factors were 24% and 27%, respectively. These same models returned negative predictive values of 96% and 97%, respectively. The positive LRs were 5.0 and 6.0, respectively, with a negative LR of 0.1 for both models.

DISCUSSION

First-trimester screening for the later development of PE is the subject of an increasing body of research and promises improved maternal and perinatal outcomes through enhanced clinical surveillance and early initiation of proven prophylactic agents, such as aspirin[29] and calcium[30]. It will also allow for the recruitment of a population at truly high risk for this condition to clinical trials of novel preventative therapies. To the best of our knowledge, this study is the first to determine the utility of maternal ophthalmic artery Doppler analysis in the first-trimester prediction of PE.

Doppler analysis of the ophthalmic artery in pregnant women was first proposed by Hata *et al.* in 1992[31]. Subsequent studies confirmed a decrease in ophthalmic vascular resistance and an increase in perfusion in patients with PE. Ohno *et al.* found higher orbital vascular perfusion in 30 pre-eclamptic patients when compared with 118 normotensive patients in the third trimester of pregnancy[32]. In 2002, Takata *et al.* examined 99 pregnancies (including 27 with severe PE, 25 with mild PE and 32 controls) and observed that the PR was significantly greater in severe PE

in the third trimester[33]. Ayaz *et al.* found the RI and the PI in the ophthalmic arteries to be lower in 30 patients with mild PE compared with 30 healthy pregnant women after 32 weeks of gestation[22]. Barbosa *et al.* observed that the RI was decreased among 26 patients with PE complicated by encephalopathy and photophobia compared with 86 normotensive gravidas[34]. Brandão *et al.* found the RI to be lower among 26 patients with early-onset PE and in 30 patients with late-onset PE compared with 28 healthy controls in a cross-sectional study during the third trimester[35].

Previous studies have evaluated other cerebrovascular changes as predictive markers for PE. A nested case–control study within a prospective cohort study evaluated 20 pre-eclamptic patients and 40 normotensive patients and found statistically significant differences in the Doppler indices of the MCA in the third trimester (28–32 weeks), but not in the second trimester (20–24 weeks)[36]. A recent prospective cohort study of 166 normotensive pregnant women at 19–28 weeks of gestation found lower values of MCA Doppler indices (RI and PI) in the 10 patients who subsequently developed PE[19]. This early decrease in cerebrovascular impedance among women destined to develop PE is corroborated by the findings of our study, in which maternal ophthalmic artery diastolic velocities were increased between 11 and 14 weeks in subsequently pre-eclamptic pregnancies.

In this study, the incidence of PE was 7%. This is comparable with the rates of 2–8% reported in the literature for a population of undetermined risk in developing countries[10,27]. However, studies published by The Fetal Medicine Foundation (FMF) have reported lower rates of PE (1.2–2.2%), and early-onset PE (0.3–0.8%), in contrast to the 2% rate at which the latter occurred in this study[13,14,37]. The high incidence of early PE and PE in our study may be explained by the fact that this research was conducted in a tertiary hospital, to which pregnancies at risk of later complications are referred.

A prior history of PE was the most important predictive factor identified in our study, followed by nulliparity and a family history of PE. These findings are in accordance with observations reported earlier, of an eight- to 11-fold increased risk of PE with a personal history of the condition, and a four-fold increased risk with a family history of this condition[38–41]. We observed that nulliparous women had a five-fold greater risk of developing PE, double the risk reported by another study[39], and supporting the National Institute for Health and Care Excellence (NICE; UK) guidance in this respect[42]. However, having had prior pregnancies unaffected by PE or GH was a strong protective factor against PE in our study (OR = 0.05), in keeping with other authors' findings[43,44]. An elevated BMI was also associated with a higher risk for PE, with those who developed early-onset PE having the highest average BMI, as noted by others[14,38,39].

In this study, the efficiency of maternal ophthalmic artery PD1 as a predictive marker was approximately equal to that of uterine artery Doppler PI, which is the most studied biophysical marker for the prediction of PE. Our findings also correlate closely with the predictive performance of UtA-PI and maternal factors reported by other authors[14,45,46]. In isolation, the parameters PD1 and UtA-PI had low detection rates for PE. However, when these parameters were combined with maternal history and BMI, an improved detection rate was achieved. The fact that multiparametric tests are required to achieve clinically useful prediction of PE highlights the multifactorial origins of PE.

Our study found that Doppler analysis of the maternal ophthalmic artery was more efficient in detecting late PE, whereas uterine artery Doppler was more effective in predicting early PE. This finding is consistent with the hypothesis that two distinct pathophysiological processes underlie early- and late-onset PE. Early-onset PE is more often associated with a failure of trophoblastic invasion and thus altered uterine artery Doppler parameters, whereas late-onset PE has a stronger association with maternal cardiovascular risk factors[5]. As reported by other authors, we found late-onset PE to be more frequent, generally less severe and less predictable with screening algorithms compared with early-onset PE. In this study, the presence of increased orbital (and thus presumably cerebral) perfusion supports the hypothesis that late-onset PE is associated with increased cardiac output[47] and variable peripheral resistance[48].

This study is the first, to our knowledge, to have assessed maternal cerebrovascular changes in the first trimester of pregnancy and the predictive value of these changes for the later development of PE. Its main limitation is sample size, which yielded only nine cases of early-onset PE. Furthermore, ophthalmic artery Doppler indices were not adjusted for maternal factors such as alcohol consumption (although the rates of such factors were similar between cases and controls), and raw values rather than MoM were used in statistical analyses.

We conclude that maternal ophthalmic artery Doppler analysis in the first trimester of pregnancy is a novel predictive parameter for PE. It makes the same contribution to multiparametric predictive models for PE as does uterine artery Doppler PI, although it did not add to the detection rate achieved by the latter alone in multiparametric predictive models. As a consequence, given that uterine artery Doppler interrogation is becoming a well-established component of obstetric sonography, it will not be replaced by ophthalmic artery sonography in such testing regimens. Our results do, however, provide an insight into the systemic maternal vascular changes that precede the development of PE, demonstrating that such changes are not limited to the uteroplacental vascular bed.

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