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Ophthalmic artery Doppler in combination with other biomarkers in prediction of pre-eclampsia at 19–23 weeks' gestation

I. SAPANTZOGLOU[1], A. WRIGHT[2], M. GALLARDO AROZENA[1], R. VALLENAS CAMPOS[1], M. CHARAKIDA[1] and K. H. NICOLAIDES[1]

[1]*Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK;* [2]*Institute of Health Research, University of Exeter, Exeter, UK*

KEYWORDS: ophthalmic artery Doppler; pre-eclampsia; second trimester

CONTRIBUTION

What are the novel findings of this work?
Ophthalmic artery Doppler at 19–23 weeks' gestation improves the prediction of pre-eclampsia (PE), especially preterm PE with delivery at < 37 weeks, provided by various combinations of maternal characteristics, medical history, uterine artery pulsatility index, mean arterial pressure, serum placental growth factor and serum soluble fms-like tyrosine kinase-1.

What are the clinical implications of this work?
Ophthalmic artery Doppler could be incorporated into second-trimester screening for subsequent development of PE.

ABSTRACT

Objective *To examine the potential value of maternal ophthalmic artery Doppler at 19–23 weeks' gestation on its own and in combination with the established biomarkers of pre-eclampsia (PE), including uterine artery (UtA) pulsatility index (PI), mean arterial pressure (MAP), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFlt-1), in the prediction of subsequent development of PE.*

Methods *This was a prospective observational study of women attending for a routine hospital visit at 19 + 1 to 23 + 3 weeks' gestation. This visit included recording of maternal demographic characteristics and medical history, ultrasound examination for fetal anatomy and growth, assessment of flow velocity waveforms from the maternal ophthalmic arteries, and measurement of MAP, UtA-PI, serum PlGF and serum sFlt-1. Waveforms were obtained from the ophthalmic arteries in sequence from the right eye, left eye and again from the right and then left eye. We recorded the average of the four measurements, two from each eye, for the following four indices: first peak of systolic velocity; second peak of systolic velocity; PI; and the ratio of the second to first peak of systolic velocity (PSV ratio). The measurements of the four indices were standardized to remove the effects of maternal characteristics and elements from the medical history. The competing-risks model was used to estimate the individual patient-specific risks of delivery with PE at < 37 and ≥ 37 weeks' gestation and to determine the area under the receiver-operating-characteristics curve (AUC) and detection rate (DR), at a 10% false-positive rate (FPR), in screening by a combination of maternal demographic characteristics and medical history with biomarkers. The modeled performance of screening for PE was also estimated.*

Results *The study population of 2853 pregnancies contained 76 (2.7%) that developed PE, including 18 (0.6%) that delivered with PE at < 37 weeks' gestation. The ophthalmic artery PSV ratio was significantly increased in PE pregnancies, and the PE effect depended on gestational age at delivery; the deviation from normal was greater for early than late PE. The second peak of systolic velocity was also increased in PE pregnancies, but the effect did not depend on gestational age at delivery. The other two ophthalmic artery indices of first peak of systolic velocity and PI were not significantly affected by PE. The PSV ratio improved the prediction of preterm PE provided by maternal factors alone (from 56.1% to 80.2%), maternal factors, MAP and UtA-PI (80.7% to 87.9%), maternal factors, MAP, UtA-PI and PlGF (85.5% to 90.3%) and maternal factors, MAP,*

Correspondence to: Prof. K. H. Nicolaides, Fetal Medicine Research Institute, King's College Hospital, 16–20 Windsor Walk, Denmark Hill, London SE5 8BB, UK (e-mail: kypros@fetalmedicine.com)

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UtA-PI, PlGF and sFlt-1 (84.9% to 89.8%), at a FPR of 10%. The PSV ratio also improved the prediction of term PE provided by maternal factors alone (from 33.8% to 46.0%), maternal factors, MAP and UtA-PI (46.6% to 54.2%), maternal factors, MAP, UtA-PI and PlGF (45.2% to 53.4%) and maternal factors, MAP, UtA-PI, PlGF and sFlt-1 (43.0% to 51.2%), at a FPR of 10%. The empirical results for DR at a 10% FPR were consistent with the modeled results. The second peak of systolic velocity did not improve the prediction of either preterm or term PE provided by maternal factors alone.

Conclusion *Ophthalmic artery PSV ratio at 19–23 weeks' gestation, both on its own and in combination with other biomarkers, is potentially useful for prediction of subsequent development of PE, especially preterm PE, but larger studies are needed to validate this finding. © 2020 International Society of Ultrasound in Obstetrics and Gynecology*

INTRODUCTION

Assessment of risk for pre-eclampsia (PE) should be undertaken in each of the three trimesters of pregnancy. Screening for PE at 11–13 weeks' gestation by a combination of maternal demographic characteristics and medical history with measurements of mean arterial pressure (MAP), uterine artery (UtA) pulsatility index (PI) and serum placental growth factor (PlGF) can identify about 90% of women who develop early PE with delivery at < 32 weeks' gestation, 75% of those with preterm PE at < 37 weeks and 40% with term PE, at a false-positive rate (FPR) of 10%[1–4]. Administration of aspirin (150 mg/day from 11–14 weeks' gestation to 36 weeks) in the high-risk group reduces the rate of early PE by about 90% and preterm PE by 60%, but has no significant effect on term PE[5]. Screening for PE should also be carried out at around 20 and 36 weeks' gestation[6–12]. The rationale for such second- and third-trimester screening is not prevention of PE, but rather identification of a high-risk group that would benefit from close monitoring to minimize adverse perinatal events for those who develop PE by determining the appropriate timing and place for delivery. Useful biomarkers of PE at 20 weeks' gestation are MAP, UtA-PI, PlGF and serum soluble fms-like tyrosine kinase-1 (sFlt-1)[7,8] and at 36 weeks are MAP, PlGF, sFlt-1 and probably ophthalmic artery Doppler[9–14].

The ophthalmic artery, which has anatomical and functional similarities with the intracranial vasculature, is an easily accessible vessel for Doppler assessment that provides information on the less accessible intracranial circulation[15]. Extensive evidence suggests that, in pregnancies with PE, compared to normal pregnancies, there is a decrease in impedance to flow and an increase in flow velocity in the ophthalmic arteries[15]. There is also some contradictory evidence that alterations in ophthalmic artery Doppler may precede the clinical onset of PE[13,14,16–18]. In a recent prospective observational study in a population of 2287 singleton pregnancies undergoing routine screening at 35–37 weeks' gestation, we found that, first, the ratio of the second to first peak of systolic velocity (PSV ratio) (Figure 1) was the only ophthalmic artery index that provided useful prediction of PE, second, the best performance of screening for PE was achieved by taking the average of four measurements (two from each eye), and, third, the PSV ratio both alone and in combination with other biomarkers provided useful prediction of subsequent development of PE[13,14].

The objective of this study in a population undergoing routine screening at 19–23 weeks' gestation was to examine the performance of maternal ophthalmic artery Doppler in combination with the established biomarkers of PE, including MAP, UtA-PI, PlGF and sFlt-1, in the prediction of subsequent development of PE.

METHODS

Study design and participants

This was a prospective observational study of women attending for a routine hospital visit at 19 + 1 to 23 + 3 weeks' gestation at King's College Hospital, London, UK, between August 2019 and April 2020. This visit included recording of maternal demographic characteristics and medical history, ultrasound examination for fetal anatomy and growth, assessment of flow velocity waveforms from the maternal ophthalmic arteries, measurement of MAP using validated automated devices and a standardized protocol[19], transvaginal color Doppler ultrasound of the left and right UtAs and calculation of

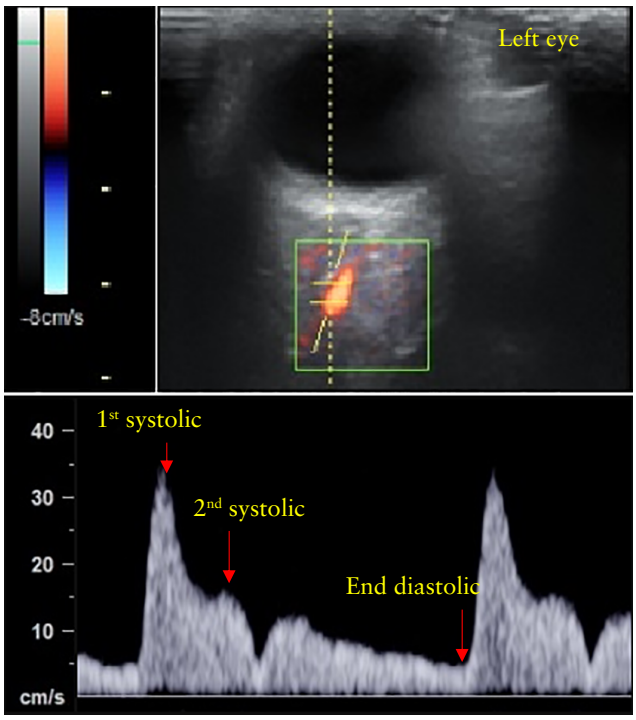

Figure 1 Ultrasound image of left orbit with color flow demonstration of left ophthalmic artery. At the bottom is flow velocity waveform from ophthalmic artery obtained by pulsed-wave Doppler, showing first and second peaks of systolic velocity and end-diastolic velocity.

the mean UtA-PI[20], and measurement of serum concentrations of PlGF and sFlt-1 using an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS, Thermo Fisher Scientific, Hennigsdorf, Germany). During the study period, there was no policy of first-trimester screening for PE by a combination of maternal factors, MAP, UtA-PI and PlGF and treatment of the high-risk group with aspirin. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[21,22]. The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

The inclusion criteria for this study were singleton pregnancy delivering a non-malformed liveborn or stillborn neonate. We excluded pregnancies with aneuploidy and major fetal abnormality.

Ophthalmic artery Doppler

The mother was in the supine position for the routine 19 + 1 to 23 + 3-week scan, and at the end of this procedure a 7.5-MHz linear transducer (Canon Aplio i900 PLT-704SBT Linear Probe, Canon Medical Systems Europe BV, Zoetermeer, The Netherlands) was placed transversely and gently over her closed upper eyelid after application of conduction gel. Color flow was used to identify the ophthalmic artery, which is found superior and medial to the hypoechoic band representing the optic nerve[23]. Pulsed-wave Doppler was then used to record three to five similar waveforms; the angle of insonation was kept at < 20°, the sample gate was 2 mm, the depth was 3.0–4.5 cm, the high-pass filter was 50 Hz, and the pulse repetition frequency was set at 125 kHz. In order to minimize any potential adverse effects on the eyes, the duration of the examination was always less than 1 min and a special preset was used with significant reduction in output power and the maximum mechanical index was 0.4.

The ultrasound scans were carried out by obstetricians or sonographers, and minimal training (five supervised scans) was necessary to visualize the ophthalmic arteries, obtain flow velocity waveforms and record the necessary indices without technical difficulties in any of the patients. Waveforms were obtained in sequence from the right eye, left eye and again from the right and then left eye. The following four indices were used for analysis: first peak of systolic velocity, second peak of systolic velocity, PI and the ratio of the second to first peak of systolic velocity (PSV ratio). The first peak of systolic velocity and PI were obtained automatically by the machine, the second peak of systolic velocity was measured manually and the PSV ratio was calculated.

Outcome measures

Outcome measures were delivery with PE at < 37 and ≥ 37 weeks' gestation. Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with chronic hypertension or pregnancy-associated hypertension were examined to determine the diagnosis of PE. This was based on the finding of new-onset hypertension (systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg on at least two occasions 4 h apart, developing after 20 weeks' gestation in previously normotensive women) or chronic hypertension and at least one of the following: proteinuria (≥ 300 mg/24 h or protein-to-creatinine ratio ≥ 30 mg/mmol or ≥ 2+ on dipstick testing); renal insufficiency with serum creatinine > 97 μmol/L in the absence of underlying renal disease; hepatic dysfunction with blood concentration of transaminases more than twice the upper limit of normal (≥ 65 IU/L for our laboratory); thrombocytopenia (platelet count < 100 000/μL); neurological complications (for example, cerebral or visual symptoms); or pulmonary edema[24].

Statistical analysis

Data were expressed as median (interquartile range) for continuous variables and as *n* (%) for categorical variables. Student's *t*-test and chi-square or Fisher's exact test were used for comparing outcome groups for continuous and categorical data, respectively.

Distributional properties of the four ophthalmic artery indices (first peak of systolic velocity, second peak of systolic velocity, PI and PSV ratio) were investigated using histograms and by plotting marker measurements against gestational age and maternal weight in PE and unaffected pregnancies. On the basis of these exploratory analyses, we determined the relevancy or need for transformation, for example $\log_{10}$, of any of the four indices. Multivariate linear regression models were fitted between each of the four indices and maternal characteristics and elements from their medical history. To determine whether the ophthalmic artery indices would be useful in predicting PE, terms for PE and gestational age at delivery with PE were included in the models. Backwards elimination was used for variable selection. The partial residuals, after excluding the contribution of PE, comprised either the $\log_{10}$ multiples of the median (MoM) values or the deviations from the median (deltas), depending on the transformation of the outcome variable in the original model fitting.

The competing-risks model was used to estimate the individual patient-specific risks of delivery with PE at < 37 and ≥ 37 weeks' gestation by a combination of maternal demographic characteristics and medical history with biomarkers[25]. The posterior distribution of gestational age at delivery with PE was obtained using Bayes' theorem by multiplying the prior probability density from maternal factors by the likelihood function from biomarker MoM or delta values, where appropriate. The measured values of biomarkers were converted to MoMs or deltas to remove the effects of characteristics associated with the individual being measured, such as gestational age, weight, race, method of conception,

medical conditions and elements from their obstetric history, and of characteristics associated with the instrument used for the measurement. Areas under the receiver-operating-characteristics curve (AUC) and detection rates (DRs) of delivery with PE, at a 10% FPR, were assessed for various combinations of MAP, UtA-PI, serum PlGF and sFlt-1 with maternal factors and ophthalmic artery PSV ratio (the other ophthalmic artery indices were not found to be useful in predicting PE; see Results).

Model-based estimates of screening performance for these various combinations of markers were also produced. A dataset containing 10 000 unaffected pregnancies and 10 000 PE pregnancies was obtained by bootstrapping maternal characteristics and medical and pregnancy history, along with outcome, from our original dataset of 2853 records. Delta values for ophthalmic artery PSV ratio and MoM values for MAP, UtA-PI, serum PlGF and serum sFlt-1 were simulated from a multivariate Gaussian distribution[6]. DRs for a FPR of 10% were calculated and compared to empirical results.

The statistical software package R was used for data analyses[26].

RESULTS

Study participants

The study population of 2853 pregnancies contained 76 (2.7%) that developed PE, including 18 (0.6%) that delivered with PE at < 37 weeks' gestation; there were 64 cases that developed gestational hypertension (GH) and 2713 that were unaffected by PE or GH. The cases of GH were excluded from further analysis. Maternal and pregnancy characteristics of the study population are summarized in Table 1. In the PE group, compared to the unaffected pregnancies, there was higher median maternal weight and body mass index, and a higher incidence of chronic hypertension, diabetes mellitus, family history of PE, conception by assisted reproduction, nulliparity and history of PE in a previous pregnancy.

Factors affecting ophthalmic artery indices

Multivariate linear regression models were fitted to $\log_{10}$ first peak of systolic velocity, $\log_{10}$ second peak of systolic velocity, $\log_{10}$ PI and untransformed PSV ratio. The effects of variables contributing significantly to measurement values of each ophthalmic artery marker are shown in Table 2. Those variables relating to maternal characteristics and medical history were used for standardization into MoM or delta values. PSV ratio was significantly increased in PE pregnancies, and the PE effect depended on gestational age at delivery; for example, the standardized effect size at delivery with PE at 36 weeks was 1.25 and at 40 weeks it was 0.79 (Figure 2). The second peak of systolic velocity was significantly raised in PE pregnancies, with a standardized effect of 0.64, but the PE effect was not dependent on gestational age at delivery with PE. The first peak of systolic velocity and PI were not significantly affected by PE (Table 2).

Distribution of biomarkers

The distribution of ophthalmic artery PSV ratio delta values in pregnancies that developed PE and correlations with the other biomarkers of PE are shown in Table 3.

Performance of screening

The empirical AUC and DR and the modeled DR, at a 10% FPR, of delivery with PE at < 37 and ≥ 37 weeks' gestation, in screening by maternal factors, ophthalmic artery PSV ratio and combinations with MAP, UtA-PI, serum PlGF and sFlt-1, are shown in Table 4. The empirical results for DR at a 10% FPR were consistent with the modeled results, for both PE with delivery < 37 weeks' gestation and PE with delivery ≥ 37 weeks (Figure 3).

In the modeled results, the addition of PSV ratio improved the prediction of preterm PE provided by maternal factors alone (from 56.1% to 80.2%), maternal factors and MAP (69.1% to 83.0%), maternal factors and UtA-PI (74.8% to 85.7%), maternal factors and PlGF (75.5% to 86.3%), maternal factors and sFlt-1 (60.4%

Table 1 Maternal and pregnancy characteristics of 2789 pregnancies, according to development of pre-eclampsia (PE)

Characteristic	*Normal* (n = *2713*)	*PE* (n = *76*)	P
Age (years)	33.3 (30.3–36.5)	34.95 (30.0–38.1)	0.414
Weight (kg)	70.6 (63.4–79.5)	74.5 (65.8–86.7)	0.0047
Height (cm)	166 (162–171)	165 (158–171)	0.310
BMI (kg/m^2)	25.4 (23.0–28.6)	27.3 (24.0–32.0)	0.0009
GA (weeks)	21.4 (21.0–21.6)	21.3 (20.7–21.6)	0.039
Racial origin			0.069
White	2013 (74.2)	47 (61.8)	
Black	367 (13.5)	19 (25.0)	
South Asian	153 (5.6)	5 (6.6)	
East Asian	80 (3.0)	2 (2.6)	
Mixed	100 (3.7)	3 (4.0)	
Medical history			
Chronic hypertension	39 (1.4)	7 (9.2)	< 0.00001
Diabetes mellitus	27 (1.0)	3 (3.9)	0.003
SLE/APS	5 (0.2)	0 (0)	1.0
Smoker	37 (1.4)	0 (0)	0.605
Family history of PE	79 (2.9)	9 (11.8)	0.00005
Method of conception			0.00001
Natural	2534 (93.4)	60 (79.0)	
In-vitro fertilization	163 (6.0)	15 (19.7)	
Ovulation drugs	16 (0.6)	1 (1.3)	
Parity			< 0.00001
Nulliparous	1452 (53.5)	54 (71.1)	
Parous, no previous PE	1219 (44.9)	12 (15.8)	
Parous, previous PE	42 (1.6)	10 (13.2)	

Data are given as median (interquartile range) or *n* (%). Comparisons between outcome groups were by chi-square or Fisher's exact test for categorical variables and *t*-test for continuous variables. APS, antiphospholipid syndrome; BMI, body mass index; GA, gestational age; SLE, systemic lupus erythematosus.

to 80.5%), maternal factors, MAP and UtA-PI (80.7% to 87.9%), maternal factors, MAP, UtA-PI and PlGF (85.5% to 90.3%) and maternal factors, MAP, UtA-PI, PlGF and sFlt-1 (84.9% to 89.8%), at a FPR of 10%.

The PSV ratio also improved the prediction of term PE provided by maternal factors alone (from 33.8% to 46.0%), maternal factors and MAP (41.8% to 50.5%), maternal factors and UtA-PI (41.1% to 51.4%), maternal factors and PlGF (30.5% to 44.1%), maternal factors and sFlt-1 (31.4% to 45.2%), maternal factors, MAP and UtA-PI (46.6% to 54.2%), maternal factors, MAP, UtA-PI and PlGF (45.2% to 53.4%) and maternal factors, MAP, UtA-PI, PlGF and sFlt-1 (43.0% to 51.2%), at a FPR of 10%.

In the modeled results, the second peak of systolic velocity did not improve the prediction of either preterm or term PE provided by maternal factors alone.

DISCUSSION

Principal findings of study

This screening study of singleton pregnancies at 19–23 weeks' gestation has demonstrated that maternal ophthalmic artery Doppler is a potentially useful biomarker of subsequent delivery with PE, especially preterm PE with delivery at < 37 weeks. We investigated four indices (first peak of systolic velocity, second peak of systolic velocity, PSV ratio and PI) and found that, first, the PSV ratio was significantly increased in PE pregnancies and the deviation from normal was greater for early than late PE, second, the second peak of systolic velocity was increased in PE pregnancies but the effect did not depend on gestational age at delivery, and, third, the first peak of systolic velocity and PI were not significantly affected by PE.

Table 2 Effect of variables from maternal characteristics and medical history with significant contribution to measurement of each ophthalmic artery Doppler marker

Parameter	*Estimate (95% CI)*	P
First peak of systolic velocity		
Intercept	1.513299 (1.507508 to 1.519089)	< 0.0001
Weight (in kg) – 69	0.000757 (0.000361 to 0.001154)	0.0002
(Weight (in kg) – 69)^2	−0.000015 (−0.000026 to −0.000004)	0.0056
Age (in years) – 35	−0.001891 (−0.002653 to −0.001128)	< 0.0001
Height (in cm) – 164	0.000687 (0.000139 to 0.001234)	0.014
Black racial origin	−0.023355 (−0.034231 to −0.012478)	< 0.0001
South Asian racial origin	−0.015939 (−0.031769 to −0.000108)	0.0485
Smoker	0.033721 (0.001848 to 0.065595)	0.0382
Parous, no previous pre-eclampsia	0.008146 (0.000638 to 0.015654)	0.0335
Second peak of systolic velocity		
Intercept	1.296962 (1.291824 to 1.302100)	< 0.0001
Pre-eclampsia	0.073329 (0.046918 to 0.099739)	< 0.0001
Weight (in kg) – 69	0.001268 (0.000821 to 0.001716)	< 0.0001
(Weight (in kg) – 69)^2	−0.000019 (−0.000031 to −0.000006)	0.0037
Age (in years) – 35	0.001846 (0.000972 to 0.002720)	< 0.0001
Black racial origin	−0.028595 (−0.041346 to −0.015844)	< 0.0001
East Asian racial origin	−0.039126 (−0.064706 to −0.013547)	0.0027
Smoker	0.068656 (0.031071 to 0.106241)	0.0003
Chronic hypertension	0.042256 (0.007781 to 0.076730)	0.0164
Pulsatility index		
Intercept	0.239881 (0.235762 to 0.243999)	< 0.0001
Weight (in kg) – 69	−0.000968 (−0.001341 to −0.000595)	< 0.0001
(Weight (in kg) – 69)^2	0.000011 (0.000001 to 0.000021)	0.0279
Height (in cm) – 164	0.001056 (0.000549 to 0.001564)	< 0.0001
Black racial origin	0.016137 (0.006060 to 0.026215)	0.0017
East Asian racial origin	0.039016 (0.018613 to 0.059420)	0.0002
Smoker	−0.045726 (−0.075438 to −0.016014)	0.0026
Chronic hypertension	−0.055513 (−0.082833 to −0.028193)	< 0.0001
Parous, previous pre-eclampsia	−0.031689 (−0.056684 to −0.006694)	0.013
PSV ratio		
Intercept	0.610732 (0.606672 to 0.614792)	< 0.0001
Pre-eclampsia	0.503075 (0.213746 to 0.792403)	0.0007
Gestational age at delivery with pre-eclampsia	−0.010752 (−0.018372 to −0.003133)	0.0057
Weight (in kg) – 69	0.000511 (0.000253 to 0.000768)	0.0001
Age (in years) – 35	0.005024 (0.004326 to 0.005723)	< 0.0001
Height (in cm) – 164	−0.001269 (−0.001778 to −0.000760)	< 0.0001
East Asian racial origin	−0.037322 (−0.057908 to −0.016736)	0.0004
Smoker	0.045739 (0.015509 to 0.075968)	0.003
Chronic hypertension	0.070468 (0.042809 to 0.098127)	< 0.0001

PSV ratio, ratio of second to first peak of systolic velocity.

The PSV ratio may be superior to MAP, UtA-PI, PlGF or sFlt-1 as individual biomarkers in the prediction of both preterm and term PE. The PSV ratio improved the prediction provided by maternal factors alone from 56% to 80% for preterm PE and from 34% to 46% for term PE, at a FPR of 10%; similarly, the PSV ratio improved the prediction of both preterm and term PE provided by MAP, UtA-PI, PlGF and sFlt-1, both individually and in various combinations with each other. The second peak of systolic velocity did not improve the prediction of either preterm or term PE provided by maternal factors alone.

Development of clinical signs of PE is preceded by maternal cardiovascular changes that are apparent from the first trimester of pregnancy, including an increase in both cardiac output and peripheral vascular resistance[27,28]. It is therefore not surprising that development of PE is also preceded by alterations in the cerebral circulation, reflected in the observed changes in the waveforms obtained from the ophthalmic arteries.

Comparison with previous studies

Our finding of high second peak of systolic velocity in pregnancies that subsequently develop PE is consistent with the results of several previous studies which reported that, in women with established PE, there is an increase in flow velocity in the ophthalmic arteries[15]. However, in these studies of established PE, in addition to increased velocities, there was also reduced PI[15], whereas in our study, PI was not altered in women who subsequently developed PE. Our finding that the best ophthalmic artery index for prediction of PE is the PSV ratio is consistent with the results of our previous screening study for PE at 35–37 weeks' gestation[13].

Two previous studies examined the potential value of ophthalmic artery Doppler during the second trimester of pregnancy in screening for subsequent development of PE[17,18]. In both studies, high-risk pregnancies were included and only the right ophthalmic artery was examined. In the first study, 347 pregnancies, including 40 (11.5%) that developed PE, were examined at

Table 3 Fitted regression model for effect of ophthalmic artery second to first peak of systolic velocity ratio delta values on mean gestational age at delivery in pregnancies with pre-eclampsia

Parameter	*Estimate (95% CI)*
Intercept	0.6732 (0.5245 to 0.8515)
Slope	−0.0154 (−0.0197 to −0.0120)
Standard deviation	0.0924 (0.0902 to 0.0947)
Correlations	
Log_{10} MAP MoM	0.1519 (0.1160 to 0.1911)
Log_{10} UtA-PI MoM	0.0263 (−0.0096 to 0.0619)
Log_{10} PlGF MoM	−0.0251 (−0.0610 to 0.0115)
Log_{10} sFlt-1 MoM	−0.0141 (−0.0512 to 0.0216)

MAP, mean arterial pressure; MoM, multiples of the median; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UtA-PI, uterine artery pulsatility index.

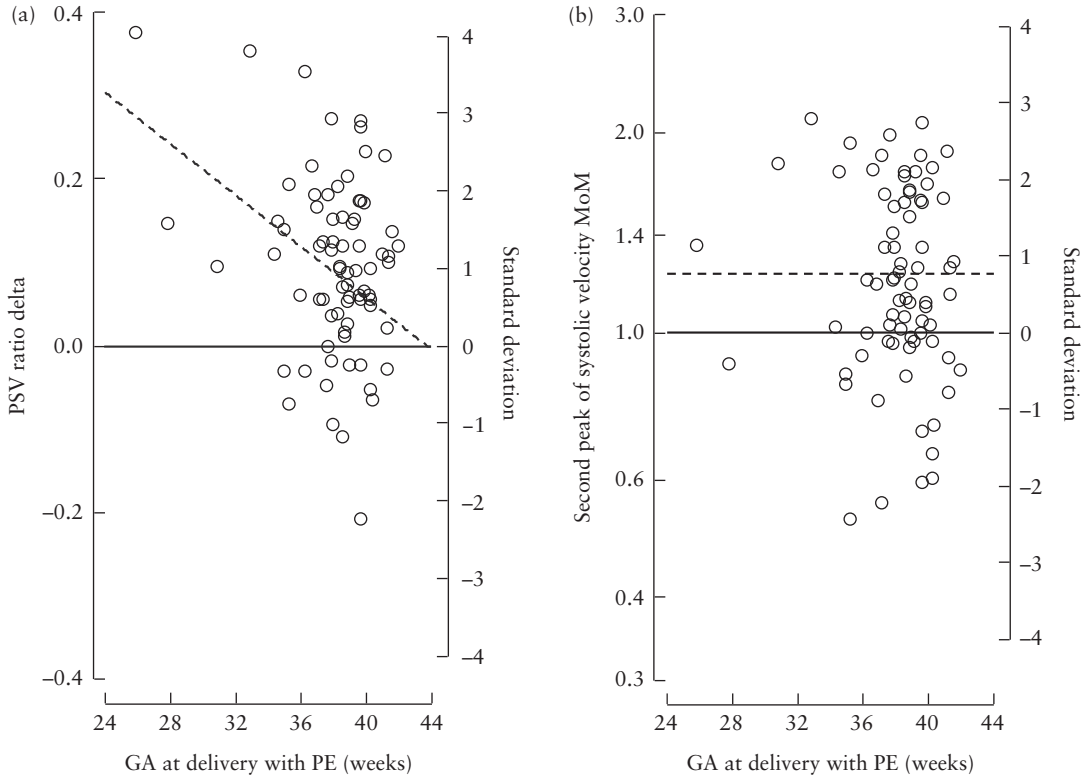

Figure 2 Relationship between ratio of ophthalmic artery second to first peak of systolic velocity (PSV ratio) delta (a) and second peak of systolic velocity multiples of the median (MoM) (b) and gestational age (GA) at delivery with pre-eclampsia (PE). Circles illustrate cases with PE and dashed lines show relationship between ophthalmic artery index and GA at delivery. Solid lines are median value for unaffected pregnancies.

20–28 weeks' gestation[17]. The authors reported that, in the pregnancies that developed PE, compared to unaffected pregnancies, the first and second peaks of systolic velocity and the PSV ratio were increased; the greatest difference between the groups was observed for the second peak of systolic velocity, and, in screening by this marker, the DR for PE was 70% at a FPR of 25%. In the second study, 372 pregnancies, including 40 (10.8%) that developed PE, were examined at 18–23 weeks' gestation[18]. The authors reported that, in the pregnancies that developed PE, compared to unaffected pregnancies, there was no significant difference in the second peak of systolic velocity, PSV ratio or PI.

Strengths and limitations

The main strengths of this study are, first, examination of a large population of pregnant women attending for care at a gestational-age range which is used routinely for assessment of fetal anatomy and growth, second, use of a standardized technique for Doppler assessment of the ophthalmic artery and obtaining two recordings from each eye to minimize the effect of variability in measurements, third, measurement of all potentially useful biomarkers of PE to allow comparison with the ophthalmic artery PSV ratio and assessment of the potential value of combining biomarkers, and, fourth, application of the competing-risks approach to estimate patient-specific risks and the performance of predicting delivery with PE at different stages after assessment.

Despite the relatively large study population, the number of cases of PE was small; consequently, there is a large degree of uncertainty surrounding our estimates of empirical AUC and DR at a 10% FPR. We tried to overcome the problem of the small numbers of cases of PE by using modeling, which produced results that were consistent with the empirical results.

Conclusion

Ophthalmic artery Doppler at 19–23 weeks' gestation could potentially improve the performance of screening for PE, especially preterm PE, but further studies are needed to validate this finding.

Table 4 Performance of screening at 19–23 weeks' gestation for delivery with pre-eclampsia (PE) at < 37 weeks' gestation or at ≥ 37 weeks, at 10% false-positive rate, by maternal factors (MF) combined with ophthalmic artery second to first peak of systolic velocity ratio (PSV ratio), mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFlt-1)

Method of screening	*AUC (95% CI)*	*DR (n (%; 95% CI))*	*Modeled DR (%)*
PE with delivery < 37 weeks ($n = 18$)			
MF	0.8529 (0.7753–0.9304)	10 (55.6; 30.8–78.5)	56.1
MF + PSV ratio	0.8985 (0.8092–0.9878)	14 (77.8; 52.4–93.6)	80.2
MF + MAP	0.8813 (0.8178–0.9449)	11 (61.1; 35.7–82.7)	69.1
MF + UtA-PI	0.7952 (0.6593–0.9311)	11 (61.1; 35.7–82.7)	74.8
MF + PlGF	0.9554 (0.9258–0.9849)	15 (83.3; 58.6–96.4)	75.5
MF + sFlt-1	0.8718 (0.7967–0.9469)	11 (61.1; 35.7–82.7)	60.4
MF + MAP + UtA-PI	0.8227 (0.6996–0.9458)	12 (66.7; 41.0–86.7)	80.7
MF + MAP + UtA-PI + PlGF	0.9053 (0.8141–0.9965)	13 (72.2; 46.5–90.3)	85.5
MF + MAP + UtA-PI + PlGF + sFlt-1	0.9209 (0.8377–1.0000)	14 (77.8; 52.4–93.6)	84.9
MF + MAP + PSV ratio	0.9109 (0.8327–0.9891)	14 (77.8; 52.4–93.6)	83.0
MF + UtA-PI + PSV ratio	0.8682 (0.7699–0.9666)	12 (66.7; 41.0–86.7)	85.7
MF + PlGF + PSV ratio	0.9693 (0.9460–0.9926)	16 (88.9; 65.3–98.6)	86.3
MF + sFlt-1 + PSV ratio	0.9001 (0.8096–0.9906)	14 (77.8; 52.4–93.6)	80.5
MF + MAP + UtA-PI + PSV ratio	0.8848 (0.7975–0.9720)	14 (77.8; 52.4–93.6)	87.9
MF + MAP + UtA-PI + PlGF + PSV ratio	0.9483 (0.9015–0.9952)	16 (88.9; 65.3–98.6)	90.3
MF + MAP + UtA-PI + PlGF + sFlt-1 + PSV ratio	0.9583 (0.9199–0.9966)	16 (88.9; 65.3–98.6)	89.8
PE with delivery ≥ 37 weeks ($n = 58$)			
MF	0.7592 (0.7029–0.8155)	18 (31.0; 19.5–44.5)	33.8
MF + PSV ratio	0.8166 (0.7624–0.8708)	28 (48.3; 35.0–61.8)	46.0
MF + MAP	0.8194 (0.7727–0.8662)	30 (51.7; 38.2–65.0)	41.8
MF + UtA-PI	0.7348 (0.6747–0.7949)	16 (27.6; 16.7–40.9)	41.1
MF + PlGF	0.7897 (0.7332–0.8462)	24 (41.4; 28.6–55.1)	30.5
MF + sFlt-1	0.7589 (0.7022–0.8156)	19 (32.8; 21.0–46.3)	31.4
MF + MAP + UtA-PI	0.8026 (0.7546–0.8505)	24 (41.4; 28.6–55.1)	46.6
MF + MAP + UtA-PI + PlGF	0.8103 (0.7618–0.8588)	25 (43.1; 30.2–56.8)	45.2
MF + MAP + UtA-PI + PlGF + sFlt-1	0.8103 (0.7630–0.8575)	24 (41.4; 28.6–55.1)	43.0
MF + MAP + PSV ratio	0.8552 (0.8123–0.8982)	31 (53.4; 39.9–66.7)	50.5
MF + UtA-PI + PSV ratio	0.8069 (0.7525–0.8614)	24 (41.4; 28.6–55.1)	51.4
MF + PlGF + PSV ratio	0.8420 (0.7926–0.8914)	33 (56.9; 43.2–69.9)	44.1
MF + sFlt-1 + PSV ratio	0.8174 (0.7631–0.8717)	28 (48.3; 35.0–61.8)	45.2
MF + MAP + UtA-PI + PSV ratio	0.8848 (0.7975–0.9720)	23 (39.7; 27.0–53.4)	54.2
MF + MAP + UtA-PI + PlGF + PSV ratio	0.8586 (0.8183–0.8990)	28 (48.3; 35.0–61.8)	53.4
MF + MAP + UtA-PI + PlGF + sFlt-1 + PSV ratio	0.8605 (0.8206–0.9003)	32 (55.2; 41.5–68.3)	51.2

AUC, area under the receiver-operating-characteristics curve; DR, detection rate.

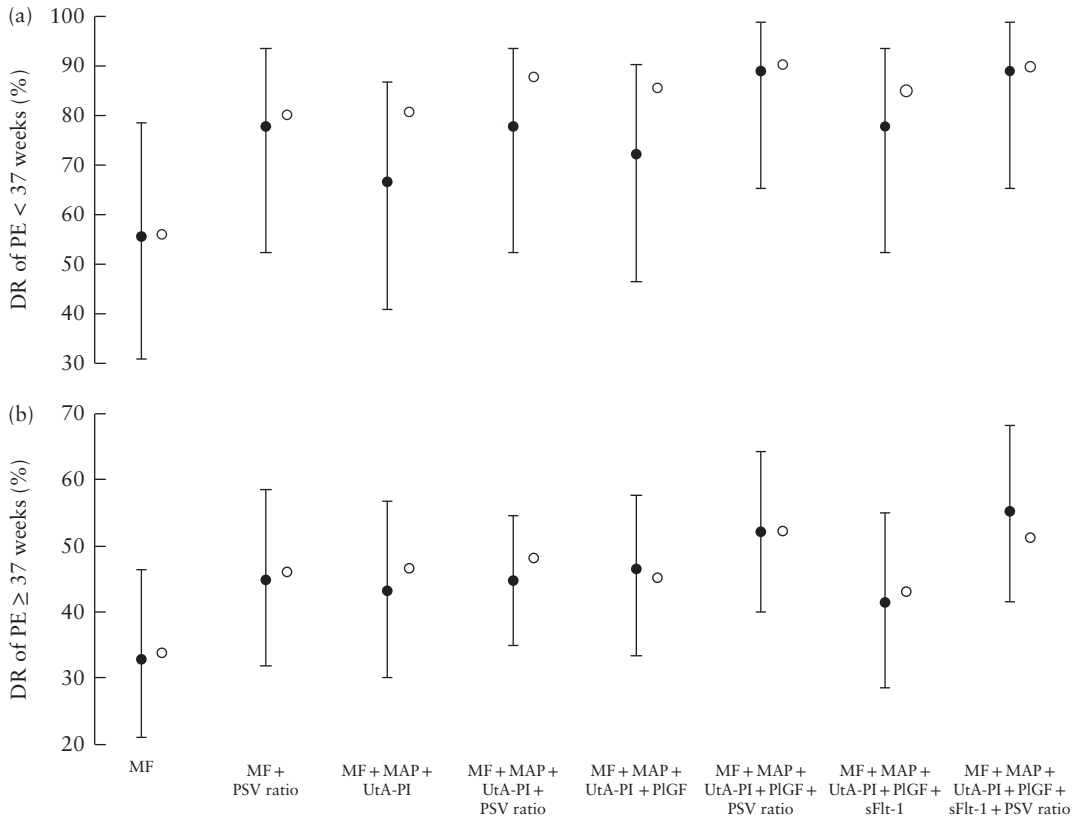

Figure 3 Empirical detection rates (DR) (●), with 95% CI, at 10% false-positive rate, of pre-eclampsia (PE) with delivery at < 37 weeks' gestation (a) and at ≥ 37 weeks (b) in screening by combination of maternal factors (MF) with ophthalmic artery second to first peak of systolic velocity ratio (PSV ratio), mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1). Model-based DRs (○) are shown.

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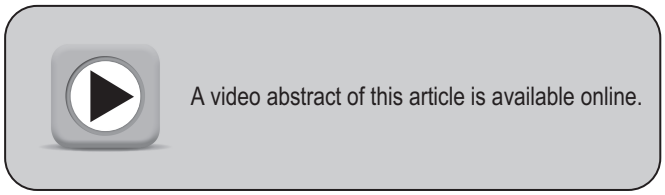

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Doppler de la arteria oftálmica en combinación con otros biomarcadores para la predicción de la preeclampsia a las 19–23 semanas de gestación

RESUMEN

Objetivo Estudiar el valor potencial del Doppler de la arteria oftálmica materna a las 19–23 semanas de gestación, tanto por sí solo como en combinación con los biomarcadores establecidos de la preeclampsia (PE), a saber, el índice de pulsatilidad (IP) de la arteria uterina (AUt), la presión arterial media (PAM), el factor de crecimiento placentario (FCPl) sérico y la tirosina quinasa-1 (sFlt-1) tipo fms soluble en suero, en la predicción del desarrollo posterior de la PE.

Métodos Este fue un estudio prospectivo de observación a mujeres que acudieron al hospital a una consulta de rutina entre las 19+1 y las 23+3 semanas de gestación. Esta consulta incluyó el registro de las características demográficas y el historial médico de la madre, el examen ecográfico de la anatomía y el crecimiento del feto, la evaluación de la forma de onda de velocidad de flujo de las arterias oftálmicas maternas, y la medición de la PAM, el IP-AUt, el FCPl sérico y la sFlt-1 sérica. La forma de onda se obtuvo de las arterias oftálmicas consecutivamente del ojo derecho, el ojo izquierdo y de nuevo del ojo derecho y luego del izquierdo. Se registró el promedio de las cuatro mediciones, dos de cada ojo, para los siguientes cuatro índices: primer pico de velocidad sistólica; segundo pico de velocidad sistólica; IP; y el cociente entre el segundo y el primer pico de velocidad sistólica (cociente PVS). Las mediciones de los cuatro índices se estandarizaron, a fin de eliminar los efectos de las características y los elementos maternos del historial clínico. Se utilizó el modelo de riesgos en competencia para estimar los riesgos específicos de cada paciente en el parto en cuanto a la PE a <37 y ≥37 semanas de gestación y para determinar el área bajo la curva de la característica operativa del receptor (ABC) y la tasa de detección (TD), con una tasa de falsos positivos (TFP) del 10%, en la detección mediante una combinación de características demográficas maternas e historial médico con biomarcadores. También se estimó el rendimiento del modelo de la detección de la PE.

Resultados La población de estudio de 2853 embarazos contenía 76 (2.7%) mujeres que desarrollaron PE, entre ellas 18 (0.6%) que dieron a luz con PE a <37 semanas de gestación. El cociente de PVS de la arteria oftálmica aumentó significativamente en los embarazos con PE, y el efecto de la PE dependió de la edad gestacional en el momento del parto; la desviación de la curva normal fue mayor en el caso de la PE temprana que en el de la tardía. El segundo pico de velocidad sistólica también aumentó en los embarazos con PE, pero el efecto no dependió de la edad gestacional en el momento del parto. Los otros dos índices de la arteria oftálmica del primer pico de velocidad sistólica e IP no se vieron afectados significativamente por la PE. El cociente de PVS mejoró la predicción de la PE pretérmino proporcionada exclusivamente por los factores maternos (del 56,1% al 80,2%), los factores maternos, la PAM y el IP-AUt (del 80,7% al 87,9%), los factores maternos, la PAM, el IP-AUt y el FCPl (del 85,5% al 90,3%) y los factores maternos, la PAM, el IP-AUt, el FCPl y la sFlt-1 (del 84,9% al 89,8%), con una TFP del 10%. La tasa de PVS también mejoró la predicción de la PE a término proporcionada exclusivamente por los factores maternos (del 33,8% al 46,0%), los factores maternos, la PAM y el IP-AUt (del 46,6% al 54,2%), los factores maternos, la PAM, el IP-AUt y el FCPl (del 45,2% al 53,4%) y los factores maternos, la PAM, el IP-AUt, el FCPl y la sFlt-1 (del 43,0% al 51,2%), con una TFP del 10%. Los resultados empíricos de la TD con una TFP del 10% concordaron con los resultados del modelo. El segundo pico de velocidad sistólica no mejoró la predicción de la PE pretérmino o a término proporcionada exclusivamente por los factores maternos.

Conclusiones La proporción de PVS de la arteria oftálmica a las 19–23 semanas de gestación, tanto por sí sola como en combinación con otros biomarcadores, es potencialmente útil para la predicción del desarrollo posterior de la PE, especialmente la PE pretérmino, pero se necesitan estudios más amplios para validar este hallazgo.

将眼动脉多普勒检查与其他生物指标结合来预测妊娠后19-23周期间的先兆子痫

摘要

目的 旨在检验在妊娠后19-23周期间母体眼动脉多普勒检查本身以及与先兆子痫（PE）已确立的生物指标相结合后预测随后出现先兆子痫的潜在价值，这些生物指标有子宫动脉（UtA）搏动指数（PI）、平均动脉血压（MAP）、血清胎盘生长因子（PlGF）和血清可溶性fms样酪氨酸激酶-1（sFlt-1）。

方法 这是一项前瞻性观察研究，由妊娠后19^{+1}-23^{+3}周参加常规医院检查的妇女组成。该产检包括产妇个人背景特征记录和病史、对胎儿身体结构及生长的超声检查、对产妇眼动脉流速波形的评估，以及对MAP、UtA-PI、血清PlGF和血清sFlt-1的测量。波形是从眼动脉获取，从右眼至左眼，再从右眼至左眼的顺序进行。我们记录了四项测量的平均值，每只眼两项，按照以下四项指标：收缩期峰值流速（第一峰）、收缩期峰值流速（第二峰）、PI，以及收缩期第二峰与第一峰的最大流速的比值（PSV比值）。对四项指标的测量进行标准化，以移除产妇特征和病史要素的影响。通过结合产妇特征和含生物指标的病史，在筛检中采用互竞风险模型来估计在妊娠<37周和≥37周时患PE分娩的个体患者特异风险，并在接受者操作特性曲线（AUC）和检出率（DR）下确定该区域，假阳性率（FPR）为10%。筛检PE的模型性能也得到了预估。

结果 研究人群为2853名孕妇，其中76例患有PE（占2.7%），包括18例在妊娠<37周时患PE分娩的（占0.6%）。在患有PE的孕妇中眼动脉PSV比值显著增高，而且PE的影响取决于分娩时的胎龄；对于PE患者，胎龄早与胎龄晚相比，偏离正常值更大。在患有PE的孕妇中，收缩期峰值流速（第二峰）也有所增加，但其影响并不取决于分娩时的胎龄。其他两个眼动脉指标——收缩期峰值流速（第一峰）和PI——受PE的影响不大。PSV比值改善了仅由产妇因素推知的早产PE预测（从56.1%到80.2%），产妇因素、MAP和UtA-PI（80.7%—87.9%），产妇因素、MAP、UtA-PI和PlGF（85.5%—90.3%），以及产妇因素、MAP、UtA-PI、PlGF和sFlt-1（84.9%—89.8%），假阳性率（FPR）为10%。PSV比值还改善了仅由产妇因素推知的妊娠期瞒PE的预测（从33.8%到46.0%），产妇因素、MAP和UtA-PI（46.6%—54.2%），产妇因素、MAP、UtA-PI和PlGF（45.2%—53.4%），以及产妇因素、MAP、UtA-PI、PlGF和sFlt-1（43.0%—51.2%），假阳性率（FPR）为10%。FPR为10%时的DR检验结果与模型结果一致。收缩期峰值流速（第二峰）未改善仅由产妇因素推知的早产或足月PE的预测。

结论 妊娠后19-23周期间的眼动脉PSV比值，不论是单独还是与其他生物指标相结合，都对预测随后出现PE具有潜在用处，尤其是早产PE，但是需要更大型的研究来验证这一发现。