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

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What are the novel findings of this work

Ophthalmic artery Doppler at 19-23 weeks' gestation improves the prediction of preeclampsia (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 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

Objectives: 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 preeclampsia (PE), including uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFLT), in the prediction of subsequent development of PE.

Methods: This was a prospective observational study in women attending for a routine hospital visit at 19^{+1} - 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. Waveforms were obtained in sequence from the right eye, left eye, and again right and then left eye. We recorded the average of the four measurements, two from the right and two from the left eye, for the following four indices: first peak systolic velocity (PSV), second PSV, pulsatility index, and ratio of second to first PSV. 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 determine the area under the operating characteristic curve (AUC) and detection rate (DR), at 10% false positive rate (FPR), in screening by a combination of maternal demographic characteristics and medical history with biomarkers. The modelled performance of screening for PE was also estimated.

Results: The study population of 2,853 pregnancies contained 76 (2.7%) that developed PE, including 18 (0.6%) that delivered with PE at <37 weeks' gestation. The ophthalmic artery second to first 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 PSV 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 PSV and pulsatility index 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 plus UtA-PI (80.7% to 87.9%), maternal factors, MAP, UtA-PI plus PlGF (85.5% to 90.3%) and maternal factors, MAP, UtA-PI, PlGF plus sFLT (84.9% to 89.8%), at 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 plus UtA-PI (46.6% to 54.2%), maternal factors, MAP, UtA-PI plus PlGF (45.2% to 53.4%) and maternal factors, MAP, UtA-PI, PlGF plus sFLT (from 43.0% to 51.2%), at FPR of 10%. The empirical results on DR at 10% FPR were consistent with the modelled results. The second PSV 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.

INTRODUCTION

Assessment of risk for preeclampsia (PE) should be undertaken in each of the three 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 pulsatility index (UtA-PI) and serum placental growth factor (PLGF) can identify about 90% of women that 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 falsepositive rate 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 that develop PE by determining the appropriate time and place for delivery. Useful biomarkers of PE at 20 weeks' gestation ate MAP, UtA-PI, PlGF and serum soluble fms-like tyrosine kinase-1 (sFLT) [7,8] and at 36 weeks are MAP, PlGF, sFLT 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 decrease in impedance to flow and increase in velocities in the flow velocity waveforms from 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 2,287 singleton pregnancies undergoing routine screening at 35-37 weeks' gestation, we found that: first, the second to first peak 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 objectives of this study in a population undergoing routine screening at 19-23 weeks' gestation are to examine the performance of maternal ophthalmic artery Doppler in combination with the established biomarkers of PE, including MAP, UtA-PI, PlGF and sFLT, in the prediction of subsequent development of PE.

METHODS

Study design and participants

This was a prospective observational study in women attending for a routine hospital visit at 19^{+1} - 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 by validated automated devices and a standardized protocol [19] transvaginal color Doppler ultrasound of the left and right uterine arteries and calculation of the mean UtA-PI,[20] and measurement of serum concentration of PlGF and sFLT by 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 the 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 pregnancies delivering a non-malformed live birth or stillbirth. We excluded pregnancies with aneuploidies and major fetal abnormalities.

Ophthalmic artery Doppler

The mother was in the supine position for the routine 19^{+1} - 23^{+3} weeks 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 medially to the hypoechoic band representing the optic nerve.[23] Pulsed wave Doppler was then used to record 3-5 similar waveforms; the angle of insonation was kept at $<20^0$, the sample gate was 2 mm, the depth was 3.0-4.5 cm, the high-pass filter was 50-Hz filter, and the pulse repetition frequency was set at 125 kHz. 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 right and then left eye. The following four indices were used for analysis: first peak systolic velocity (PSV), second PSV, pulsatility index (PI), and ratio of second to first PSV. The first PSV and PI were obtained automatically by the machine, the second PSV was measured manually and the ratio of second to first PSV 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 mm Hg or diastolic blood pressure of ≥90 mmHg on at least two occasions four hours apart developing after 20 weeks' gestation in previously normotensive women) or chronic hypertension and at least one of the following: proteinuria (≥300 mg/24h 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 (e.g. cerebral or visual symptoms), or pulmonary edema.[24]

Statistical analysis

Data were expressed as median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. Students t-test and $\chi 2$-square test 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 PSV, second PSV, PI index and second to first 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 the 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 such as gestational age, weight and race, method of conception, medical conditions, elements from the obstetric history associated with the individual being measured, and for characteristics associated with the instrument used for the measurement. The areas under the receiver operating characteristic (ROC) curve (AUC) and detection rates (DRs) of delivery with PE, at a 10% false positive rate (FPR), were assessed for various combinations of MAP, UtA-PI, serum PlGF and sFLT with maternal factors and ophthalmic artery second to first 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 data set containing 10,000 unaffected pregnancies and 10,000 PE pregnancies was obtained by bootstrapping maternal characteristics and medical and previous pregnancy history, along with outcome, from our original data set of 2,287 records. Delta values for ophthalmic artery second to first PSV ratio and MoM values for MAP, UtA-PI, serum PlGF and sFLT and were simulated from a multivariate Gaussian distribution.[6] Detection rates for FPRs 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 2,853 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 2,713 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 a higher median maternal weight and body mass index, and higher incidence of chronic hypertension, diabetes mellitus, family history of PE, conception by assisted reproduction, nulliparity and previous history of PE.

Factors affecting ophthalmic artery indices

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

Distribution of biomarkers

The distribution of ophthalmic artery second to first 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, at 10% FPR, and modelled DR, at 10% FPR, of delivery with PE at <37 and ≥37 weeks' gestation by maternal factors, ophthalmic artery second to first PSV ratio and combinations with MAP, UtA-PI, serum PlGF and sFLT are shown in Tables 4 and 5. The empirical results on DR at 10% FPR were consistent with the modelled results, both for PE with delivery <37 weeks' gestation and delivery ≥37 weeks (Figure 3).

In the modelled 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 plus MAP (69.1% to 83.0%), maternal factors plus UtA-PI (74.8% to 85.7%), maternal factors plus PlGF (75.5% to 86.3%), maternal factors plus sFLT (60.4% to 80.5%), maternal factors, MAP plus UtA-PI (80.7% to 87.9%), maternal factors, MAP, UtA-PI plus PlGF (85.5% to 90.3%), and maternal factors, MAP, UtA-PI, PlGF plus sFLT (84.9% to 89.8%), at 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 plus MAP (41.8% to 50.5%), maternal factors plus UtA-PI (41.1% to 51.4%), maternal factors plus PlGF (30.5% to 44.1%), maternal factors plus sFLT (31.4% to 45.2%), maternal factors, MAP plus UtA-PI (46.6% to 54.2%), maternal factors, MAP, UtA-PI plus PlGF (45.2% to 53.4%) and maternal factors, MAP, UtA-PI, PlGF plus sFLT (from 43.0% to 51.2%), at FPR of 10%.

In the modelled results, the second PSV did not improve the prediction of either preterm or term PE provided by maternal factors alone.

DISCUSSION

Principal findings of this 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 PSV, second PSV, second to first 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 PSV was increased in PE pregnancies but the effect did not depend on gestational age at delivery, and third, the first PSV and PI were not significantly affected by PE.

The PSV ratio may be superior to MAP, UtA-PI, PlGF or sFLT 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 FPR of 10%; similarly, the PSV ratio improved the prediction of both preterm and term PE provided by MAP, UtA-PI, PlGF and sFLT, both individually and in various combinations between each other. The second PSV did not improve the prediction of either preterm or term PE provided by maternal factors alone.

Development of the clinical signs of PE is preceded by maternal cardiovascular changes that are apparent from the first trimester of pregnancy, including 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 PSV 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 increase in velocities in the flow velocity waveforms from the ophthalmic arteries.[15] However in these studies of established PE in addition to increased velocities there was also reduced PI, whereas in our study PI was not altered in women that subsequently developed PE.[15] Our results that the best ophthalmic artery index for prediction of PE is the second to first 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 20-28 weeks' gestation.[17] The authors reported that in the pregnancies that developed PE, compared to unaffected pregnancies, the first PSV, second PSV and

second to first PSV ratio were increased; the greatest difference between the groups was observed for the second PSV and in screening by this marker the DR for PE was 70% at 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 second PSV, second to first PSV ratio or PI.

Strengths and limitations

The main strengths of the study are first, examination of a large population of pregnant women attending for care in a gestational age range which is routinely used 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 second to first 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 10% FPR. We tried to overcome the problem of small numbers of cases of PE, by modeling which produced results that were consistent with the empirical results.

Conclusions

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.

Conflict of interest: None

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FIGURE LEGENDS

Figure 1. Color flow demonstration of left ophthalmic artery. At the bottom is the flow velocity waveform from the ophthalmic artery obtained by pulsed-wave Doppler illustrating the first and second systolic velocity and end-diastolic velocity.

Figure 2. Relationship between the ratio of the second to first systolic peak velocity delta (left) and second systolic peak velocity multiple of the median (right) with gestational age at delivery with preeclampsia. The y-axis on the right of the plot shows a standard deviation scale. The open circles illustrate the cases with preeclampsia and interrupted lines the relationship between the ophthalmic artery index and gestational age at delivery. The horizontal lines are the median value for unaffected pregnancies.

Figure 3. Empirical detection rates, with 95% confidence intervals, at 10% false positive rate, of preeclampsia with delivery at <37 weeks' gestation (top) and at ≥37 weeks (bottom) in screening by combination of maternal factors with ophthalmic artery second to first peak systolic velocity ratio (PSV), mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFLT). The open diamonds represent the model-based detection rates.

Table 1. Maternal and pregnancy characteristics of the study population.

Characteristic	Unaffected (n=2,713)	Preeclampsia (n=76)	p-value
Maternal age (years)	33.3 (30.3, 36.5)	34.95 (30.0, 38.1)	0.414
Maternal weight (kg)	70.6 (63.4, 79.5)	74.5 (65.8, 86.7)	0.0047
Maternal height (cm)	166 (162, 171)	165 (158, 171)	0.310
Body mass index (kg/m^2)	25.4 (23.0, 28.6)	27.3 (24.0, 32.0)	0.0009
Gestational age (weeks)	21.4 (21.0, 21.6)	21.3 (20.7, 21.6)	0.039
Racial origin			0.069
White	2,013 (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 (0.0)	
Smoker	37 (1.4)	0 (0.0)	0.605
Family history of PE	79 (2.9)	9 (11.8)	0.00005
Method of conception			0.00001
Natural	2,534 (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	1,452 (53.5)	54 (71.1)	
Parous no previous PE	1,219 (44.9)	12 (15.8)	
Parous previous PE	42 (1.6)	10 (13.2)	

Values given as median (interquartile range) or n (%)
PE = preeclampsia; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome.

Comparisons between outcome groups were by chi-square or Fisher exact test for categorical variables and Mann Whitney-U test for continuous variables.

Table 2. Effects of variables from maternal characteristics and medical history with significant contribution to the measurement of each ophthalmic artery marker.

	Estimate (95% CI)	p-value
First systolic peak velocity		
Intercept	1.513299 (1.507508, 1.507508)	<0.0001
Weight in Kg - 69	0.000757 (0.000361, 0.000361)	0.0002
(Weight in Kg - 69)^2	-0.000015 (-0.000026, -0.000026)	0.0056
Age in years - 35	-0.001891 (-0.002653, -0.002653)	<0.0001
Height in cm - 164	0.000687 (0.000139, 0.000139)	0.014
Black racial origin	-0.023355 (-0.034231, -0.034231)	<0.0001
South Asian racial origin	-0.015939 (-0.031769, -0.031769)	0.0485
Smoker	0.033721 (0.001848, 0.001848)	0.0382
Parous no previous preeclampsia	0.008146 (0.000638, 0.000638)	0.0335
Second systolic peak velocity		
Intercept	1.296962 (1.291824, 1.291824)	<0.0001
Preeclampsia	0.073329 (0.046918, 0.046918)	<0.0001
Weight in Kg - 69	0.001268 (0.000821, 0.000821)	<0.0001
(Weight in Kg - 69)^2	-0.000019 (-0.000031, -0.000031)	0.0037
Age in years - 35	0.001846 (0.000972, 0.000972)	<0.0001
Black racial origin	-0.028595 (-0.041346, -0.041346)	<0.0001
East Asian racial origin	-0.039126 (-0.064706, -0.064706)	0.0027
Smoker	0.068656 (0.031071, 0.031071)	0.0003
Chronic hypertension	0.042256 (0.007781, 0.007781)	0.0164
Pulsatility index		
Intercept	0.239881 (0.235762, 0.235762)	<0.0001
Weight in Kg - 69	-0.000968 (-0.001341, -0.001341)	<0.0001
(Weight in Kg - 69)^2	0.000011 (0.000001, 0.000001)	0.0279
Height in cm - 164	0.001056 (0.000549, 0.000549)	<0.0001
Black racial origin	0.016137 (0.006060, 0.006060)	0.0017
East Asian racial origin	0.039016 (0.018613, 0.018613)	0.0002
Smoker	-0.045726 (-0.075438, -0.075438)	0.0026
Chronic hypertension	-0.055513 (-0.082833, -0.082833)	<0.0001

Parous previous preeclampsia	-0.031689 (-0.056684, -0.056684)	0.013
Ratio of second to first systolic peak velocity		
Intercept	0.610732 (0.606672, 0.606672)	<0.0001
Preeclampsia	0.503075 (0.213746, 0.213746)	0.0007
Gestational age at delivery with preeclampsia	-0.010752 (-0.018372, -0.018372)	0.0057
Weight in Kg - 69	0.000511 (0.000253, 0.000253)	0.0001
Age in years - 35	0.005024 (0.004326, 0.004326)	<0.0001
Height in cm - 164	-0.001269 (-0.001778, -0.001778)	<0.0001
East Asian racial origin	-0.037322 (-0.057908, -0.057908)	0.0004
Smoker	0.045739 (0.015509, 0.015509)	0.003
Chronic hypertension	0.070468 (0.042809, 0.042809)	<0.0001

Table 3. Fitted regression model for ophthalmic artery second to first systolic peak velocity ratio delta values on mean gestational age at delivery for pregnancies with preeclampsia. Standard deviations (SD) and correlations for log_{10} multiples of the median (MoM) values of mean arterial pressure, uterine artery pulsatility index, placental growth factor and soluble fms-like tyrosine kinase-1.

Preeclampsia mean	
Intercept (95% confidence limits)	0.6732 (0.5245, 0.8515)
Slope (95% confidence limits)	-0.0154 (-0.0197, -0.0120)
Standard deviation (95% confidence limits)	0.0924 (0.0902, 0.0947)
Correlations (95% confidence limits)	
Mean arterial pressure	0.1519 (0.1160, 0.1911)
Uterine artery pulsatility index	0.0263 (-0.0096, 0.0619)
Placental growth factor	-0.0251 (-0.0610, 0.0115)
soluble fms-like tyrosine kinase-1	-0.0141 (-0.0512, 0.0216)

Table 4. Area under the operating characteristic curve and detection rate of delivery with preeclampsia at <37 weeks' gestation, at 10% false positive rate, after screening at 19-23 weeks' gestation by maternal factors, ophthalmic artery second to first peak systolic velocity ratio (PSV ratio) and combinations with mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFLT).

Method of screening	Preeclampsia with delivery at <37 weeks' gestation (n=18)		
	AUC (95% CI)	n (DR, 95% CI)	Modelled DR
Maternal factors	0.8529 (0.7753 - 0.9304)	10 (55.6, 30.8 - 78.5)	56.1
+ PSV ratio	0.8985 (0.8092 - 0.9878)	14 (77.8, 52.4 - 93.6)	80.2
+ MAP	0.8813 (0.8178 - 0.9449)	11 (61.1, 35.7 - 82.7)	69.1
+ UtA-PI	0.7952 (0.6593 - 0.9311)	11 (61.1, 35.7 - 82.7)	74.8
+ PlGF	0.9554 (0.9258 - 0.9849)	15 (83.3, 58.6 - 96.4)	75.5
+ sFLT	0.8718 (0.7967 - 0.9469)	11 (61.1, 35.7 - 82.7)	60.4
+ MAP + UtA-PI	0.8227 (0.6996 - 0.9458)	12 (66.7, 41.0 - 86.7)	80.7
+ MAP + UtA-PI + PlGF	0.9053 (0.8141 - 0.9965)	13 (72.2, 46.5 - 90.3)	85.5
+ MAP + UtA-PI + PlGF + sFLT	0.9209 (0.8377 - 1.0000)	14 (77.8, 52.4 - 93.6)	84.9
+ MAP + PSV ratio	0.9109 (0.8327 - 0.9891)	14 (77.8, 52.4 - 93.6)	83.0
+ UtA-PI + PSV ratio	0.8682 (0.7699 - 0.9666)	12 (66.7, 41.0 - 86.7)	85.7
+ PlGF + PSV ratio	0.9693 (0.9460 - 0.9926)	16 (88.9, 65.3 - 98.6)	86.3
+ sFLT + PSV ratio	0.9001 (0.8096 - 0.9906)	14 (77.8, 52.4 - 93.6)	80.5
+ MAP + UtA-PI + PSV ratio	0.8848 (0.7975 - 0.9720)	14 (77.8, 52.4 - 93.6)	87.9
+ MAP + UtA-PI + PlGF + PSV ratio	0.9483 (0.9015 - 0.9952)	16 (88.9, 65.3 - 98.6)	90.3
+ MAP + UtA-PI + PlGF + sFLT + PSV ratio	0.9583 (0.9199 - 0.9966)	16 (88.9, 65.3 - 98.6)	89.8

Table 5. Area under the operating characteristic curve and detection rate of delivery with preeclampsia at ≥37 weeks' gestation, at 10% false positive rate, after screening at 19-23 weeks' gestation by maternal factors, ophthalmic artery second to first systolic peak velocity ratio and combinations with mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFLT).

Method of screening	Preeclampsia with delivery at ≥37 weeks' gestation (n=58)		
	AUC (95% CI)	n (DR, 95% CI)	Modelled DR
Maternal factors	0.7592 (0.7029 - 0.8155)	18 (31.0, 19.5 - 44.5)	33.8
+ PSV ratio	0.8166 (0.7624 - 0.8708)	28 (48.3, 35.0 - 61.8)	46.0
+ MAP	0.8194 (0.7727 - 0.8662)	30 (51.7, 38.2 - 65.0)	41.8
+ UtA-PI	0.7348 (0.6747 - 0.7949)	16 (27.6, 16.7 - 40.9)	41.1
+ PlGF	0.7897 (0.7332 - 0.8462)	24 (41.4, 28.6 - 55.1)	30.5
+ sFLT	0.7589 (0.7022 - 0.8156)	19 (32.8, 21.0 - 46.3)	31.4
+ MAP + UtA-PI	0.8026 (0.7546 - 0.8505)	24 (41.4, 28.6 - 55.1)	46.6
+ MAP + UtA-PI + PlGF	0.8103 (0.7618 - 0.8588)	25 (43.1, 30.2 - 56.8)	45.2
+ MAP + UtA-PI + PlGF + sFLT	0.8103 (0.7630 - 0.8575)	24 (41.4, 28.6 - 55.1)	43.0
+ MAP + PSV ratio	0.8552 (0.8123 - 0.8982)	31 (53.4, 39.9 - 66.7)	50.5
+ UtA-PI + PSV ratio	0.8069 (0.7525 - 0.8614)	24 (41.4, 28.6 - 55.1)	51.4
+ PlGF + PSV ratio	0.8420 (0.7926 - 0.8914)	33 (56.9, 43.2 - 69.9)	44.1
+ sFLT + PSV ratio	0.8174 (0.7631 - 0.8717)	28 (48.3, 35.0 - 61.8)	45.2
+ MAP + UtA-PI + PSV ratio	0.8848 (0.7975 - 0.9720)	23 (39.7, 27.0 - 53.4)	54.2
+ MAP + UtA-PI + PlGF + PSV ratio	0.8586 (0.8183 - 0.8990)	28 (48.3, 35.0 - 61.8)	53.4
+ MAP + UtA-PI + PlGF + sFLT + PSV ratio	0.8605 (0.8206 - 0.9003)	32 (55.2, 41.5 - 68.3)	51.2

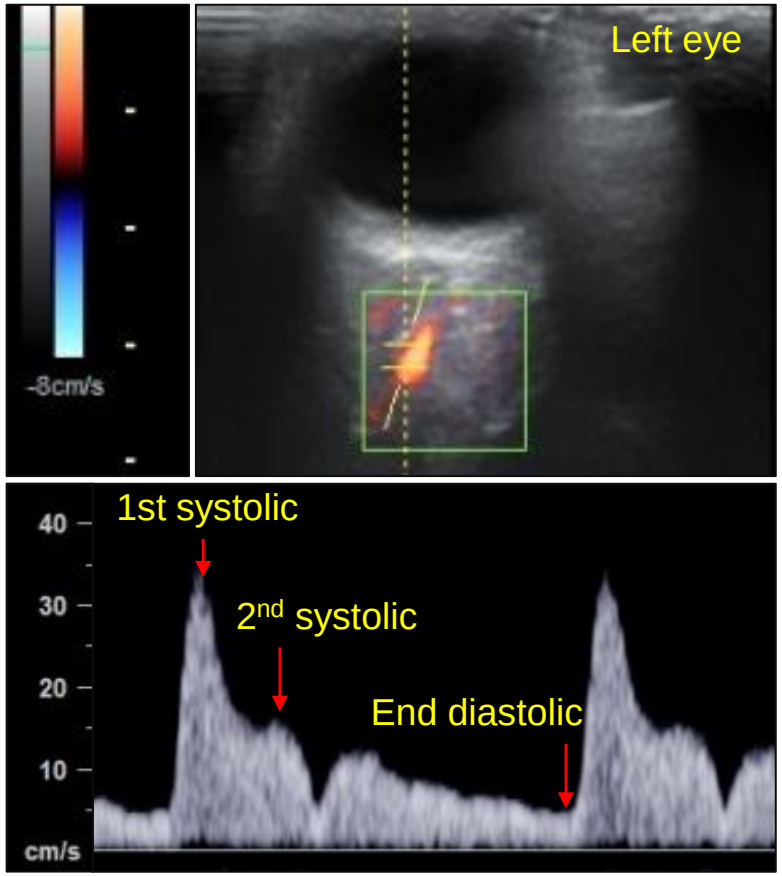

Figure 1

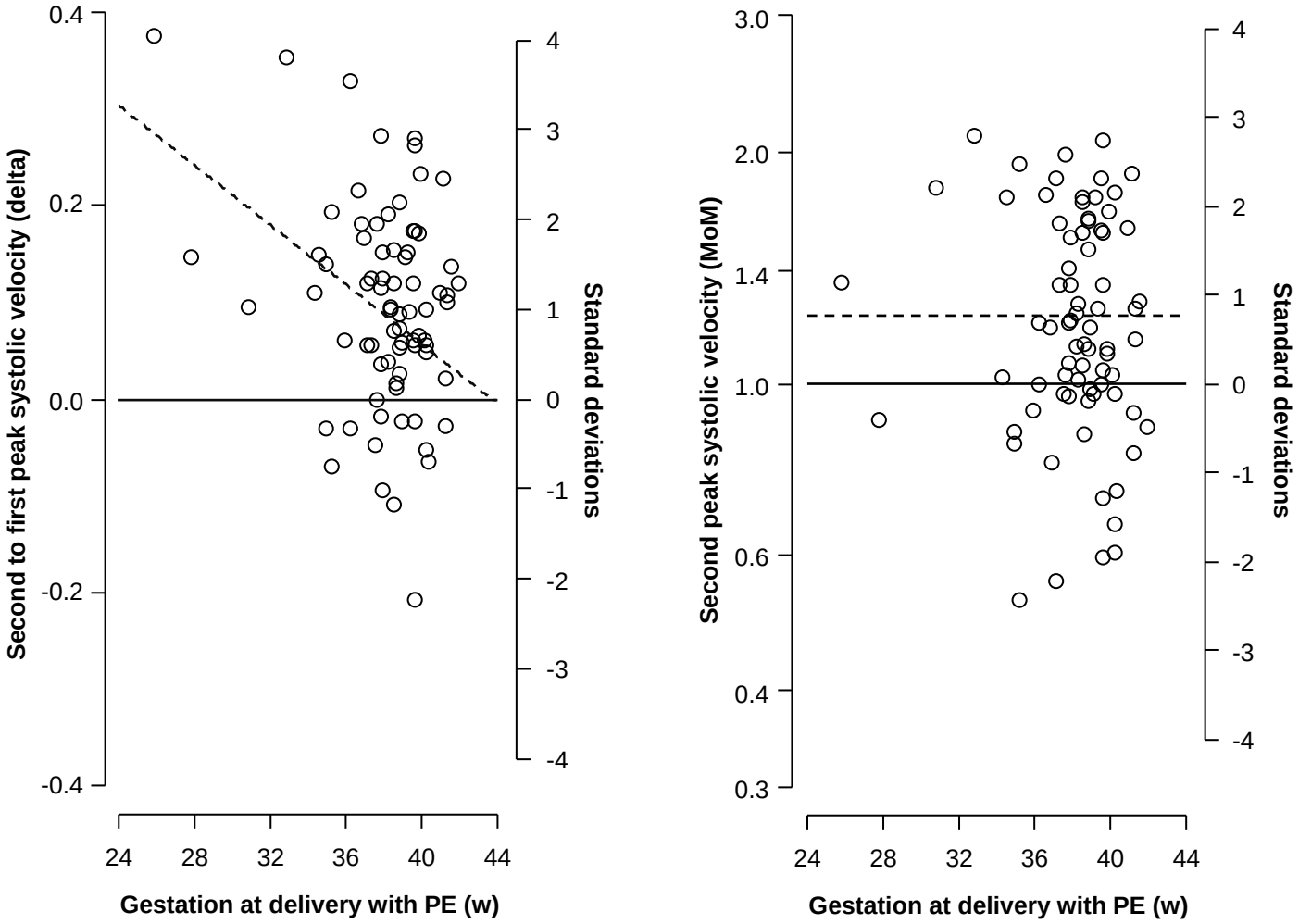

Figure 2

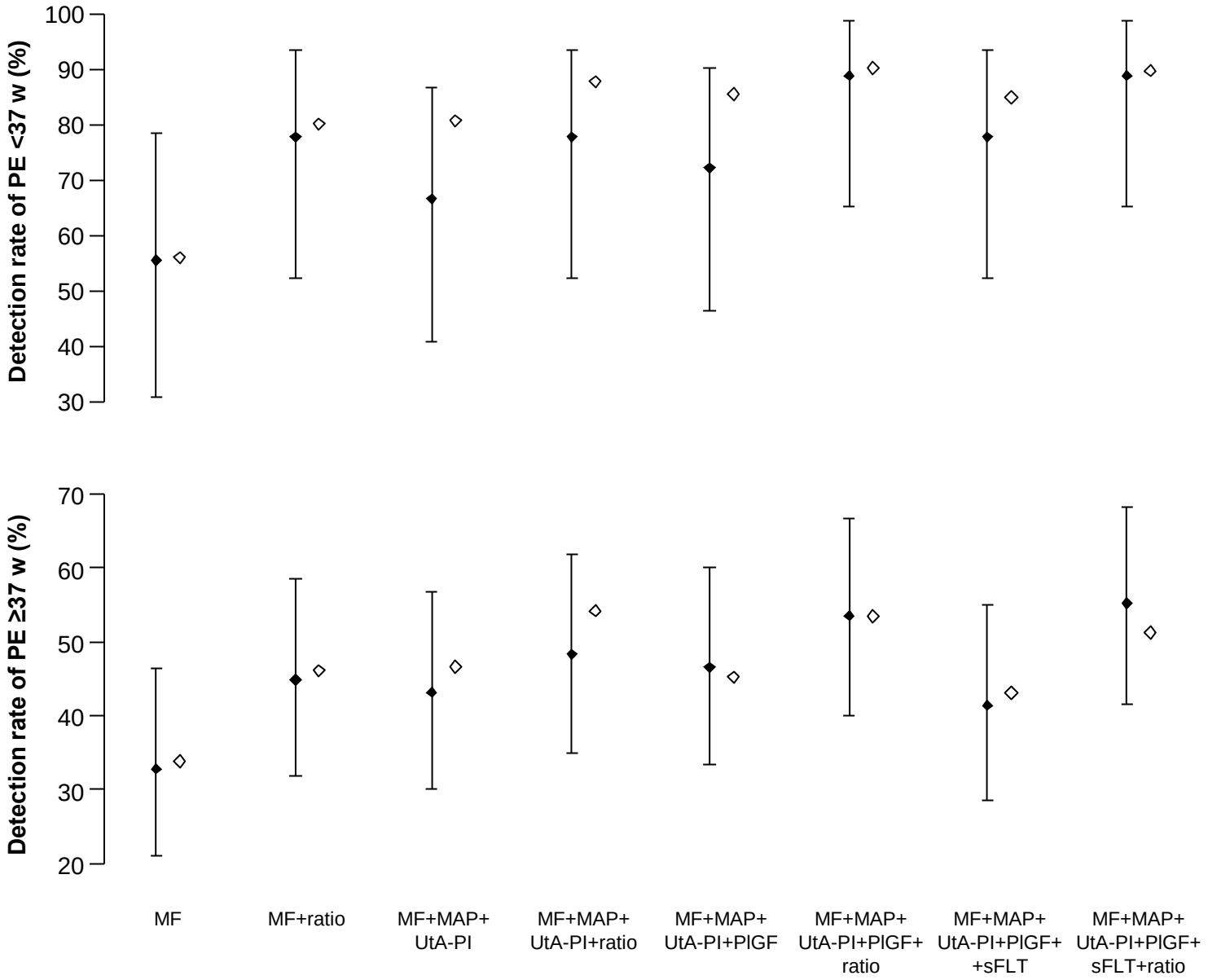

Figure 3