Ophthalmic artery Doppler in combination with other biomarkers in the prediction of pre-eclampsia at 35–37 weeks' gestation

M. SARNO,[1,2] A. WRIGHT,[3] N. VIEIRA,[1] I. SAPANTZOGLOU,[1]
M. CHARAKIDA,[1] K. H. NICOLAIDES.[1]

1. Harris Birthright Research Centre for Fetal Medicine, King's College, London, UK.
2. Department of Obstetrics and Gynecology, Federal University of Bahia (UFBA), Salvador-Bahia, Brazil.
3. Institute of Health Research, University of Exeter, Exeter, UK.

Correspondence:
Professor KH Nicolaides, Fetal Medicine Research Institute,
King's College Hospital, 16-20 Windsor Walk, Denmark Hill, London SE5 8BB
email: kypros@fetalmedicine.com

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What are the novel findings of this work

Ophthalmic artery Doppler at 35-37 weeks' gestation improves the prediction of PE, especially imminent PE with delivery within three weeks from assessment, provided by a combination of maternal characteristics, medical history, mean arterial pressure and serum placental growth factor.

What are the clinical implications of this work

Ophthalmic artery Doppler could be incorporated into routine screening for third trimester prediction of imminent preeclampsia, but further studies are needed to validate this finding.

ABSTRACT

Objectives: To examine the potential value of maternal ophthalmic artery Doppler at 35-37 weeks' gestation in combination with the established biomarkers of preeclampsia (PE), including mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), 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 35^{+0} - 36^{+6} 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. The competing risks model was used to estimate the individual patient-specific risks of delivery with PE at any time and at <3 weeks from assessment by a combination of maternal demographic characteristics and medical history with biomarkers. The area under the operating characteristic curve (AUC) and detection rate (DR) of delivery with PE, at 10% false positive rate (FPR), after screening by maternal factors, ophthalmic artery second to first peak systolic velocity (PSV) ratio and combinations with MAP, UtA-PI, serum PlGF and sFLT were determined. The modelled performance of screening for PE was also estimated.

Results: The study population of 2,287 pregnancies contained 60 (2.6%) that developed PE, including 19 (0.8%) that delivered with PE at <3 weeks from assessment. The PSV ratio improved the prediction of PE with delivery at any stage after assessment provided by maternal factors alone (from 25.4% to 50.6%), maternal factors plus MAP (54.3% to 62.7%), maternal factors, MAP, plus PlGF (68.3% to 70.8%) and maternal factors, MAP, PlGF plus sFLT (75.7% to 76.7%), at FPR of 10%. The PSV ratio also improved the prediction of PE with delivery at <3 weeks from assessment provided by maternal factors alone (from 31.0% to 69.4%), maternal factors plus MAP (74.1% to 83.4%), maternal factors, MAP plus UtA-PI (77.1% to 85.0%) and maternal factors, MAP plus PlGF (88.6% to 90.7%). The empirical results on DR at 10% FPR were consistent with the modelled results. Screening by a combination of maternal factors with MAP and second to first PSV ratio also detected 60.9% (56.8 - 81.2) of GH with delivery at any stage after assessment, and 80.0% (95% CI 66.9 - 98.7) of GH with delivery at <3 weeks from assessment.

Conclusion: Ophthalmic artery Doppler could potentially improve the performance of screening for PE at 35-37 weeks, especially imminent PE with delivery within three weeks of assessment, but further studies are needed to validate this finding.

INTRODUCTION

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.[1] Several studies reported that in pregnancies with preeclampsia (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.[2-12] There is also some evidence that development of PE is preceded by decrease in impedance to flow in the cerebral circulation. Three small prospective studies, involving <450 patients each examined the potential value of ophthalmic artery Doppler in the prediction of PE during the first or second trimester of pregnancy; two of the studies reported that ophthalmic artery Doppler was useful and one that it was not.[13-15]

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, there was good correlation between the first and second measurements of the ratio from the same eye, but poorer correlation in the first and second measurements between the two eyes and it was estimated that the best performance of screening for PE was achieved by taking the average of four measurements (two from each eye), and third, the detection rate (DR), at 10% false positive rate (FPR), of delivery with PE at any time from assessment by maternal factors was 25% and this increased to 50% with the addition of the second to first PSV ratio; the respective values for delivery with PE within three weeks from assessment were 32% and 58%.[16]

The objectives of this study in the same population as above,[16] undergoing routine screening at 35-37 weeks' gestation are to examine the performance of maternal ophthalmic artery second to first PSV ratio in combination with the established biomarkers of PE, including mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (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 35^{+0} - 36^{+6} weeks' gestation at King's College Hospital, London, UK between June 2019 and March 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 [17] color flow imaging of the left and right uterine arteries by transabdominal ultrasound and measurement of mean UtA-PI,[18] and measurement of serum concentration of PlGF and sFLT in pg/mL by an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS, Thermo Fisher Scientific, Hennigsdorf, Germany). 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.[19,20] 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 examined at 35^{+0} - 36^{+6} weeks' gestation and delivering a non-malformed live birth. We excluded pregnancies with aneuploidies and major fetal abnormalities and those with PE at the time of screening.

Ophthalmic artery Doppler

The mother was in the supine position for the routine 35-37 weeks scan and at the end of this procedure a 6-15-MHz linear transducer (GE ML6-15-D Matrix Linear Probe, GE Healthcare Ultrasound, Milwaukee, WI, USA) 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 (Figure 1).[21] 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.[16]

Waveforms were obtained in sequence from the right eye, left eye, and again right and then left eye. The first PSV was obtained automatically by the machine and the second PSV was measured manually, because this is not given automatically. In each recording the ratio of second to first PSV was calculated and the average of the four measurements was used for analysis.

Outcome measures

Outcome measures were delivery with PE or GH at any time and within three weeks after assessment. 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 or GH. Diagnosis of GH was based on the finding of 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). Diagnosis of PE was based on the finding of new onset hypertension 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.[22]

Statistical analysis

Data were expressed as median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. Students t-test and χ2-square test or Fisher's exact test, were used for comparing outcome groups for continuous and categorical data, respectively.

The competing risks model was used to estimate the individual patient-specific risks of delivery with PE at any time and at <3 weeks from assessment by a combination of maternal demographic characteristics and medical history with biomarkers.[23]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 multiple of the median (MoM) or difference from the median (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 DRs of delivery with PE or GH, 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.

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. MoM values for MAP, UtA-PI, serum PlGF and sFLT and Delta values for

ophthalmic artery second to first PSV were simulated from a multivariate Gaussian distribution.[16,24] Detection rates for FPRs of 10% were calculated and compared to empirical results.

The statistical software package R was used for data analyses.[25]

RESULTS

Study participants

The study population of 2,287 pregnancies contained 60 (2.6%) that developed PE, including 19 (0.8%) that delivered with PE at <3 weeks from assessment, and 64 (2.8%) that developed GH, including 15 (0.7%) that delivered with GH at <3 weeks from assessment. Maternal and pregnancy characteristics of the study population are summarized in Table 1. In the PE and GH groups, compared to the unaffected pregnancies, there was a higher median maternal weight and body mass index, and higher incidence of nulliparity and previous history of PE.

Performance of screening

The empirical AUC and DR, at 10% FPR, and modelled DR, at 10% FPR, of delivery with PE or GH at any time and at <3 weeks from assessment by maternal factors, ophthalmic artery second to first PSV and combinations with MAP, UtA-PI, serum PlGF and sFLT, as well as PlGF concentration alone and the sFLT / PlGF ratio are shown in Tables 2 and 3. The empirical results on DR at 10% FPR were consistent with the modelled results, both for delivery with PE at any time and at <3 weeks from assessment (Figure 2).

In the modelled results, the best individual biomarker marker, in combination with maternal factors, of delivery with PE at any time after assessment was sFLT, followed by PlGF, MAP, ophthalmic artery PSV ratio and then UtA-PI, with respective DRs, at 10% FPR, of 67.3%, 59.5%, 54.3%, 50.6% and 31.2% (Table 2). Addition of PSV ratio improved the prediction of PE with delivery at any stage after assessment provided by maternal factors alone (from 25.4% to 50.6%), maternal factors plus MAP (54.3% to 62.7%), maternal factors plus UtA-PI (31.2% to 53.3%), maternal factors plus PlGF (59.5% to 65.7%), maternal factors plus sFLT (67.3% to 71.4%), maternal factors, MAP plus UtA-PI (56.8% to 64.2%), maternal factors, MAP, plus PlGF (68.3% to 70.8%) and maternal factors, MAP, PlGF plus sFLT (75.7% to 76.7%), at FPR of 10%. Such performance was superior to screening by PlGF concentration alone or the sFLT / PlGF ratio with respective DRs of 53.3% and 63.3%.

In screening for PE with delivery at <3 weeks from assessment, the best individual biomarker, in combination with maternal factors, was sFLT, followed by MAP, PlGF, second to first PSV ratio and then UtA-PI, with respective DRs, at 10% FPR, of 84.3%, 74.1%, 73.3%, 69.4% and 43.0% (Table 3). Addition of PSV ratio improved the prediction of PE with delivery at <3 weeks from assessment provided by maternal factors alone (from 31.0% to 69.4%), maternal factors plus MAP (74.1% to 83.4%), maternal factors plus UtA-PI (43.0% to 71.4%), maternal factors plus PlGF (73.3% to 81.4%), maternal factors plus sFLT (84.3% to 87.5%), maternal factors, MAP plus UtA-PI (77.1% to 85.0%), and maternal factors, MAP plus PlGF (84.8% to 88.6%), but not the prediction provided by maternal factors, MAP, PlGF plus sFLT (93.2% with and without addition of PSV ratio), at

FPR of 10%. Such performance was superior to screening by PlGF concentration alone or the sFLT / PlGF ratio with respective DRs of 57.9% and 78.9%.

Screening by a combination of maternal factors with MAP and second to first PSV ratio also detected 59.4% (58.6 - 82.5) of GH with delivery at any stage after assessment (Table 2), and 86.7% (95% CI 82.4 - 100) of GH with delivery at <3 weeks from assessment (Table 3).

DISCUSSION

Principal findings of this study

This study in singleton pregnancies undergoing routine assessment at 35^{+0} - 36^{+6} weeks' gestation has demonstrated that maternal ophthalmic artery Doppler is a useful biomarker of subsequent delivery with PE, especially imminent PE with delivery within three weeks of assessment. The second to first PSV ratio in combination with maternal medical history and MAP improved the prediction of delivery with PE, at 10% FPR, both within three weeks and at any time after assessment from 31.0% and 25.4%, respectively, achieved by maternal history alone to 83.4% and 62.7%. Such performance is rather inferior to that achieved by a combination of maternal history, MAP, PlGF and sFLT using the competing risk approach, with respective DRs of 93.2% and 75.7%; however, the performance is superior to that achieved from the measurement of PlGF alone[26] (57.9% and 53.3%, respectively) and similar or superior to that of the sFLT / PlGF ratio[27] (78.9% and 63.3%, respectively). An important advantage of assessment of the ophthalmic artery, by comparison with biochemical testing, is that it can easily be incorporated into a routine 35-37 weeks scan with no real additional cost and the results are available immediately.

Comparison with previous studies

A previous screening study at 35-37 weeks' gestation, involving 13,350 pregnancies and including 272 (2.0%) that subsequently developed PE, demonstrated that first, the performance of screening for term PE at 35-37 weeks was superior to that of screening at 12, 22 or 32 weeks, and second, the best performance of screening was achieved by a combination of maternal factors, MAP, PLGF and sFLT, with no evidence of improvement by the addition of UtA-PI.[28] Our results are consistent with those of the previous screening study.

Previous studies in heterogeneous groups of women presenting with signs and / or symptoms of hypertensive disorders reported that low serum PlGF or high sFLT / PlGF ratio were highly predictive of imminent PE, within the subsequent 1-3 weeks, and that these tests could be used to stratify women into a high-risk group in need of intensive surveillance or hospitalization and delivery and a low-risk group that could be reassured that imminent PE was unlikely.[26,27] Our approach to prediction of PE takes into account maternal characteristics, medical history and blood pressure in addition to PlGF and sFLT

to estimate the individual patient-specific risk for delivery with PE at any prespecified interval from assessment. In a screening study at 35-37 weeks' gestation, involving 15,247 pregnancies and including 326 (2.1%) that subsequently developed PE, we demonstrated that screening by a combination of maternal factors, MAP, PlGF and sFLT was superior to that of PlGF alone or the sFLT / PLGF ratio in predicting delivery with PE within two and within four weeks of assessment.[29] In this study we confirmed that in screening for imminent PE the combined test, which includes maternal factors and MAP in addition to PlGF and sFLT, is superior to that of screening by PlGF alone or the sFLT / PLGF ratio. Furthermore, we found that the performance of the combined test is further improved by the addition of the ophthalmic artery second to first PSV ratio.

Strengths and limitations

The main strengths of the study are first, examination of a large population of pregnant women attending for routine care in a gestational age range which is increasingly being used for prediction of late PE, assessment of fetal growth and wellbeing, determination of fetal position and diagnosis of fetal abnormalities,[29-39] 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. In a previous screening study at 35-37 weeks' gestation which demonstrated that screening by a combination of maternal factors, MAP, PlGF and sFLT was superior to that of PlGF alone or the sFLT / PLGF ratio, the number of patients was 15,247, including 326 (2.1%) that subsequently developed PE.[29] We tried to overcome the problem of small numbers of cases of PE, especially PE with delivery within three weeks of assessment, by modeling which produced results that were consistent with the empirical results and those of previous larger studies.[28,29]

Conclusions

Ophthalmic artery Doppler could potentially improve the performance of screening for PE at 35-37 weeks, especially imminent PE with delivery within three weeks of assessment, but more extensive studies are needed to validate this finding.

Conflict of interest: None

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FIGURE LEGEND

Figure 1. 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. Empirical detection rates, with 95% confidence intervals, at 10% false positive rate, of preeclampsia at any stage after assessment at 35-37 weeks' gestation (left) and within three weeks from assessment (right) in screening by combination of maternal factors with ophthalmic artery second to first peak systolic velocity ration (PSV), mean arterial pressure (MAP, placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFLT). The open circles represent the model-based detection rates.

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

Characteristic	Normal (n=2,163)	Preeclampsia (n=60)	p-value	Gestational hypertension (n=64)	p-value
Age in years	33.6 (30.6, 36.8)	34.0 (30.3, 37.0)	0.988	34.6 (30.8, 38.2)	0.273
Weight in kg	78.0 (70.3, 87.2)	85.5 (76.0, 93.4)	0.0012	83.7 (71.4, 101.7)	0.019
Height in cm	166 (162, 171)	166 (163, 171)	0.557	166 (163, 168)	0.299
Body mass index in kg/m2	28.1 (25.6, 31.2)	30.6 (27.7, 33.6)	0.0019	29.7 (26.5, 36.5)	0.005
Gestational age in weeks	35.7 (35.6, 36.0)	35.8 (35.5, 36.0)	0.969	35.9 (35.6, 36.1)	0.054
Racial origin			0.606		0.103
White	1,623 (75.0)	45 (75.0)		48 (75.0)	
Black	263 (12.2)	10 (16.7)		13 (20.3)	
South Asian	125 (5.8)	1 (1.7)		0 (0.0)	
East Asian	74 (3.4)	2 (3.3)		1 (1.6)	
Mixed	78 (3.6)	2 (3.3)		2 (3.1)	
Medical history					
Chronic hypertension	33 (1.5)	2 (3.3)	0.559	0 (0.0)	0.638
Diabetes mellitus type 1	5 (0.2)	1 (1.7)	0.094	2 (3.1)	0.255
Diabetes mellitus type 2	22 (1.0)	1 (1.7)		0 (0.0)	
SLE/APS	7 (0.3)	0 (0.0)	1	1 (1.6)	0.567
Smoker	9 (0.4)	1 (1.7)	0.653	0 (0.0)	1
Family history of PE	68 (3.1)	5 (8.3)	0.063	3 (4.7)	0.740
Method of conception			0.191		0.249
Natural	2,047 (94.6)	54 (90.0)		58 (90.6)	
In vitro fertilization	107 (4.9)	6 (10.0)		6 (9.4)	
Use of ovulation drugs	9 (0.4)	0 (0.0)		0 (0.0)	
Parity			0.00002		0.0008
Nulliparous	1,136 (52.5)	49 (81.7)		39 (60.9)	
Parous no previous PE	986 (45.6)	9 (15.0)		20 (31.3)	
Parous previous PE	41 (1.9)	2 (3.3)		5 (7.8)	
Pregnancy interval in years	2.4 (1.6, 4.2)	3.2 (2.0, 5.6)	0.25	3.2 (2.2, 5.2)	0.089

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. Area under the operating characteristic curve and detection rate of delivery with preeclampsia or gestational hypertension, at 10% false positive rate, after screening at 35-37 weeks' gestation by maternal factors, ophthalmic artery second to first systolic peak velocity 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	All PE (n=60)			All GH (n=64)	
	AUC (95% CI)	n (DR, 95% CI)	Modelled DR	AUC (95% CI)	n (DR, 95% CI)
Maternal factors	0.7353 (0.6792 - 0.7915)	15 (25.0, 14.7 - 37.9)	25.4	0.6662 (0.5938 - 0.7386)	20 (31.3, 14.7 - 37.9)
+ PSV ratio	0.8341 (0.7912 - 0.8769)	30 (50.0, 36.8 - 63.2)	50.6	0.7350 (0.6724 - 0.7977)	23 (35.9, 36.8 - 63.2)
+ MAP	0.8907 (0.8549 - 0.9264)	38 (63.3, 49.9 - 75.4)	54.3	0.8634 (0.8153 - 0.9116)	41 (64.1, 49.9 - 75.4)
+ MAP + PSV ratio	0.9118 (0.8827 - 0.9409)	43 (71.7, 58.6 - 82.5)	62.7	0.8589 (0.8131 - 0.9047)	38 (59.4, 58.6 - 82.5)
+ UtA-PI	0.7027 (0.6379 - 0.7675)	18 (30.0, 18.9 - 43.2)	31.2	0.6585 (0.5873 - 0.7298)	19 (29.7, 18.8 - 43.2)
+ UtA-PI + PSV ratio	0.8184 (0.7740 - 0.8629)	22 (36.7, 24.6 - 50.1)	53.3	0.7349 (0.6738 - 0.7960)	25 (39.1, 24.6 - 50.1)
+ PlGF	0.8513 (0.8008 - 0.9017)	34 (56.7, 43.2 - 69.4)	59.5	0.7936 (0.7399 - 0.8472)	24 (37.5, 43.2 - 69.4)
+ PlGF + PSV ratio	0.8798 (0.8364 - 0.9233)	38 (63.3, 49.9 - 75.4)	65.7	0.8196 (0.7741 - 0.8650)	27 (42.2, 49.9 - 75.4)
+ sFLT	0.8596 (0.8173 - 0.9019)	34 (56.7, 43.2 - 69.4)	67.3	0.7950 (0.7434 - 0.8467)	23 (35.9, 43.2 - 69.4)
+ sFLT + PSV ratio	0.8843 (0.8484 - 0.9202)	41 (68.3, 55.0 - 79.7)	71.4	0.8190 (0.7744 - 0.8635)	26 (40.6, 55.0 - 79.7)
+ MAP + UtA-PI	0.8763 (0.8370 - 0.9156)	42 (70.0, 56.8 - 81.2)	56.8	0.8581 (0.8078 - 0.9085)	39 (60.9, 56.8 - 81.2)
+ MAP + UtA-PI + PSV ratio	0.9006 (0.8690 - 0.9321)	40 (66.7, 53.3 - 78.3)	64.2	0.8573 (0.8119 - 0.9027)	37 (57.8 53.3 - 78.3)
+ MAP + PlGF	0.9093 (0.8741 - 0.9445)	47 (78.3, 65.8 - 87.9)	68.3	0.8766 (0.8326 - 0.9206)	36 (56.3, 65.8 - 87.9)
+ MAP + PlGF + PSV ratio	0.9183 (0.8862 - 0.9505)	46 (76.7, 64.0 - 86.6)	70.8	0.8836 (0.8456 - 0.9217)	38 (59.4, 58.6 - 82.5)
+ MAP + sFLT	0.9031 (0.8694 - 0.9369)	41 (68.3, 55.0 - 79.7)	73.0	0.8711 (0.8312 - 0.9110)	39 (60.9, 56.8 - 81.2)
+ MAP + sFLT + PSV ratio	0.9140 (0.8843 - 0.9436)	43 (71.7, 58.6 - 82.5)	74.4	0.8771 (0.8414 - 0.9129)	34 (53.1, 58.6 - 82.5)
+ MAP + PlGF + sFLT	0.9093 (0.8760 - 0.9426)	45 (75.0, 62.1 - 85.3)	75.7	0.8741 (0.8331 - 0.9151)	40 (62.5, 62.1 - 85.3)
+ MAP + PlGF + sFLT + PSV ratio	0.9160 (0.8847 - 0.9472)	45 (75.0, 62.1 - 85.3)	76.7	0.8797 (0.8423 - 0.9170)	39 (60.9, 56.8 - 81.2)
+ MAP + UtA-PI + PlGF + sFLT	0.9002 (0.8646 - 0.9359)	43 (71.7, 58.6 - 82.5)	75.8	0.8714 (0.8295 - 0.9132)	36 (56.3, 65.8 - 87.9)
+ MAP + UtA-PI + PlGF + sFLT + PSV ratio	0.9078 (0.8744 - 0.9411)	43 (71.7, 58.6 - 82.5)	77.2	0.8772 (0.8390 - 0.9154)	38 (59.4, 58.6 - 82.5)
+ PlGF + sFLT	0.8761 (0.8351 - 0.9171)	40 (66.7, 53.3 - 78.3)	71.5	0.8177 (0.7684 - 0.8669)	29 (45.3, 53.3 - 78.3)
+ PlGF + sFLT + PSV ratio	0.8922 (0.8548 - 0.9296)	42 (70.0, 56.8 - 81.2)	74.4	0.8345 (0.7912 - 0.8778)	29 (45.3, 53.3 - 78.3)
PlGF concentration	0.8202 (0.7605 - 0.8798)	32 (53.3, 40.0 - 66.3)		0.7659 (0.7068 - 0.8249)	25 (39.1, 24.6 - 50.1)
sFLT / PlGF ratio	0.8505 (0.7968 - 0.9042)	38 (63.3, 49.9 - 75.4)		0.7894 (0.7325 - 0.8463)	28 (43.8, 49.9 - 75.4)

Table 3. Area under the operating characteristic curve and detection rate of delivery with preeclampsia or gestational hypertension within 3 weeks of assessment, at 10% false positive rate, after screening at 35-37 weeks' gestation by maternal factors, ophthalmic artery second to first systolic peak velocity 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	PE (n=19)			GH (n=15)	
	AUC (95% CI)	n (DR, 95% CI)	Modelled DR	AUC (95% CI)	n (DR, 95% CI)
Maternal factors	0.7943 (0.7131 - 0.8755)	6 (31.6, 12.6 - 56.6)	31.0	0.7749 (0.6547 - 0.8951)	5 (33.3, 12.6 - 56.6)
+ PSV ratio	0.8897 (0.8340 - 0.9453)	11 (57.9, 33.5 - 79.8)	69.4	0.8014 (0.6809 - 0.9220)	9 (60.0, 33.5 - 79.8)
+ MAP	0.9511 (0.9120 - 0.9902)	17 (89.5, 66.9 - 98.7)	74.1	0.9555 (0.9298 - 0.9811)	12 (80.0, 66.9 - 98.7)
+ MAP + PSV ratio	0.9701 (0.9538 - 0.9865)	18 (94.7, 74.0 - 99.9)	83.4	0.9470 (0.9055 - 0.9884)	13 (86.7,82.4 - 100)
+ UtA-PI	0.7565 (0.6434 - 0.8696)	10 (52.6, 28.9 - 75.6)	43.0	0.7975 (0.6766 - 0.9184)	7 (46.7, 28.9 - 75.6)
+ UtA-PI + PSV ratio	0.8757 (0.8169 - 0.9344)	10 (52.6, 28.9 - 75.6)	71.4	0.8211 (0.7054 - 0.9368)	10 (66.7, 28.9 - 75.6)
+ PlGF	0.8936 (0.8138 - 0.9733)	15 (78.9, 54.4 - 93.9)	73.3	0.8599 (0.7675 - 0.9524)	10 (66.7, 28.9 - 75.6)
+ PlGF + PSV ratio	0.9249 (0.8659 - 0.9839)	15 (78.9, 54.4 - 93.9)	81.4	0.8807 (0.8021 - 0.9592)	10 (66.7, 28.9 - 75.6)
+ sFLT	0.8872 (0.8129 - 0.9615)	14 (73.7, 48.8 - 90.9)	84.3	0.8807 (0.8144 - 0.9471)	8 (53.3, 48.8 - 90.9)
+ sFLT + PSV ratio	0.9187 (0.8613 - 0.9762)	16 (84.2, 60.4 - 96.6)	87.5	0.8845 (0.8136 - 0.9554)	9 (60.0, 33.5 - 79.8)
+ MAP + UtA-PI	0.9605 (0.9411 - 0.9799)	18 (94.7, 74.0 - 99.9)	77.1	0.9553 (0.9264 - 0.9842)	12 (80.0, 66.9 - 98.7)
+ MAP + UtA-PI + PSV ratio	0.9708 (0.9567 - 0.9848)	19 (100, 82.4 - 100)	85.0	0.9499 (0.9118 - 0.9879)	13 (86.7, 82.4 - 100)
+ MAP + PlGF	0.9678 (0.9448 - 0.9908)	18 (94.7, 74.0 - 99.9)	84.8	0.9401 (0.8800 - 1.0000)	13 (86.7, 82.4 - 100)
+ MAP + PlGF + PSV ratio	0.9728 (0.9512 - 0.9945)	18 (94.7, 74.0 - 99.9)	88.6	0.9474 (0.8997 - 0.9952)	13 (86.7, 82.4 - 100)
+ MAP + sFLT	0.9462 (0.9107 - 0.9817)	17 (89.5, 66.9 - 98.7)	90.7	0.9499 (0.9220 - 0.9779)	13 (86.7, 82.4 - 100)
+ MAP + sFLT + PSV ratio	0.9568 (0.9274 - 0.9861)	17 (89.5, 66.9 - 98.7)	92.6	0.9470 (0.9169 - 0.9770)	12 (80.0, 66.9 - 98.7)
+ MAP + PlGF + sFLT	0.9439 (0.9054 - 0.9824)	17 (89.5, 66.9 - 98.7)	93.2	0.9472 (0.9048 - 0.9896)	13 (86.7, 82.4 - 100)
+ MAP + PlGF + sFLT + PSV ratio	0.9579 (0.9265 - 0.9892)	17 (89.5, 66.9 - 98.7)	93.2	0.9480 (0.9151 - 0.9809)	12 (80.0, 66.9 - 98.7)
+ MAP + UtA-PI + PlGF + sFLT	0.9439 (0.9054 - 0.9824)	17 (89.5, 66.9 - 98.7)	92.5	0.9472 (0.9048 - 0.9896)	13 (86.7, 82.4 - 100)
+ MAP + UtA-PI + PlGF + sFLT + PSV ratio	0.9539 (0.9207 - 0.9871)	17 (89.5, 66.9 - 98.7)	94.0	0.9475 (0.9123 - 0.9827)	12 (80.0, 66.9 - 98.7)
+ PlGF + sFLT	0.9015 (0.8317 - 0.9713)	15 (78.9, 54.4 - 93.9)	87.2	0.8935 (0.8322 - 0.9547)	11 (73.3, 54.4 - 93.9)
+ PlGF + sFLT + PSV ratio	0.9221 (0.8637 - 0.9805)	16 (84.2, 60.4 - 96.6)	89.2	0.8951 (0.8364 - 0.9539)	9 (60.0, 33.5 - 79.8)
PlGF concentration	0.8659 (0.7867 - 0.9452)	11 (57.9, 33.5 - 79.8)		0.8383 (0.7234 - 0.9531)	9 (60.0, 33.5 - 79.8)
sFLT / PlGF ratio	0.8987 (0.8312 - 0.9662)	15 (78.9, 54.4 - 93.9)		0.8624 (0.7589 - 0.9659)	10 (66.7, 28.9 - 75.6)

At 35-37 weeks' gestation the best performance of screening for subsequent development of PE is provided by a combination of maternal factors, MAP, PlGF and sFLT

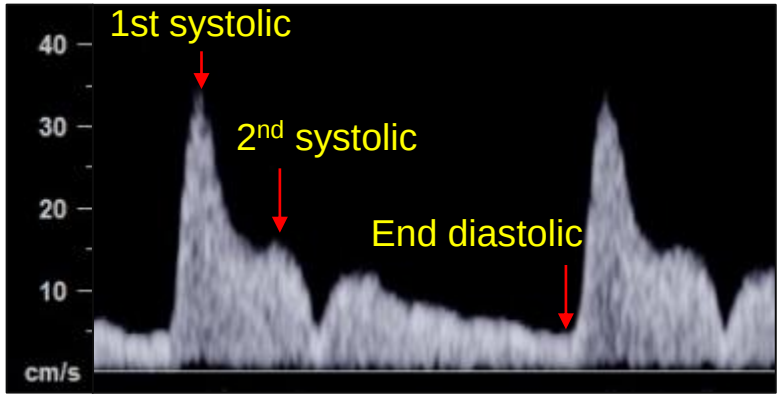

Figure 1

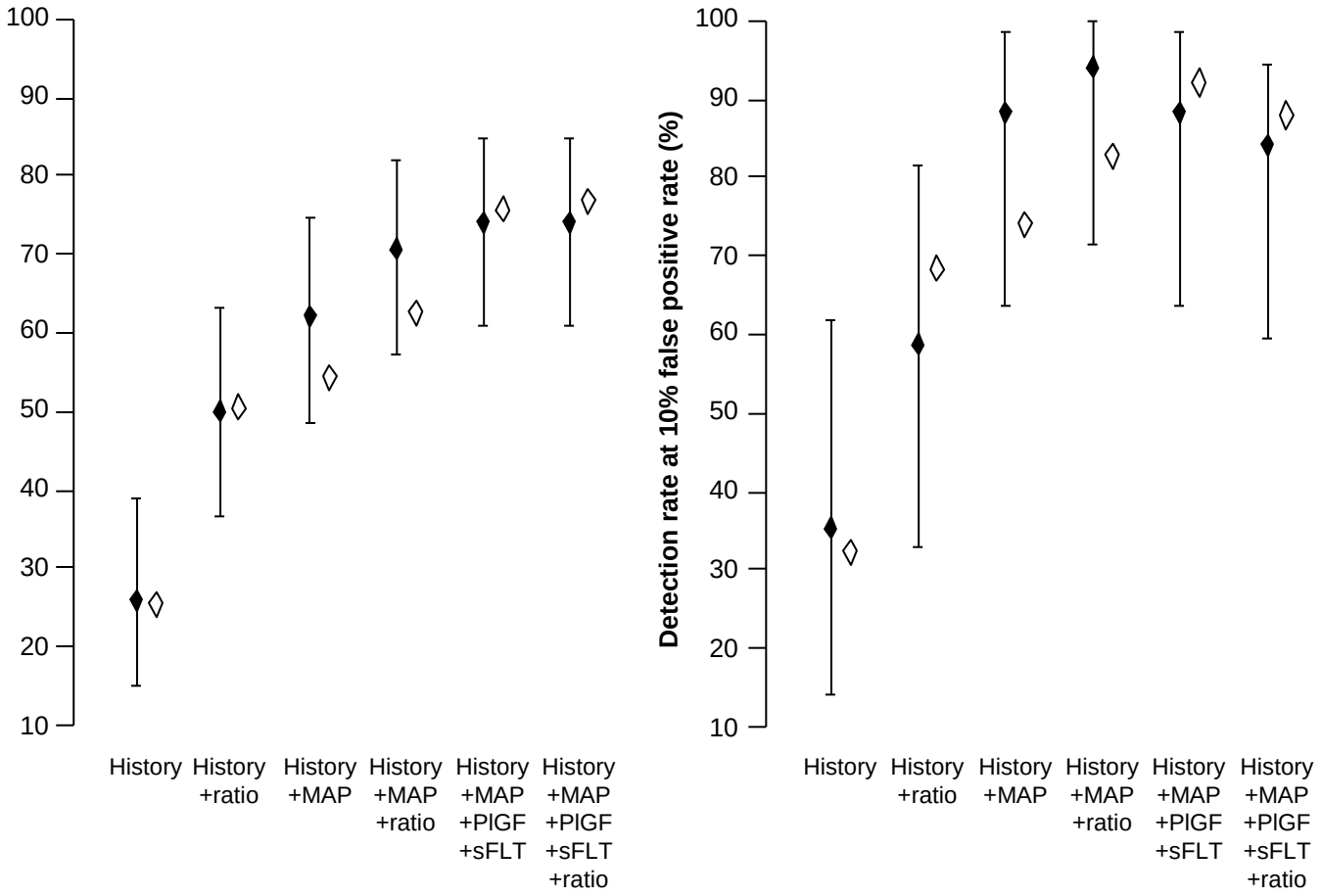

Figure 2