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

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Contribution

What are the novel findings of this work?

Ophthalmic artery Doppler at 35-37 weeks' gestation can predict subsequent development of preeclampsia, especially if this occurs within three weeks from assessment. The most useful Doppler index of the ophthalmic artery is the ratio of the second to the first systolic peak velocity. In the assessment of ophthalmic artery Doppler it is necessary to use the average of one measurement from each eye to minimize variability of measurements.

What are the clinical implications of this work?

Ophthalmic artery Doppler may be useful in the prediction of preeclampsia, but further studies are needed to determine the potential additive value to that of other established biophysical and biochemical markers.

ABSTRACT

Objectives: First, to examine the potential value of maternal ophthalmic artery Doppler at 35-37 weeks' gestation in the prediction of subsequent development of preeclampsia (PE), and second, to examine the variability between repeat measurements in the same eye and variability in measurements between the two eyes.

Methods: This was a prospective observational study in women attending for a routine hospital visit at 35^{+0} - 36^{+6} weeks' gestation. The visit included recording of maternal demographic characteristics and medical history and assessment of flow velocity waveforms from the maternal ophthalmic artery. 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 systolic peak velocity (SPV), second SPV, pulsatility index, and ratio of second to first SPV. 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 determine the detection rate (DR) of delivery with PE at any time and at <3 weeks from assessment, at 10% false positive rate (FPR), in screening by maternal factors alone and a combination of maternal factors and the adjusted value of each of the four ophthalmic artery indices.

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 DR, at 10% FPR, of delivery with PE at any time from assessment by maternal factors was 25.0% (95% CI 14.7-37.9) and this increased by 25% (p=0.005) to 50.0% (95% CI 36.8-63.2) with the addition of the adjusted second to first SPV ratio; the respective values for delivery with PE at <3 weeks from assessment were 31.6% (95% CI 12.6-56.6) and 57.9% (95% CI 33.5-79.8). The other ophthalmic artery indices did not improve the prediction provided by maternal factors alone. There was good correlation between the first and second measurements of the ratio from the same eye (right r=0.823, left r

=0.840), but poorer correlation in the first and second measurements between the two eyes (first ratio r=0.690, second ratio r=0.682). In screening by maternal factors and second to first SPV ratio for PE with delivery at any stage after assessment the estimated DR, at 10% FPR, was 50.0% when the average of four measurements was used (two from each eye), 49.1% when the average of one measurement from two separate eyes was used, 47.3% when the average of two measurements from the same eye was used, and 45.8% when one measurement from the same eye was used.

Conclusion: Ophthalmic artery second to first SPV ratio at 35-37 weeks' gestation can predict subsequent delivery with PE, especially if this occurs within three weeks from assessment. In the assessment of ophthalmic artery Doppler it is necessary to use the average of one measurement from each eye to minimize variability of measurements.

INTRODUCTION

The ophthalmic artery, which is the first branch of the internal carotid artery and has embryological, 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; cross sectional studies have reported 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.[1-12] There is also some evidence that development of PE is preceded by decrease in impedance to flow in the cerebral circulation.[13,14] 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.[15-17]

The objectives of this prospective observational study in a population undergoing routine screening at 35-37 weeks' gestation are first, to examine the potential value of maternal ophthalmic artery Doppler in the prediction of subsequent development of PE, and second to examine the variability between repeat measurements in the same eye and variability in measurements between the two eyes.

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, and assessment of flow velocity waveforms from the maternal ophthalmic arteries. 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. 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.[18,19] 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).[20] 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.[12]

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 systolic peak velocity (SPV), second SPV, pulsatility index, and ratio of second to first SPV. The first SPV and PI were obtained automatically by the machine, the second SPV was measured manually and the ratio of second to first SPV was calculated.

Outcome measures

Outcome measures were delivery with PE or gestational hypertension GH at any time and at <3 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.[21]

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 SPV, second SPV, pulsatility index and second to first SPV ratio) were investigated using histograms and by plotting marker measurements against gestational age and maternal weight in PE, GH 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 or GH, terms for PE and the gestational age at delivery with PE and GH were included in the models. Backwards elimination was used for variable selection. The partial residuals, after excluding the contribution of PE or GH, 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 PE and gestational age at delivery with PE effects from these models, alongside the standard deviation of the Delta or $\log_{10}$ MoM, allowed for individual inclusion of each of the four ophthalmic artery indices in the competing risks model.[22] The prior distribution of gestational age at delivery with PE, based upon maternal characteristics and medical history was combined with each individual ophthalmic artery marker (MoM or Delta) via Bayes theorem to produce risks of delivery with PE at any time and within 3 weeks of assessment. Performance of screening of the four markers was assessed in terms of detection rates (DR) at pre-specified false positive rate (FPR) of 10%.

In this study we used an average of four measurements, two from each eye, to quantify first SVP, second SVP, PI and the ratio of second to first SPV. We found that the ratio was

useful in the prediction of PE (see Results). To investigate the potential impact on screening of taking fewer repeated measurements of the ratio, we fitted a mixed effects model to all ratios available, with fixed effects for maternal characteristics and medical history and random effects for woman, eye (left or right) and repetition (1 or 2). From these models, we took various linear combinations of the variance components for woman, eye and repetition, to estimate the residual standard error for the average ratio Delta for the following scenarios: one measurement in each eye, two measurements in the same eye and one measurement only. Using these estimates, impact on screening of taking an average of fewer measurements was assessed via modelling. The process of modelling was as follows: first, we bootstrapped maternal characteristics and medical history, along with outcome, from our original data set of 2,287 records to produce a data set with 100,000 records; second, we simulated Delta values from Gaussian distributions according to the previously fitted multivariate linear regression models; third, we scaled the Deltas according to the various residual standard errors calculated from the mixed effects models; finally, we assessed the performance of screening in this modelled data set.

The statistical software package R was used for data analyses.[23]

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. The population also contained 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.

Factors affecting ophthalmic artery indices

Multivariate linear regression models were fitted to $\log_{10}$ first SPV, $\log_{10}$ second SPV, $\log_{10}$ pulsatility index and untransformed second to first SPV 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 SPV ratio was significantly increased in both PE and GH 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 1.81and at 40 weeks it was 0.87 (Figure 2). The first SPV was significantly raised in GH pregnancies with standardised effect size of 0.37; there was no evidence of an effect of gestational age at delivery with GH on SPV levels, or evidence of an effect from PE (Supplementary Figure 1). The second SPV was significantly raised in both PE and GH pregnancies with respective standardised effects of 0.74 and 0.64; there was no evidence of an effect of gestational age at delivery with either PE or GH on SPV (Supplementary Figure 2). The pulsatility index was significantly reduced in both PE and GH pregnancies with respective standardised effects of -0.73 and

-0.52; there was no evidence of an effect of gestational age at delivery with either PE or GH on pulsatility index (Supplementary Figure 3).

Performance of screening

The DR, with 95% confidence interval, of delivery with PE or GH at any time and within three weeks from assessment by maternal factors and ophthalmic artery Doppler indices, at 10% FPR is shown in Table 3. The DR of delivery with PE at any time from assessment by maternal factors was 25.0% (95% CI 14.7-37.9) and this increased by 25% (p=0.005) to 50.0% (95% CI 36.8-63.2) with the addition of the adjusted second to first SPV ratio; the respective values for delivery with PE at <3 weeks from assessment were 31.6% (95% CI 12.6-56.6) and 57.9% (95% CI 33.5-79.8). The other ophthalmic artery indices did not improve the prediction provided by maternal factors alone.

Effect of the type and number of measurements on performance of screening.

Figure 3 shows plots of the first vs the second measurements of the ratio from the same eye and plots of measurement in the left vs right eye for the first and second repetitions. Repeated measurements from the same eye were highly correlated, r=0.823 and 0.840 for the right and left eyes, respectively. Measurements between eyes were less correlated, r=0.690 and 0.683 for the first and second measurements, respectively.

On fitting a mixed effects model to all available second to first SPV ratios, the variance components for woman, eye and repetition were used to estimate the residual standard errors for scenarios where: one measurement from each eye is averaged, two measurements from the same eye are averaged and only one measurement taken. Further details on this can be found in Appendix 1. Screening performance of maternal factors plus second to first SPV ratio, measured according to the above scenarios was assessed in a modelled data set of 100,000 pregnancies. For a 10% FPR, the DR was 50.0% when the average of four measurements was used (two from each eye), 49.1%

when the average of one measurement from each eye was used, 47.3% when the average of two measurements from the same eye was used, and 45.8% when only one measurement was used.

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 provides a potentially useful biomarker of subsequent development of PE and GH. We found that before the development of PE and GH the ophthalmic artery pulsatility index, a marker of impedance to flow, is reduced and the second SPV, a marker of perfusion, was increased. From the different indices that we investigated we found that the second to first SPV ratio was the most useful one for prediction of PE and that for this ratio good results could be achieved if the average of one measurement from two separate eyes is used, rather than one measurement from the same eye.

Comparison with previous studies

Three previous studies examined the potential value of ophthalmic artery Doppler in screening for PE.[15-17] In the first study ophthalmic artery Doppler assessment was performed at 11-14 weeks' gestation in 440 singleton pregnancies, including 31 (7%) that subsequently developed PE and 9 (2%) with early PE before 34 weeks' gestation.[15] Only the right ophthalmic artery was examined and the same indices as in the current study were recorded. The authors reported that in the pregnancies that developed PE, compared to unaffected pregnancies, the second SPV was increased; all other indices were not significantly different. Screening by maternal factors identified 45% of all PE and 63% of early PE, at 10% FPR; addition of ophthalmic artery second SPV improved the DR to 48% and 67%, respectively.

The second study examined at 20-28 weeks' gestation 347 high-risk pregnancies, including 40 (11.5%) that developed PE.[16] Only the right ophthalmic artery was examined and the same indices as in the current study were recorded. The authors reported that in

the pregnancies that developed PE, compared to unaffected pregnancies, the first SPV, second SPV and second to first SPV ratio were increased. The greatest difference between the groups was observed for the second SPV and in screening by this marker the DR for PE was 70% at FPR of 25%. The third study examined at 18-23 weeks' gestation 372 pregnancies, including 40 (10.8%) that developed PE.[17] Only the right ophthalmic artery was examined and the same indices as in the current study were recorded. The authors reported that in the pregnancies that developed PE, compared to unaffected pregnancies, there was no significant difference in second SPV, second to first SPV ratio or pulsatility index.

Implications for clinical practice and research

More than 70% of cases of PE occur at term and the predictive performance of screening for term-PE by a combination of maternal characteristics and medical history with mean arterial pressure, uterine artery pulsatility index and serum placental growth factor is typically poor. When screening at 12 and at 20 weeks' gestation with this combination of markers, 40-50% of term PE is detected at a FPR of 10%. When screening at 32 weeks about 60% of term PE is detected and at 36 weeks about 70% of term PE is detected.[24-27] This study has established that ophthalmic artery Doppler at 35-37 weeks' gestation may be useful in the prediction of PE, but further studies are needed to determine the potential additive value to that of other biophysical and biochemical markers. Effective identification of a high risk group at 35-37 weeks' gestation may be beneficial because interventions such as early delivery could prevent the development of PE and potentially reduce maternal and perinatal death and morbidity.

Strengths and limitations

The strengths of this 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,[27-37] second, recording of data on maternal characteristics and medical history to define the *prior* risk for PE, third, use of a standardized technique for Doppler assessment of the ophthalmic artery, examination of four potentially useful indices, and obtaining two recordings from each eye to allow assessment of the variability in measurements, 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.

The number of cases of PE was too small for accurate assessment of the effect of the type and number of measurements on performance of screening; for example, when we defined the protocol for measurement of the mean arterial pressure we relied on data from 587 pregnancies that developed PE and 22,900 that were unaffected by hypertensive disorders.[38] Consequently, we used modeling, rather than empirical data, to define the best protocol for assessment of the ophthalmic artery and concluded that the minimum of one measurement should be obtained from each eye and the average of the two used in risk calculation.

Conclusions

Ophthalmic artery second to first SPV ratio at 35-37 weeks' gestation can predict subsequent delivery with PE, especially if this occurs within three weeks from assessment. In the assessment of ophthalmic artery Doppler it is necessary to use the average of one measurement from each eye to minimize variability of measurements.

Conflict of interest: None

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FIGURE LEGEND

Figure 1. Ultrasound image of left and right orbit color flow demonstration of left and right 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 and gestational age at delivery with preeclampsia (left) and gestational hypertension (right). The y-axis on the right of the plots show a standard deviation scale. The open circles illustrate the cases with hypertensive disorders and interrupted lines the relationship between the ratio delta and gestational age at delivery. The horizontal lines are the median value for unaffected pregnancies.

Figure 3. Relationships between the first and second measurements of the ratio of the second to first systolic peak velocity taken from the same and different eyes.

Supplementary Figure 1. Relationship between the ratio of the first systolic peak velocity multiple of the median and gestational age at delivery with preeclampsia (left) and gestational hypertension (right). The y-axis on the right of the plots show a standard deviation scale. The open circles illustrate the cases with hypertensive disorders and interrupted lines the relationship between the ratio delta and gestational age at delivery. The horizontal lines are the median value for unaffected pregnancies.

Supplementary Figure 2. Relationship between the ratio of the second systolic peak velocity multiple of the median and gestational age at delivery with preeclampsia (left) and gestational hypertension (right). The y-axis on the right of the plots show a standard deviation scale. The open circles illustrate the cases with hypertensive disorders and interrupted lines the relationship between the ratio delta and gestational age at delivery. The horizontal lines are the median value for unaffected pregnancies.

Supplementary Figure 3. Relationship between the ratio of the pulsatility index multiple of the median and gestational age at delivery with preeclampsia (left) and gestational hypertension (right). The y-axis on the right of the plots show a standard deviation scale. The open circles illustrate the cases with hypertensive disorders and interrupted lines the relationship between the ratio delta and gestational age at delivery. The horizontal lines are the median value for unaffected pregnancies.

Appendix 1 Mixed effects variance components

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)	0.74
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 Students t-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	15.2676 (4.4228, 26.1123)	0.006
Gestational hypertension	0.0361 (0.0114, 0.0608)	0.004
GA in days - 77	-0.1549 (-0.2795, -0.0304)	0.015
(GA in days - 77)^2	0.0004 (0.00008, 0.0008)	0.017
Weight in Kg - 69	0.0007 (0.0004, 0.0010)	<0.0001
Age in years - 35	-0.0018 (-0.0027, -0.0010)	<0.0001
Black racial origin	-0.0276 (-0.0402, -0.0151)	0.00002
South Asian racial origin	-0.0211 (-0.0389, -0.0032)	0.021
Mixed racial origin	-0.0264 (-0.0483, -0.0046)	0.018
Parous previous preeclampsia	-0.0302 (-0.0586, -0.0017)	0.038
Second systolic peak velocity		
Intercept	1.3416 (1.3338, 1.3494)	<0.0001
Preeclampsia	0.1006 (0.0656, 0.11356)	<0.0001
Gestational hypertension	0.0872 (0.0532, 0.1213)	<0.0001
Weight in Kg - 69	0.0007 (0.0002, 0.0011)	0.002
Age in years - 35	0.0014 (0.0003, 0.0025)	0.015
Height in cm - 164	-0.0018 (-0.0027, -0.0009)	0.0001
Black racial origin	-0.0600 (-0.0773, -0.0427)	<0.0001
East Asian racial origin	-0.0532 (-0.0848, -0.0216)	0.001
Mixed racial origin	-0.0441 (-0.0743, -0.0139)	0.004
Pulsatility index		
Intercept	0.1909 (0.1857, 0.1961)	<0.0001
Preeclampsia	-0.0683 (-0.0924, -0.04429)	<0.0001
Gestational hypertension	-0.0491 (-0.0724, -0.0257)	<0.0001
Weight in Kg - 69	-0.0005 (-0.0008, -0.0002)	0.0006
Height in cm - 164	0.0015 (0.0009, 0.0021)	<0.0001
Black racial origin	0.0365 (0.0247, 0.0484)	<0.0001
East Asian racial origin	0.0442 (0.0226, 0.0659)	<0.0001
Ratio of second to first systolic peak velocity		
Intercept	0.3351 (0.0699, 0.6003)	0.013
Preeclampsia	1.091 (0.3270, 1.8555)	0.005

Gestational age at delivery with preeclampsia	-0.0250 (-0.0444, -0.0055)	0.012
Gestational hypertension	0.0752 (0.0486, 0.1018)	<0.0001
GA in days - 77	0.0018 (0.0002, 0.0033)	0.024
Age in years - 35	0.0051 (0.0042, 0.0060)	<0.0001
Height in cm - 164	-0.0027 (-0.0033, -0.0020)	<0.0001
Black racial origin	-0.0396 (-0.0532, -0.0261)	<0.0001
East Asian racial origin	-0.0497 (-0.0742, -0.0251)	0.00007
Mixed racial origin	-0.0283 (-0.0519, -0.0047)	0.019
Chronic hypertension	0.0447 (0.0088, 0.0805)	0.015
Parous no previous preeclampsia	-0.0172 (-0.0264, -0.0080)	0.0003

Table 3: Detection rates, with 95% confidence intervals, for delivery with preeclampsia or gestational hypertension at any time and within three weeks from assessment by maternal factors and ophthalmic artery Doppler indices, at a 10% false positive rate.

Method of screening	Preeclampsia	Gestational hypertension
	n/N (DR, 95% CI)	n/N (DR, 95% CI)
At any stage		
Maternal factors	15/60 (25.0, 14.7 to 37.9)	20/64 (31.3, 14.7 to 37.9)
+ Second to first systolic peak velocity ratio	30/60 (50.0, 36.8 to 63.2)	23/64 (35.9, 36.8 to 63.2)
+ Second systolic peak velocity	15/60 (25.0, 14.7 to 37.9)	20/64 (31.3, 14.7 to 37.9)
+ Pulsatility index	15/60 (25.0, 14.7 to 37.9)	20/64 (31.3, 14.7 to 37.9)
At <3 weeks		
Maternal factors	6/19 (31.6, 12.6 to 56.6)	5/15 (33.3, 12.6 to 56.6)
+ Second to first systolic peak velocity ratio	11/19 (57.9, 33.5 to 79.8)	9/15 (60.0, 33.5 to 79.8)
+ Second systolic peak velocity	6/19 (31.6, 12.6 to 56.6)	5/15 (33.3, 12.6 to 56.6)
+ Pulsatility index	6/19 (31.6, 12.6 to 56.6)	5/15 (33.3, 12.6 to 56.6)

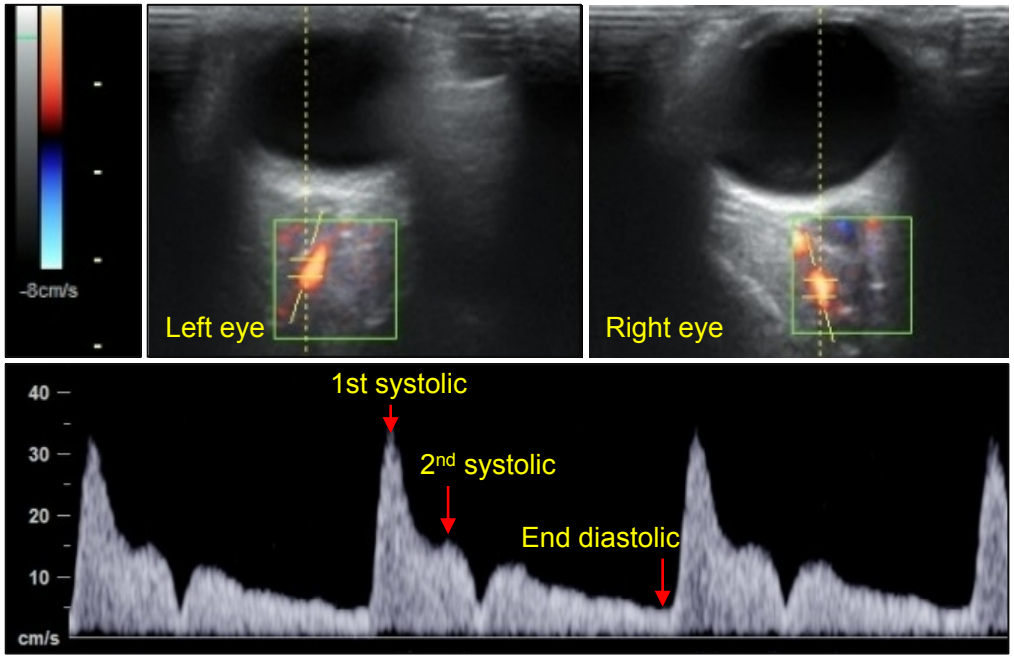

Figure 1

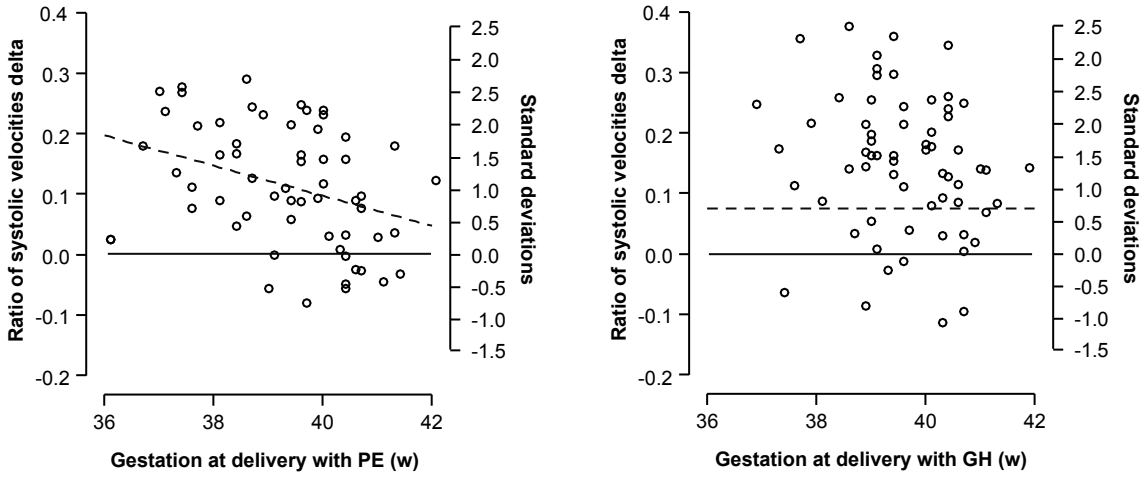

Figure 2

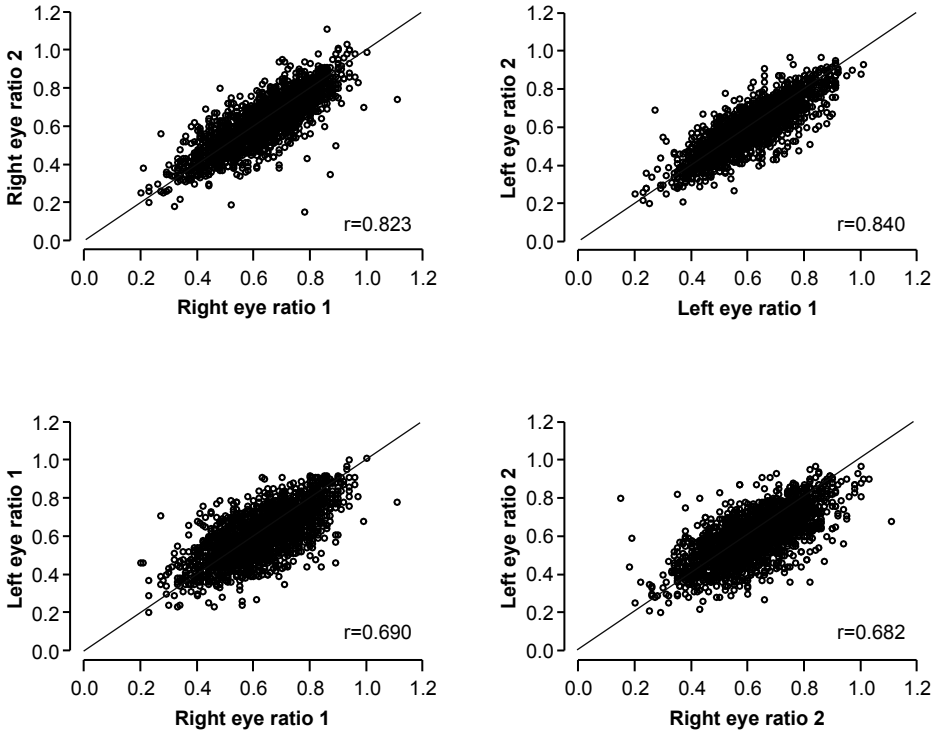

Figure 3