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Comparison of ophthalmic artery Doppler with PlGF and sFlt-1/PlGF ratio at 35–37 weeks' gestation in prediction of imminent pre-eclampsia

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KEYWORDS: Doppler; ophthalmic artery; placental growth factor; PlGF; pre-eclampsia; soluble fms-like tyrosine kinase-1

CONTRIBUTION

What are the novel findings of this work?
At 35–37 weeks' gestation, prediction of imminent pre-eclampsia with delivery at < 3 weeks from assessment provided by combined testing with maternal risk factors, mean arterial pressure and ophthalmic artery Doppler may be superior to screening by serum placental growth factor (PlGF) or the soluble fms-like tyrosine kinase-1 (sFlt-1)/PlGF ratio.

What are the clinical implications of this work?
Ophthalmic artery Doppler in combination with recording maternal risk factors and measuring blood pressure could potentially replace measurement of PlGF or the sFlt-1/PlGF ratio in the prediction of imminent pre-eclampsia.

ABSTRACT

Objective *To compare the predictive performance for delivery with pre-eclampsia (PE) at < 3 weeks and at any stage after assessment at 35 + 0 to 36 + 6 weeks' gestation of serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1)/PlGF ratio with that of a competing-risks model utilizing maternal risk factors, mean arterial pressure (MAP) and ophthalmic artery peak systolic velocity (PSV) ratio.*

Methods *This was a prospective observational study of women attending for a routine hospital visit at 35 + 0 to 36 + 6 weeks' gestation. This visit included recording of maternal demographic characteristics and medical history, ultrasound examination of fetal anatomy and growth, assessment of flow velocity waveforms from the maternal ophthalmic arteries and measurement of MAP, serum PlGF and serum sFlt-1. The performance of screening for delivery with PE at < 3 weeks and at any time after the examination was assessed using areas under the receiver-operating-characteristics curves and detection rates (DRs), at a 10% false-positive rate (FPR). McNemar's test was used to compare DRs, at a 10% FPR, between screening by PlGF concentration, the sFlt-1/PlGF concentration ratio and the competing-risks model utilizing maternal risk factors, MAP and ophthalmic artery PSV ratio. Model-based estimates of screening performance for different methods of screening were also produced.*

Results *The study population of 2338 pregnancies contained 75 (3.2%) cases that developed PE, including 30 (1.3%) that delivered with PE at < 3 weeks from assessment, and 2263 cases unaffected by PE. The DR of PE at < 3 weeks from assessment, at a 10% FPR, of sFlt-1/PlGF ratio (70.0% (95% CI, 50.6–85.3%)) was superior to that of PlGF (50.0% (95% CI, 31.3–68.7%)) or PSV ratio (56.7% (95% CI, 37.4–74.5%)) but inferior to that of the combination of maternal risk factors, MAP multiples of the median (MoM) and PSV ratio delta (96.7% (95% CI, 82.8–99.9%)). Similarly, the DR of PE at any stage after assessment of sFlt-1/PlGF ratio (62.7% (95% CI, 50.7–73.6%)) was superior to that of PlGF (52.0% (95% CI, 40.2–63.7%)) or PSV ratio (41.3% (95% CI, 30.1–53.3%)) but inferior to that of the combination of maternal risk factors, MAP MoM and PSV ratio delta (78.7% (95% CI, 67.7–87.3%)). The empirical results for DR at a 10% FPR were consistent with the modeled results, both for delivery with PE at < 3 weeks and at any time after assessment.*

Conclusion *Ophthalmic artery Doppler in combination with maternal risk factors and blood pressure could*

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potentially replace measurement of PlGF and sFlt-1/PlGF ratio in the prediction of imminent PE. © 2022 International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

Development of pre-eclampsia (PE) is preceded by a decrease in the concentration of maternal serum angiogenic placental growth factor (PlGF) and an increase in the level of antiangiogenic soluble fms-like tyrosine kinase-1 (sFlt-1)[1–9]. In women presenting to specialist clinics with signs or symptoms of hypertensive disorders, cut-off values for PlGF concentration or the ratio of sFlt-1 to PlGF concentrations have been used to predict the development of PE within the subsequent 1–4 weeks[3,4,6,7]. This approach has the advantage of simplicity in terms of clinical implementation. However, it does not take into account the prior risk of an individual patient in the study population or patient's blood pressure at presentation, which is a prerequisite in the diagnosis of PE, and ignores the effects of maternal characteristics and gestational age on the measured serum marker concentrations. An alternative approach for the prediction of PE at predefined intervals from assessment is the use of a competing-risks model to derive patient-specific risks for PE by various combinations of maternal risk factors with multiples of the median (MoM) values of biomarkers, including PlGF, sFlt-1 and mean arterial pressure (MAP)[5,8–13]. In a large prospective observational study, we found that the performance of this approach is superior to that of PlGF or sFlt-1/PlGF ratio alone[9].

Large prospective observational screening studies at mid-gestation and at 35–37 weeks' gestation reported that development of PE is preceded by alterations in the Doppler velocity waveforms of the ophthalmic arteries[14–16]. The waveform from these vessels is characterized by the presence of two systolic peaks. The first systolic wave (PSV1) is created by cardiac systole, with the opening of the aortic valve and ejection of blood into the aorta, whilst the second systolic wave (PSV2) is a reflective wave formed by the systolic pulse wave reaching smaller, higher-resistance arterioles and being reflected back towards the heart. At the level of the aortic arch, a fraction is diverted cranially to the cerebral circulation as a forward wave to create PSV2[17,18]. In this way, PSV2 is most influenced by peripheral arterial compliance and resistance, whilst PSV1 is more affected by cardiac output. In pregnancies that develop PE, the ratio of second to first peak systolic velocity (PSV ratio) is increased, and the increase is related inversely to gestational age at delivery with PE[14–16].

The objective of this study in women with singleton pregnancy undergoing routine screening at 35 + 0 to 36 + 6 weeks' gestation was to compare the predictive performance for delivery with PE at < 3 weeks and at any stage after assessment of PlGF[4] and sFlt-1/PlGF ratio[3,6] with that of a competing-risks model utilizing maternal risk factors, MAP and ophthalmic artery PSV ratio.

METHODS

Study design and participants

This was a prospective observational study of women at 35 + 0 to 36 + 6 weeks' gestation at King's College Hospital, London, UK. The study included two populations: first, 2287 women attending for a routine hospital visit between June 2019 and March 2020[16] and, second, 51 women attending the Antenatal Hypertension Clinic between September 2020 and September 2021 because of pre-existing or newly identified hypertension during routine antenatal care.

The visit included recording of maternal demographic characteristics and medical history, ultrasound examination of fetal anatomy and growth, assessment of flow velocity waveforms from the maternal ophthalmic arteries twice from each eye and recording the average of the four measurements[15], measurement of MAP by validated automated devices twice from each arm and recording the average of the four measurements[19] and measurement of serum concentration of PlGF and sFlt-1 in pg/mL using 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 fetal head circumference at 19–24 weeks[20,21]. The findings from ophthalmic artery Doppler and PlGF and sFlt-1 measurements were not made available to the clinicians managing the patients. The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

The inclusion criteria for this study were singleton pregnancy examined at 35 + 0 to 36 + 6 weeks' gestation and delivery of a non-malformed liveborn fetus. We excluded pregnancies with aneuploidy and major fetal abnormality and those with PE at the time of screening.

Outcome measures

Outcome measure was delivery with PE at < 3 weeks and at any time after assessment. Diagnosis of PE was based on the finding of new-onset hypertension (systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg on at least two occasions 4 h apart developing after 20 weeks' gestation in previously normotensive women) or chronic hypertension and at least one of the following: proteinuria (≥ 300 mg/24 h or protein-to-creatinine ratio ≥ 30 mg/mmol or ≥ 2 + on dipstick testing), renal insufficiency with serum creatinine > 97 μmol/L in the absence of underlying renal disease, hepatic dysfunction with blood concentration of transaminases more than twice the upper limit of normal (≥ 65 IU/L for our laboratory), thrombocytopenia (platelet count < 100 000/μL), neurological complications (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 chi-square test or Fisher's exact test were used for comparing continuous and categorical data, respectively, between outcome groups.

The performance of screening for delivery with PE at < 3 weeks and at any time after examination was assessed using areas under the receiver-operating-characteristics (ROC)-curve (AUC) analysis and detections rates (DR) of delivery with PE, at a 10% false-positive rate (FPR). McNemar's test was used to compare DRs, at a 10% FPR, between screening using PlGF or sFlt-1/PlGF ratio and screening by the combination of maternal risk factors, MAP and ophthalmic artery PSV ratio. Combined testing was based on the competing-risks model; the prior distribution of gestational age at delivery with PE was derived from maternal demographic characteristics and medical history, and the posterior distribution was obtained using Bayes' theorem by multiplying the prior probability density by the likelihood function from MAP MoM and the PSV ratio difference from the median (delta)[10]. The measured values of biomarkers were converted to MoMs or deltas to remove the effects of characteristics such as gestational age, weight, race, method of conception, comorbidities and individual obstetric history[15].

Model-based estimates of screening performance for the different methods of screening were also produced. A dataset containing 10 000 unaffected pregnancies and 10 000 PE pregnancies was obtained by bootstrapping maternal characteristics, medical and obstetric history and outcome from our original dataset of 2338 records. MoM values for MAP, PSV1 and PSV2, delta values for ophthalmic artery PSV ratio and concentrations for PlGF and sFlt-1 were simulated from a multivariate Gaussian distribution[15,23]. DRs at 10% FPR were calculated and compared with empirical results. The statistical software package R was used for data analysis[24].

RESULTS

Study participants

The study population of 2338 pregnancies contained 75 (3.2%) cases that developed PE, including 30 (1.3%) that delivered with PE at < 3 weeks after assessment, and 2263 cases unaffected by PE. Maternal and pregnancy characteristics of the study population are summarized in Table 1. In the PE group, compared with unaffected pregnancies, there was a higher median maternal weight, body mass index and incidence of family history of PE and nulliparity, and a shorter interpregnancy interval.

Table 1 Maternal and pregnancy characteristics of study population of 2338 pregnancies, according to development of pre-eclampsia (PE)

Characteristic	*No PE* (n = *2263)*	*PE* (n = *75)*	P*
Age (years)	33.7 (30.6–36.9)	34.0 (29.2–37.6)	0.931
Weight (kg)	78.0 (70.3–87.5)	85.0 (75.2–94.0)	0.002
Height (cm)	166 (162–171)	166 (162–171)	0.656
Body mass index (kg/m^2)	28.1 (25.6–31.3)	30.4 (27.0–34.0)	0.003
Gestational age (weeks)	35.7 (35.6–36.0)	35.7 (35.4–36.1)	0.722
Racial origin			0.114
White	1694 (74.9)	52 (69.3)	
Black	285 (12.6)	17 (22.7)	
South Asian	125 (5.5)	3 (4.0)	
East Asian	79 (3.5)	1 (1.3)	
Mixed	80 (3.5)	2 (2.7)	
Medical history			
Chronic hypertension	32 (1.4)	2 (2.7)	0.688
Type-I diabetes mellitus	5 (0.2)	1 (1.3)	0.117
Type-II diabetes mellitus	24 (1.1)	0 (0)	0.117
SLE/APS	8 (0.4)	0 (0)	1
Smoker	9 (0.4)	1 (1.3)	0.747
Family history of PE	109 (4.8)	23 (30.7)	< 0.0001
Method of conception			0.095
Spontaneous	2138 (94.5)	67 (89.3)	
In-vitro fertilization	116 (5.1)	8 (10.7)	
Ovulation drugs	9 (0.4)	0 (0)	
Parity			< 0.0001
Nulliparous	1192 (52.7)	61 (81.3)	
Parous, no previous PE	1023 (45.2)	11 (14.7)	
Parous, previous PE	48 (2.1)	3 (4.0)	
Interpregnancy interval (years)	3.9 (3.1–4.7)	3.0 (2.4–3.6)	0.047

Data are given as median (interquartile range) or *n* (%). *Chi-square or Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

Performance of screening

The distribution of ophthalmic artery PSV ratio, PlGF and sFlt-1/PlGF ratio in cases that delivered with PE is shown in Figure 1. The median values for PSV ratio, PlGF and sFlt-1/PlGF ratio for unaffected pregnancies were 0.61, 306 pg/mL and 6.62, respectively; the 90th percentile for the PSV ratio was 0.76, the 10th percentile for PlGF was 101 pg/mL and the 90th percentile for sFlt-1/PlGF ratio was 39.5.

In cases that delivered with PE, compared with unaffected cases, there was a small but significant increase in PSV1 MoM, which was not associated with gestational age at delivery with PE, and a greater increase in PSV2 MoM, which was associated inversely with gestational age at delivery with PE (Figure 2). The strongest association was observed between PSV ratio delta and gestational age at delivery with PE (Figure 2).

The empirical AUC and DR, at a 10% FPR, and modeled DR, at a 10% FPR, of delivery with PE at

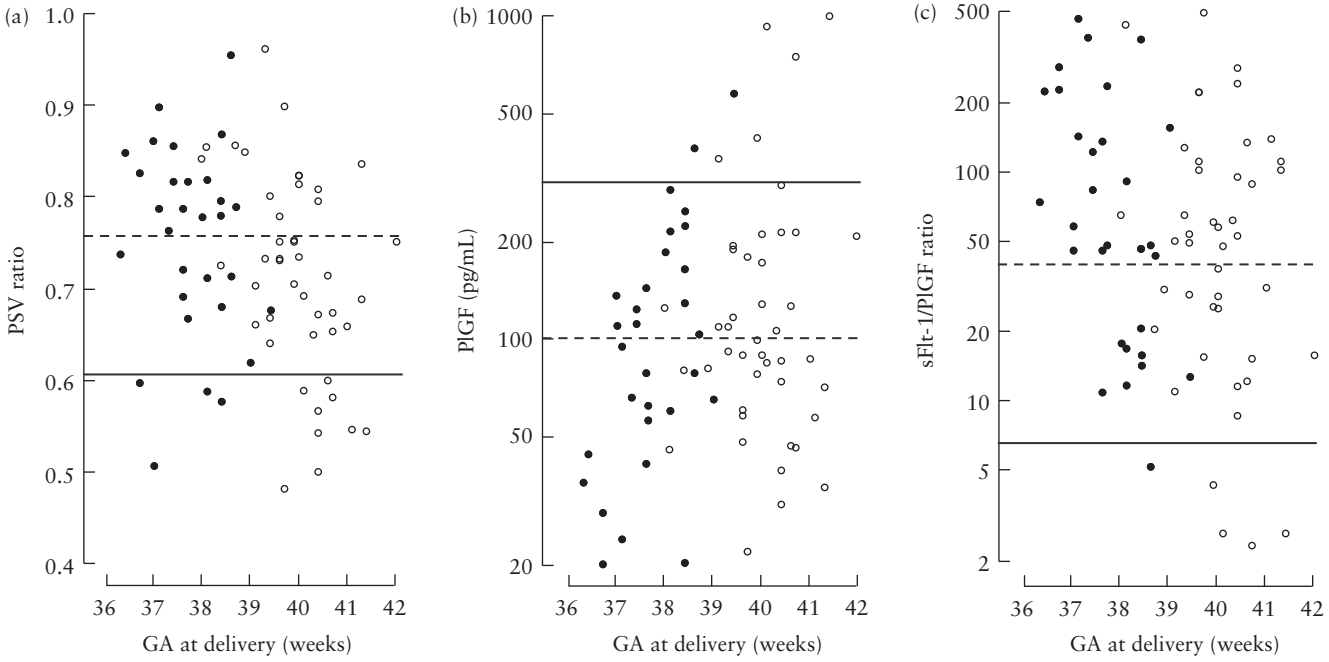

Figure 1 Distribution of ophthalmic artery peak systolic velocity (PSV) ratio (a), serum placental growth factor (PlGF) concentration (b) and soluble fms-like tyrosine kinase-1 (sFlt-1)/PlGF ratio (c) in women who delivered with pre-eclampsia at < 3 weeks (•) and at ≥ 3 weeks (○) after assessment. ——, Median for each parameter in unaffected pregnancies; – – –, 90th percentile for PSV ratio and sFlt-1/PlGF ratio and 10th percentile for PlGF. GA, gestational age.

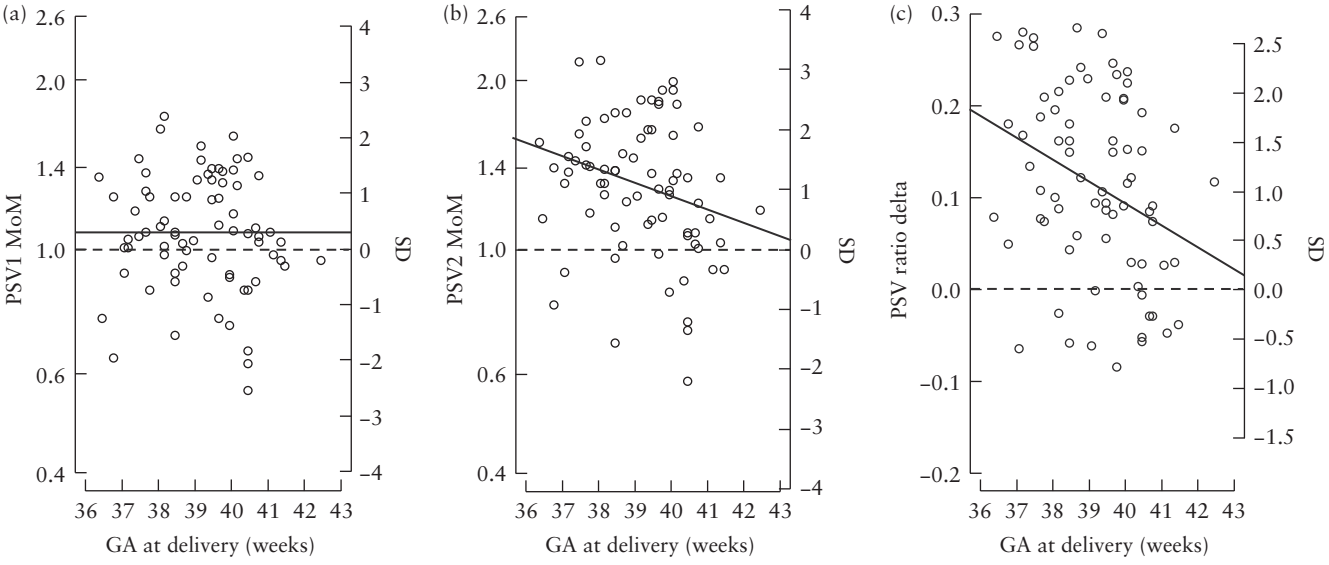

Figure 2 Distribution of ophthalmic artery first peak of systolic velocity (PSV1) multiples of the median (MoM) (a), second peak of systolic velocity (PSV2) MoM (b) and PSV ratio delta (c) in women who delivered with pre-eclampsia. ——, Regression lines indicating association between each parameter and gestational age (GA) at delivery; – – –, values for unaffected pregnancies.

Table 2 Empirical and modeled performance, at a 10% false-positive rate, of different methods of screening at 35–37 weeks for delivery with pre-eclampsia (PE) at < 3 weeks and at any time after assessment

	Empirical		
Method of screening	*AUC (95% CI)*	*DR (n (% (95% CI)))*	*Modeled DR (%)*
PE at < 3 weeks ($n = 30$)			
PSV1 MoM	0.5831 (0.4840–0.6821)	5 (16.7 (5.6–34.7))	16.2
PSV2 MoM	0.7610 (0.6833–0.8387)	9 (30.0 (14.7–49.4))	41.2
PSV ratio delta	0.8117 (0.7336–0.8898)	17 (56.7 (37.4–74.5))	56.4
PlGF	0.8197 (0.7468–0.8925)	15 (50.0 (31.3–68.7))	60.8
sFlt-1/PlGF ratio	0.8714 (0.8172–0.9256)	21 (70.0 (50.6–85.3))	79.3
MF + MAP MoM + PSV ratio delta	0.9573 (0.9428–0.9718)	29 (96.7 (82.8–99.9))	82.3
PE at any time ($n = 75$)			
PSV1 MoM	0.5927 (0.5252–0.6602)	16 (21.3 (12.7–32.3))	16.3
PSV2 MoM	0.7251 (0.6687–0.7816)	23 (30.7 (20.5–42.4))	32.2
PSV ratio delta	0.7657 (0.7102–0.8213)	31 (41.3 (30.1–53.3))	41.4
PlGF	0.8083 (0.7560–0.8606)	39 (52.0 (40.2–63.7))	53.4
sFlt-1/PlGF ratio	0.8458 (0.8004–0.8912)	47 (62.7 (50.7–73.6))	67.7
MF + MAP MoM + PSV ratio delta	0.9096 (0.8832–0.9360)	59 (78.7 (67.7–87.3))	66.5

AUC, area under the receiver-operating-characteristics curve; DR, detection rate; MAP, mean arterial pressure; MF, maternal risk factors; MoM, multiples of the median; PlGF, placental growth factor; PSV, ophthalmic artery peak systolic velocity; PSV1, first peak of systolic velocity; PSV2, second peak of systolic velocity; sFlt-1, soluble fms-like tyrosine kinase-1.

Table 3 Differences in detection rate (DR), at a 10% false-positive rate, between different methods of screening, for delivery with pre-eclampsia (PE) at < 3 weeks and at any time after assessment

Method of screening	*Comparison of DR (% vs %)*	*Difference in DR (% (95% CI))*	P*
PE at < 3 weeks			
PlGF *vs* MF + MAP MoM + PSV ratio delta	50.0 *vs* 96.7	46.7 (23.9–64.9)	0.001
sFlt-1/PlGF ratio *vs* MF + MAP MoM + PSV ratio delta	70.0 *vs* 96.7	26.7 (7.2–45.7)	0.027
PE at any time			
PlGF *vs* MF + MAP MoM + PSV ratio delta	52.0 *vs* 78.7	26.7 (13.3–39.6)	0.0005
sFlt-1/PlGF ratio *vs* MF + MAP MoM + PSV ratio delta	62.7 *vs* 78.7	16.0 (3.4–28.6)	0.025

*McNemar's test. MAP, mean arterial pressure; MF, maternal risk factors; MoM, multiples of the median; PlGF, placental growth factor; PSV, ophthalmic artery peak systolic velocity; sFlt-1, soluble fms-like tyrosine kinase-1.

< 3 weeks and at any time after assessment by ophthalmic artery PSV1 MoM, PSV2 MoM and PSV ratio delta, PlGF, sFlt-1/PlGF ratio and the combination of maternal risk factors, MAP MoM and PSV ratio delta are shown in Table 2. The screening performance of PSV ratio delta was superior to that of PSV1 MoM or PSV2 MoM. The screening performance of sFlt-1/PlGF ratio was superior to that of PlGF or PSV ratio delta but inferior to that of the combination of maternal risk factors, MAP MoM and PSV ratio delta. The empirical results on DR at a 10% FPR were consistent with the modeled results, both for delivery with PE at < 3 weeks and at any time after assessment (Table 2). Table 3 shows the differences in DRs of PE, at a 10% FPR, between screening by the combination of maternal risk factors, MAP MoM and PSV ratio delta and screening by PlGF or sFlt-1/PlGF ratio.

DISCUSSION

Principal findings of this study

This study in singleton pregnancies undergoing routine assessment at 35 + 0 to 36 + 6 weeks' gestation has demonstrated that maternal ophthalmic artery Doppler combined with MAP and maternal demographic characteristics and medical history using the competing-risks approach may be superior to serum PlGF and sFlt-1/PlGF ratio in the prediction of imminent PE with delivery at < 3 weeks of assessment. The study has also shown that the competing-risks approach is superior in the prediction of delivery with PE at any stage after assessment.

In women that developed PE, the ophthalmic artery PSV ratio was increased compared with unaffected cases, and the degree of the increase was associated inversely with gestational age at delivery with PE. We found that there was a small increase in PSV1 in PE compared with unaffected cases, possibly reflecting a small increase in cardiac output, and a considerably greater increase in PSV2, suggesting that the high PSV ratio is mainly due to increased peripheral vascular resistance[17,18].

Comparison with previous studies

Previous screening studies at 35 + 0 to 36 + 6 weeks' gestation have demonstrated that, first, useful biomarkers for prediction of PE in the late third trimester are

MAP, PlGF and sFlt-1[9,12,13,23,25], second, the predictive performance for imminent PE of a competing-risks model combining maternal factors with MAP MoM, PlGF and sFlt-1 is superior to that of PlGF or sFlt-1/PlGF ratio alone[9] and, third, maternal ophthalmic artery Doppler is a useful biomarker of subsequent delivery with PE, especially imminent PE with delivery at < 3 weeks after assessment, and PSV ratio provides additional value to screening by maternal factors, MAP and biochemical testing[16]. In the current study, we compared the predictive value of PlGF and the sFlt-1/PlGF ratio, which are the established markers for screening for imminent PE, with the predictive value of a competing-risks model incorporating maternal risk factors, MAP and ophthalmic artery PSV ratio.

Implications for clinical practice

Irrespective of whether assessment of risk for PE in the late third trimester is carried out in the general population or in women presenting with signs and/or symptoms of hypertensive disorders, the objective of identifying a high-risk group in need of intensive monitoring and/or delivery and a low-risk group that may not require hospitalization and intensive monitoring is the same. An important advantage of assessment of the ophthalmic artery compared with biochemical testing is that it can be incorporated easily into routine clinical practice, either during a routine late third-trimester scan or in a clinical service for women presenting with signs and/or symptoms of hypertensive disorders, without additional costs and with immediately available results.

Strengths and limitations

The main strengths of the study are, first, examination of a large population of pregnant women attending for routine care at a gestational age range that is being used increasingly for prediction of late PE, assessment of fetal growth and wellbeing, determination of fetal position and diagnosis of fetal abnormalities[9,26–35], 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[15], third, measurement of all potentially useful biomarkers of PE to allow comparison with the ophthalmic artery PSV ratio and, fourth, application of the competing-risks approach to estimate patient-specific risks and the prediction of delivery with PE at different stages after assessment.

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

Conclusion

Ophthalmic artery Doppler in combination with maternal risk factors and blood pressure could potentially replace PlGF and sFlt-1/PlGF ratio in the prediction of imminent PE.

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