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Prediction of adverse outcome by ophthalmic artery Doppler and angiogenic markers in pregnancies with new onset hypertension

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ABSTRACT

Objectives: To compare the ophthalmic artery Doppler peak systolic velocity ratio (OA PSV-ratio) and soluble fms-like tyrosine kinase-1/placental growth factor ratio (sFlt-1/PlGF ratio) in predicting adverse maternal and perinatal outcomes in women presenting with new onset hypertension.
Study design: Prospective cohort study in a specialist hypertension clinic, within a tertiary referral centre.
Main outcome measures: Comparison between the OA PSV-ratio and sFlt-1/PlGF ratio in predicting delivery within one week from presentation and adverse maternal and perinatal outcomes e.g. severe hypertension, neonatal unit admission, small for gestational age.
Results: Women who delivered within one week, compared to those who did not, had a higher OA PSV-ratio (0.82 vs 0.71, $p < 0.01$) and sFlt-1/PlGF ratio (93.3 vs 40.5, $p = 0.08$). Independent predictors of the OA PSV-ratio included mean arterial pressure and maternal weight and predictors of the sFlt-1/PlGF ratio included diastolic blood pressure and use of antihypertensive medications. Prediction of adverse outcomes with both ratios were similar and only modest e.g. AUROC for predicting delivery within one week for OA PSV-ratio was 0.57 (95% CI 0.47–0.67) and for sFlt-1/PlGF ratio was 0.61 (95% CI 0.52–0.70) ($p = 0.53$).
Conclusions: In women presenting with new onset hypertension, the OA PSV-ratio and sFlt-1/PlGF ratio have similar and modest performance in predicting adverse outcomes.

1. Introduction

Preeclampsia (PE) is one of the main causes of maternal and fetal morbidity and mortality worldwide, with associated adverse maternal-fetal outcomes proportional to the gestational age of presentation and severity of the disease [1,2]. Clinical presentation can be non-specific [3,4] and preventable maternal deaths are attributed to diagnostic delays, inadequate treatment and inappropriate monitoring [5–7]. Assessments for new onset hypertension include maternal history and symptoms, clinical examination, blood pressure, urine dipstick analysis and laboratory haematological and biochemical markers [8]; however, these methods perform poorly in screening for PE and associated adverse outcomes [9,10]. Accurate prediction of PE and related adverse outcomes allows women at highest risk to be identified, so appropriate decisions can be made regarding hospital admission, monitoring intensity, administration of medications, such as steroids and magnesium sulphate, and optimal timing and place of delivery [11].

Recent evidence suggests that useful prediction of PE can be provided by the soluble fms-like tyrosine kinase-1 to placental growth factor ratio (sFlt-1/PlGF) and the maternal ophthalmic artery Doppler peak systolic velocity ratio (OA PSV-ratio). In women with suspected PE, the sFlt-1/PlGF ratio has a high negative predictive value (NPV) for ruling out PE and for prediction of adverse maternal-fetal-neonatal outcomes within one week of assessment [12,13]. However, there are conflicting results concerning the value of the sFlt-1/PlGF ratio in the prediction of delivery within one week of presentation in women with established hypertensive disease [14,15]. The OA PSV-ratio, in combination with maternal characteristics and mean arterial pressure (MAP), has also been reported to be promising in the prediction of imminent delivery with PE; a screening study at 35–37 weeks' gestation reported that such combined screening detected 97% of deliveries with PE within three weeks of assessment, at 10% false positive rate, and was superior to fixed cut-offs in PlGF or the sFlt-1/PlGF ratio [16]. Another study reported that in women with established hypertensive disease, the OA

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PSV-ratio can successfully differentiate between those with PE, gestational hypertension (GH) and chronic hypertension (CHTN) [17] and between severe and mild PE [18–20].

The aim of this study was to compare the predictive ability of OA PSV-ratio and sFlt-1/PlGF ratio for adverse maternal and neonatal outcomes in a cohort of women with new-onset pregnancy hypertension.

2. Methods

2.1. Study population

This is a prospective study conducted in the Antenatal Hypertension Clinic at King's College Hospital, London between February 2019 and September 2021. Women with singleton pregnancies and newly diagnosed hypertension were referred to this dedicated clinic for the management of their pregnancy. Women with chronic (pre-existing) hypertension were excluded from this study. In some cases, patients were diagnosed with symptomatic or severe hypertension in routine antenatal settings and treated with antihypertensives before referral to the hypertension clinic. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks' or fetal head circumference at 19–24 weeks' [21,22].

The patients were managed according to local protocols and the hospital visit included, first, recording of maternal demographic characteristics and medical history, second, ultrasound examination for fetal growth and Dopplers assessment of impedance to flow in the uterine arteries, umbilical arteries and middle cerebral arteries, third, measurement of blood pressure, using a standardised protocol [23] and an automated pregnancy validated device [24], and calculation of mean arterial pressure, fourth, assessment of maternal ophthalmic artery Doppler was performed using a standardised protocol [25] and calculation of the peak systolic velocity (PSV) ratio was the average of two measurements from both the left and right eyes [25], and fifth, measurement of serum concentrations of sFlt-1 and PlGF in pg/mL with the use of an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS, Thermo Fisher Scientific, Hennigsdorf, Germany) and calculation of the sFlt-1/PlGF ratio. The operators and clinicians managing the cases were blinded to the values of the ophthalmic artery Doppler and sFlt-1/PlGF ratios.

2.2. Definitions and indications for delivery

Diagnosis of GH and PE was made according to the guidelines of the International Society for the Study of Hypertension in Pregnancy (ISSHP) [8]. In GH and PE onset of hypertension (systolic blood pressure (SBP) $\geq$ 140 mmHg and / or diastolic blood pressure (DBP) $\geq$ 90 mmHg) occurs at $\geq$ 20 weeks' gestation, with at least two episodes of high blood pressure $\geq$ 4 h apart. In PE, in addition to hypertension, there is proteinuria (24 h urinary protein $\geq$ 300 mg or protein to creatinine ratio $\geq$ 30 mg/mmol) or other maternal organ dysfunction (renal impairment with creatinine $\geq$ 90 μmol/L, liver impairment with alanine aminotransferase or aspartate aminotransferase $>$ 40 IU/L, haematological impairment with thrombocytopenia with platelet count $<$ 150000/μL, disseminated intravascular coagulation or haemolysis, neurological impairment with eclampsia, altered mental status, visual disturbances, or severe headaches. As the ISSHP guidelines recognise that the inclusion of fetal growth restriction (FGR) in the definition of PE is controversial [8], we present the data related to FGR separately to those related to maternal disease.

Indications for delivery were routinely recommended as per local hospital guidelines – by 40 + 0 in women with GH and by 38 + 0 in women with PE. Earlier delivery at any gestation was indicated for either maternal or fetal reasons. Maternal indications included eclampsia, cerebral haemorrhage, persistent symptomatology despite adequate blood pressure control (after exclusion of other pathologies), pulmonary oedema and severe haematological or biochemical complications. Fetal indications for delivery at any gestation were pathological cardiotocography, signs or symptoms of placental abruption and stillbirth. Gestation dependent maternal indications for delivery included: repeated episodes of severe hypertension ($\geq$160/110) or inability to control maternal BP despite 2 ($\geq$37 weeks) or 3 ($<$37 weeks) classes of antihypertensives in maximal doses, progressive deterioration in liver function with aspartate aminotransferase alanine aminotransferase $\geq$ 70 IU/L or albumin $<$ 20 g/L. Gestation dependent fetal indications for delivery were based on ultrasonographic findings as described by Figueras et al. [26] and Hecher et al. [27].

2.3. Study outcomes

There were seven outcome measures for the study. The primary outcome was delivery within one week of presentation. Second, PE at presentation and at delivery. Third, composite of serious adverse outcomes which individually constitute indications for iatrogenic delivery, including need for $\geq$ 3 antihypertensives, severe renal dysfunction (doubling in the level of creatinine from that found at presentation to a level higher than 90 μmol/L), severe liver dysfunction (doubling in the level of liver enzymes from that found at presentation to a level higher than 40 IU/L), thrombocytopenia with platelet count $<$ 100,000/μL, pulmonary oedema, neurological symptoms (severe irretractable headache, repeated visual scotomata or convulsions), pulse oximetry $<$ 90% on room air, haemolysis elevated liver enzymes and low platelets (HELLP) syndrome, acute fatty liver of pregnancy, proteinuria of $>$ 5000 mg/24 h, fetal growth restriction, abruption, fetal death, or neonatal death. Fetal growth restriction was defined by birthweight $<$ 3rd percentile or between the 3rd and 10th percentiles with uterine artery pulsatility index (PI) and/or umbilical artery PI $>$ 95th percentile and/or middle cerebral artery PI $<$ 5th percentile [28]. Fourth, severe maternal hypertension, defined as systolic blood pressure $\geq$ 160 mmHg and/or diastolic blood pressure $\geq$ 110 mmHg. Fifth, delivery by emergency caesarean section for suspected fetal distress (before labour FGR with abnormal Doppler findings and during labour pathological fetal heart rate patterns). Sixth, neonatal unit admission for $\geq$ 24 h. Seventh, birth of small for gestational age (SGA) neonate with birthweight $<$ 10th and $<$ 3rd percentile for gestational age [29].

2.4. Statistical analysis

The Kolmogoroff-Smirnoff test was used to determine normality of data. Data were expressed as median (interquartile range (IQR)) for continuous variables and n (%) for categorical variables. Differences between women who delivered within 1 week and those who did not, were assessed by the chi-squared test for categorical variables and the Student's *t*-test and Mann-Whitney *U* test for numerical variables who were normally or not normally distributed, respectively.

Not normally distributed data were subsequently logarithmically transformed prior to performing linear regression analysis where necessary. Univariate and multivariable linear regression analyses were performed to determine the maternal characteristics and hemodynamic variables with significant effect on the ophthalmic artery OA PSV-ratio and Log_{10}sFlt-1/PlGF ratio. The significant variables were adjusted for, and the subsequent predicted values of the OA PSV-ratio and Log_{10}sFlt-1/PlGF ratio were used in multivariable logistic regression analysis to assess their performance in the prediction of delivery within one week, composite of serious adverse outcomes and associated adverse maternal and neonatal outcomes. The areas under the receiver-operator characteristic curves (AUROC) were plotted to depict the performance of the OA PSV-ratio and Log_{10}sFlt-1/PlGF ratio. The comparison of the AUROCs was performed by the method of DeLong et al. [30].

Statistical analysis was carried out using SPSS ((IBM SPSS Statistics for Windows 2015, Version 26.0, Armonk, NY: IBM Corp)) and STATA (StataCorp. 2019. Stata Statistical Software: Release 16. College Station,

TX: StataCorp LLC).

3. Results

3.1. Study population and pregnancy outcomes

Maternal and pregnancy characteristics of the total cohort and those women who delivered within one week and after one week are presented in Table 1. There are no significant differences between the two groups in maternal demographics, haemodynamic and angiogenic variables aside from gestational age at presentation, number of women on antihypertensive medication, systolic blood pressure, 24-hour urine protein concentration, sFlt-1 concentration, ophthalmic artery peak systolic velocity 2 and OA PSV-ratio. At presentation 49.6% (57/115) women had PE and 50.4% (58/115) had GH. At delivery, an additional 8 women were diagnosed with PE.

3.2. Unadjusted values of OA PSV-ratio and sFlt-1/PlGF ratio

Women who delivered within one week, compared to those who did not, had a higher OA PSV-ratio (0.82 vs 0.71, $p < 0.01$, Fig. 1) and sFlt-1/PlGF ratio (93.3 vs 40.5, $p = 0.08$, Fig. 1). Similarly, women who had a composite serious adverse outcome, compared to those who did not, had a higher OA PSV-ratio (0.78 vs 0.71, $p = 0.01$, Fig. 1) and sFlt-1/PlGF ratio (170.6 vs 35.9, $p < 0.001$, Fig. 1). Those with PE at presentation, compared to those with GH, had a higher OA PSV-ratio (0.8 vs 0.7, $p = 0.005$) and Log_{10}sFlt-1/PlGF ratio (2.02 vs 1.37, $p < 0.0001$).

3.3. Independent predictors of OA PSV-ratio and Log_{10}sFlt-1/PlGF ratio

Univariate linear regression analysis was used to assess the association between OA PSV-ratio and Log_{10}sFlt-1/PlGF ratio and maternal age, height, booking weight, racial origin, parity (nulliparous, parous – without previous PE, parous – with previous PE), smoking, SBP, DBP, MAP, gestational age at presentation and use of antihypertensive medications.

Backward stepwise multivariable regression analysis was subsequently used to assess which of the above named variables are independent predictors of the OA PSV-ratio and Log_{10}sFlt-1/PlGF ratio. The variables significantly affecting the OA PSV-ratio were Log_{10}MAP and maternal weight at booking (OA PSV-ratio = -0.77–0.002*Weight + 0.84*Log_{10}MAP, $p < 0.001$, $R^2 = 0.15$, Fig. S1). The independent variables affecting the Log_{10}sFlt-1/PlGF ratio were DBP and use of antihypertensive medications Log_{10}sFlt-1/PlGF ratio = −7.8 + 0.44 * Antihypertensive Medication + 5.0*Log_{10}DBP, $p = 0.001$, $R^2 = 0.11$, Fig. S2).

The values of OA PSV-ratio and Log_{10}sFlt-1/PlGF ratio were subsequently adjusted for, and their predicted values were used in logistic regression analysis to assess their performance in predicting PE and adverse maternal and perinatal outcomes. Areas under the receiver-operator characteristic curves (AUROC) were used to illustrate this (Table 2).

3.4. Adjusted values of OA PSV-ratio and Log_{10}sFlt-1/PlGF ratio (Table 2)

The OA PSV-ratio and Log_{10}sFlt-1/PlGF ratio performed similarly in the prediction of delivery within one week, with both performing modestly. Similarly, there were no significant differences between the OA PSV-ratio and Log_{10}sFlt-1/PlGF ratio in the prediction of a composite of serious adverse outcome, severe maternal hypertension, delivery by emergency caesarean section for suspected fetal distress, neonatal unit admission for ≥ 24 h, or delivery of a SGA neonate with birthweight < 10th and < 3rd percentile.

3.5. Correlation between Log_{10}sFlt-1/PlGF ratio and OA PSV-ratio and their combination for improving prediction models

There was a significant correlation between Log_{10}sFlt-1/PlGF ratio and OA PSV-ratio (Log_{10}sFlt-1/PlGF ratio = -0.3 + 0.6* OA PSV-ratio, $p < 0.001$, $R^2 = 0.19$). Therefore, combining the two variables did not improve the performance of the prediction models for all outcomes,

Table 1
Maternal and pregnancy characteristics of the total population and women who delivered ≤ 1 week and > 1 week. Numerical variables are shown as median (interquartile range), mean (standard deviation) and categorical variables as n (%). P-values as shown.

Maternal and pregnancy characteristics	All women (n = 115)	Delivery ≤ 1 week (n = 27)	Delivery > 1 week (n = 88)	p-value
Age (years)	34.0 (5.1)	34.6 (5.3)	34.2 (5.4)	0.9
Height (cm)	165.0 (161.0–171.0)	163.0 (158.0–168.0)	165.0 (162.0–169.7)	0.1
Weight (Kg)	74.0 (63.0–86.0)	68.0 (63.0–78.0)	76.0 (65.0–89.7)	0.1
Gestational age at presentation (weeks)	35.6 (33.3–36.9)	37.6 (36.1–39.0)	35.3 (33.0–36.1)	<0.01
Gestational age at delivery (weeks)	38.1 (37.1–39.4)	38.1 (36.9–39.9)	38.3 (37.1–39.4)	0.9
Racial origin, n (%)				0.9
White	76 (66.1)	18 (66.7)	58 (65.9)	
Black	23 (20.0)	5 (18.5)	18 (20.5)	
Other	16 (13.9)	4 (14.8)	12 (13.6)	
Type 1 or Type 2 diabetes, n (%)	3 (2.6)	1 (3.7)	2 (2.3)	0.5
Smoker, n (%)	1 (0.9)	1 (3.7)	0 (0.0)	0.7
Family history of preeclampsia, n (%)	9 (7.8)	1 (3.7)	8 (9.8)	0.3
Assisted conception, n (%)	11 (9.6)	2 (7.4)	9 (10.2)	0.6
Parity, n (%)				0.8
Nulliparous	73 (63.5)	17 (63.0)	56 (63.6)	
Parous, no previous pre-eclampsia	35 (30.4)	9 (33.3)	26 (29.5)	
Parous, previous preeclampsia	7 (6.1)	1 (3.7)	6 (6.8)	
On antihypertensive medications, n (%)	46.0 (40.0)	18 (66.7)	28 (31.8)	0.001
Haemodynamic and biochemical variables				
Systolic blood pressure (mmHg)	140.0 (10.4)	139.4 (7.7)	140.1 (10.9)	0.02
Diastolic blood pressure (mmHg)	91.0 (86.0–95.0)	91.0 (88.0–95.0)	90.0 (85.8–94.9)	0.5
Mean arterial pressure (mmHg)	107.0 (103.0–111.0)	107.7 (103.8–110.3)	107.0 (103.0–111.0)	0.9
24-hour urine protein (mg)	301.0 (183.0–530.0)	426.0 (244.0–1103.0)	256.5 (161.0–454.7)	0.04
Ophthalmic artery peak systolic velocity 1 (cm/sec)	39.7 (9.0)	41.5 (9.6)	39.5 (9.8)	0.5
Ophthalmic artery peak systolic velocity 2 (cm/sec)	29.9 (8.6)	34.2 (9.4)	28.5 (8.4)	0.006
Ophthalmic artery peak systolic velocity ratio	0.8 (0.1)	0.82 (0.1)	0.71 (0.1)	<0.01
Soluble fms-like tyrosine kinase-1 (sFlT-1) (pg/ml)	5433.8 (2632.7–8565.3)	7025.3 (4652.8–14866.2)	4585.7 (2117.5–7583.4)	<0.01
Placental growth factor (PlGF) (pg/ml)	88.57 (47.0–172.8)	75.8 (46.4–133.6)	107.0 (51.6–247.1)	0.1
sFlT-1/PlGF ratio	66.41 (15.9–185.3)	93.3 (49.5–267.9)	40.5 (10.4–145.5)	0.08

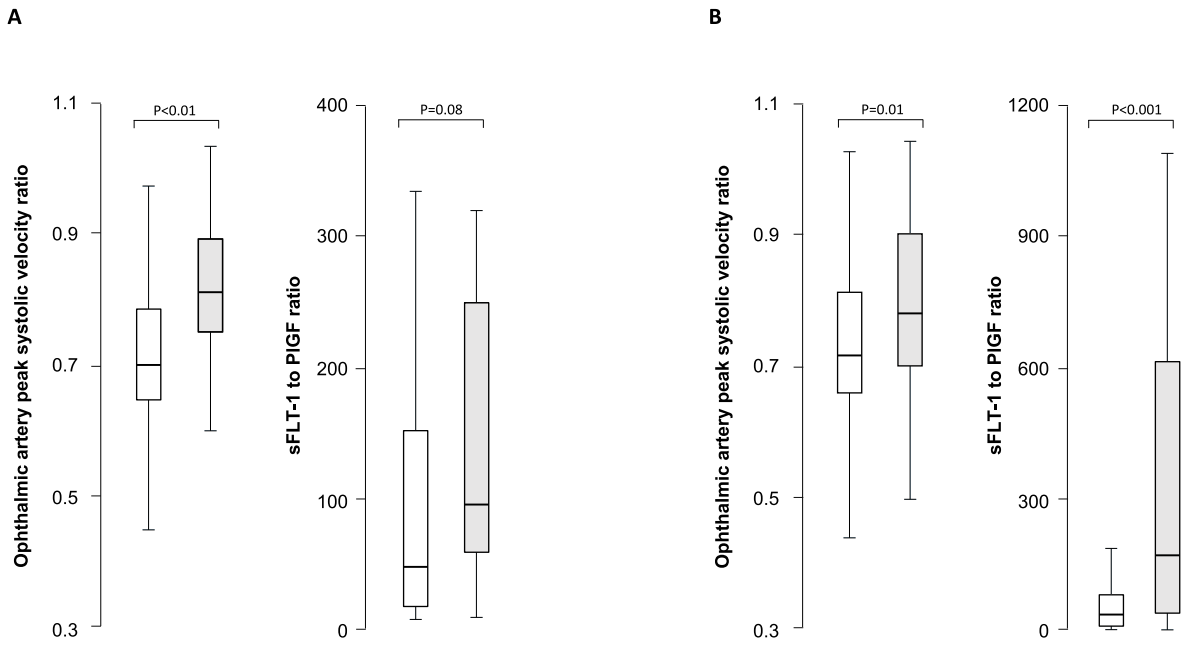

Fig. 1. Box and whisker plots with p-values, demonstrating differences in ophthalmic artery peak systolic velocity ratio and sFlt-1:PlGF ratio in women delivering within one week from presentation (A) and in women with composite of serious adverse outcomes (B). White boxes represent women delivering after one week from presentation and without composite of serious adverse outcomes, whilst grey boxes represent women delivering within one week from presentation and with composite of serious adverse outcomes.

Table 2
Areas under the receiver-operator characteristic curves (AUROC) for the prediction of pregnancy outcomes. Data presented as AUROC (95% confidence interval). The p-values denote the statistical significance for the differences in the AUROCs. OA PSV-ratio is normally distributed whilst sFlt-1/PlGF ratio is not and therefore, is logarithmically transformed.

Outcome measures	Total N = 115	OA PSV-ratio	Log_{10}sFlt-1/PlGF ratio	p-value
Delivery within 1 week of presentation	27 (23.4)	0.57 (0.47–0.67)	0.61 (0.52–0.70)	0.53
Pre-eclampsia at presentation	57 (49.6)	0.53 (0.43–0.62)	0.56 (0.46–0.65)	0.74
Pre-eclampsia at delivery	65 (56.5)	0.55 (0.45–0.64)	0.57 (0.47–0.66)	0.78
Composite of serious adverse outcomes *	37 (32.2)	0.63 (0.54–0.72)	0.61 (0.52–0.70)	0.71
Severe hypertension	20 (17.4)	0.55 (0.46–0.64)	0.60 (0.51–0.69)	0.57
Emergency caesarean section for fetal distress	22 (19.1)	0.56 (0.46–0.65)	0.63 (0.54–0.72)	0.36
Neonatal unit admission for ≥ 24 h	19 (16.5)	0.54 (0.44–0.63)	0.57 (0.48–0.66)	0.77
Small for gestational age < 10th percentile	35 (30.4)	0.64 (0.55–0.73)	0.58 (0.49–0.68)	0.44
Small for gestational age < 3rd percentile	19 (16.5)	0.60 (0.51–0.69)	0.60 (0.50–0.69)	0.93

The 37 cases of composite of serious adverse outcomes included 7 pregnancies requiring ≥ 3 antihypertensives for blood pressure control, 9 with severe renal dysfunction, 13 with severe liver dysfunction, 2 with thrombocytopenia, 2 with HELLP syndrome and 3 with severe proteinuria, 1 with fetal death and 23 with FGR. There were no cases of abruption, neonatal death, neurological symptoms, maternal stroke, pulmonary oedema, acute fatty liver of pregnancy, or pulse oximetry < 90% on room air.

apart from "Delivery within one week" where the combined model was better than both individual ones (AUROC = 0.88, (95% CI 0.79–0.97)).

4. Discussion

4.1. Main findings

The results of this study have demonstrated that in women presenting with new onset hypertension, unadjusted values of the OA-PSV ratio and Log_{10}sFlt-1/PlGF ratio are higher in women who delivered within one week or had a composite of serious adverse outcomes. However, after adjusting for maternal weight, blood pressure, and antihypertensive use both modalities have a similar and modest performance in predicting PE, delivery within one week of presentation, composite of serious adverse outcomes, severe maternal hypertension, delivery by emergency caesarean section for fetal distress, NNU admission for ≥ 24 h and birth of SGA neonates. Therefore, both the OA PSV-ratio and the Log_{10}sFlt-1/PlGF ratio, after adjusting for cofounding variables, cannot be used as independent screening tools for triaging women with new onset hypertension. Instead, they could be incorporated into multivariate prediction models and preference between the two modalities would depend on laboratory availability, sonographer experience and costs.

4.2. Comparison with existing literature in women with pregnancy hypertension

Despite the early recognition that sFlt-1, PlGF and their ratio are influenced by variables such as mean arterial pressure [31], gestational age [15,32–35], racial origin [33,34], maternal weight [33,34], cigarette smoking [33,34] and parity [33–34,14,31,33–34] screening studies in those with suspected PE have partly adjusted for some but not all values [12,13,36–37], whilst one study in women with new onset hypertension [15] have used adjusted values. Therefore, our data are not comparable to the majority of the pre-existing literature. The pre-mentioned study investigating the sFlt-1/PlGF ratio in hypertensive women, adjusted for gestational age, showing that performance was

better in women presenting at earlier gestational ages; AUROC was 0.64 and 0.86 for those above and below 35 weeks, respectively. This corroborates our findings, given that 63.5% of our study population presented at >35 weeks' gestation. Furthermore, in a meta-analysis using unadjusted values for prediction of adverse pregnancy outcomes, sFlt-1/PlGF ratio had sensitivity and specificity of 65% and 67% respectively in predicting time to delivery within seven days in women with suspected PE, which is similar to our results [15].

4.3. Interpretation of findings

A pertinent finding of our study was the modest performance of the adjusted values of Log_{10}sFlt-1/PlGF ratio for prediction of delivery within one week and adverse PE-associated outcomes. This could be explained by four reasons. First, our cohort consisted of predominantly late preterm PE and GH. Similar to the previously described study [15], Verlohren et al. also showed that after 34 weeks' the sFlt-1/PlGF ratio yielded lower sensitivity and specificity [32]. Second, our study only included women presenting with new onset hypertension rather than women with "suspected PE". Previous studies have had a much lower prevalence of PE as they included women with non-specific symptoms of PE e.g. oedema, headache and weight gain [12,13,36–39], thereby inflating their NPV. Furthermore, the fact that the odds ratio for PE increases from 3 [14] to 23 [12] when the control group is women with GH rather than normotensive women, is another example of how the performance of a screening test improves with a healthier control group and would again partly explain the modest results seen in our study. Third, given that Log_{10}sFlt-1/PlGF ratio correlates with blood pressure, adjustment by blood pressure will further reduce its performance, especially in hypertensive populations. Indeed, within our population, 49% of women had PE at recruitment, and the median systolic and diastolic blood pressures were 8 mmHg and 6 mmHg higher respectively, compared to the population of a seminal study investigating the predictive value of the sFlt-1/PlGF ratio in women with suspected PE with an approximate 20% incidence of PE [12]. Fourth, the reduced performance of Log_{10}sFlt-1/PlGF ratio could be due to the fact that 40% of the study population had been started on antihypertensive treatment prior to being reviewed in the specialist antenatal hypertension clinic. The use of antihypertensive medications has been shown to alter concentrations of endothelial anti-angiogenic and angiogenic proteins in the human uterine myometrium. In vitro studies have shown that methyldopa, hydralazine and clonidine reduce sFlt-1 concentrations [40]. Atenolol directed therapy in those at high risk of PE is associated with attenuated rises in sFlt-1 in pregnancy. This was hypothesised to be due to a medication related improvement in central haemodynamics, reducing sheer stress and therefore downregulating endothelial activation [41]. Furthermore, a study of 164 patients with early onset severe PE had a sFlt-1/PlGF ratio calculated before and after treatment with either magnesium sulphate and labetalol (group A) or magnesium sulphate alone (group B). The sFlt-1/PlGF ratio was significantly higher in both pre-treatment groups (68.86 ± 47.26 group A, 64.56 ± 48.35 in group B) when compared to after treatment (9.32 ± 6.69 group A, 11.37 ± 6.56) [42]. These studies support our findings that antihypertensive therapy should be controlled for when using the sFlt-1/PlGF ratio and raise concerns about its screening performance once blood pressure has been controlled effectively. Similarly, this may also be the reason for the modest performance of the adjusted values of the OA PSV-ratio given that, as we have previously shown, it has a strong association with blood pressure levels and antihypertensive use [17,43].

4.4. Strengths and limitations

Strengths of this study include first, its pragmatic approach, where patients presented at any gestation with new onset hypertension with or without treatment. Second, we examined a high-risk population with established disease rather than those "at risk of pre-eclampsia", in order to avoid exaggerating the performance of the test. Third, linear regression analysis allowed for cofounding factors to be controlled for and fourth, only two sonographers measured the OA PSV-ratio to reduce measurement variability. Limitations include that the study was underpowered to assess the impact of different types of antihypertensives on sFlt-1/PlGF ratio or OA PSV-ratio, and the lack of presentation of longitudinal changes with progression of the disease.

5. Conclusions

In women presenting with new onset hypertension, the OA PSV-ratio and Log_{10}sFlt-1/PlGF ratio are associated with maternal weight, MAP, DBP and antihypertensive use. Adjusted values of the OA PSV-ratio and Log_{10}sFlt-1/PlGF ratio have a modest ability to predict delivery within one week and related maternal and neonatal complications and therefore, the optimal use of these ratios would be in multivariate models in triaging hypertensive patients and screening for PE related complications.

6. Contribution

KL was involved in the collection and organisation of data and preparation of the manuscript. EK and LS-R were involved in the collection of data and editing of the manuscript. NK and KHN were involved in the conception of the study, statistical analysis and preparation of the manuscript.

7. Details of ethics approval

Written informed consent was obtained from women who agreed to participate in the study on advanced cardiovascular assessment in pregnancy. This study received a favourable opinion from the Office of Research Ethics Committee Northern Ireland on 22nd January 2018 (REC reference 18/NI/0013, IRAS ID 237936).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2023.10.001.

References

[1] L. Duley, The global impact of pre-eclampsia and eclampsia, Semin. Perinatol. 33 (2009) 130–137.
[2] J.M. Roberts, J.W. Rich-Edwards, T.F. McElrath, L. Garmire, L. Myatt, Subtypes of preeclampsia: recognition and determining clinical usefulness, Hypertension 77 (2021) 1430–1441.
[3] B.M. Sibai, C.L. Stella, Diagnosis and management of atypical preeclampsia-eclampsia, Am. J. Obstet. Gynecol. 200 (481) (2009) e1–e7.
[4] B.C. Young, S.A. Karumanchi, Toward a better diagnosis for preeclampsia, Clin. Chem. 62 (2016) 913–915.
[5] E.K. Main, C.L. McCain, C.H. Morton, S. Holtby, E.S. Lawton, Pregnancy-related mortality in California: causes, characteristics, and improvement opportunities, Obstet. Gynecol. 125 (2015) 938–947.
[6] A.H. Shennan, M. Green, L.C. Chappell, Maternal deaths in the UK: pre-eclampsia deaths are avoidable, Lancet 389 (2017) 582–584.
[7] M. Knight, D. Tuffnell, S. Kenyon, J. Shakespeare, R. Gray, J.J. Kurinczuk, On behalf of MBRRACE-UK, Saving Lives, Improving Mothers' Care: Surveillance of Maternal Deaths in the UK 2011–13 and Lessons Learned to Inform Maternity Care

From the UK and Ireland, National Perinatal Epidemiology Unit, University of Oxford. University of Oxford, Oxford, 2015.
[8] M.A. Brown, L.A. Magee, L.C. Kenny, S.A. Karumanchi, F.P. McCarthy, S. Saito, et al., Hypertensive disorders of pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice, Hypertension 72 (2018) 24–43.
[9] C.A. Meads, J.S. Cnossen, S. Meher, A. Juarez-Garcia, G. ter Riet, L. Duley, et al., Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling, Health Technol. Assess. 12 (iii–iv) (2008) 1–270.
[10] J. Menzies, L.A. Magee, Y.C. Macnab, J.M. Ansermino, J. Li, M.J. Douglas, et al., Current CHS and NHBPEP criteria for severe preeclampsia do not uniformly predict adverse maternal or perinatal outcomes, Hypertens. Pregnancy 26 (2007) 447–462.
[11] P. von Dadelszen, B. Payne, J. Li, J.M. Ansermino, F. Broughton Pipkin, A.M. Côté, et al., Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model, Lancet 377 (2011) 219–227.
[12] H. Zeisler, E. Llurba, F. Chantraine, M. Vatish, A.C. Staff, M. Sennström, et al., Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia, N. Engl. J. Med. 374 (2016) 13–22.
[13] S. Rana, C.E. Powe, S. Salahuddin, S. Verlohren, F.H. Perschel, R.J. Levine, et al., Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia, Circulation 125 (2012) 911–919.
[14] S. Verlohren, I. Herraiz, O. Lapaire, D. Schlembach, M. Moertl, H. Zeisler, et al., The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients, Am. J. Obstet. Gynecol. 206 (58) (2012) e1–e8.
[15] H. Perry, J. Binder, E. Kalafat, S. Jones, B. Thilaganathan, A. Khalil, Angiogenic marker prognostic models in pregnant women with hypertension, Hypertension 75 (2020) 755–761.
[16] K. Lau, A. Wright, M. Sarno, N.A. Kametas, K.H. Nicolaides, Comparison of ophthalmic artery Doppler with PlGF and sFlt-1-to-PlGF ratio at 35–37 weeks' gestation in prediction of imminent pre-eclampsia, Ultrasound Obstet. Gynecol. (2022).
[17] K.G.Y. Lau, A. Wright, E. Kountouris, K.H. Nicolaides, N.A. Kametas, Ophthalmic artery peak systolic velocity ratio distinguishes pre-eclampsia from chronic and gestational hypertension: A prospective cohort study, BJOG (2021).
[18] M. Takata, M. Nakatsuka, T. Kudo, Differential blood flow in uterine, ophthalmic, and brachial arteries of preeclamptic women, Obstet. Gynecol. 100 (2002) 931–939.
[19] C.A. de Oliveira, R.A. de Sá, L.G. Velarde, F.C. da Silva, F.A. doVale, H.C. Netto, Changes in ophthalmic artery Doppler indices in hypertensive disorders during pregnancy, J. Ultrasound Med. 32 (2013) 609–616.
[20] A.L. Diniz, A.F. Moron, M.C. dos Santos, N. Sass, C.R. Pires, C.L. Debs, Ophthalmic artery Doppler as a measure of severe pre-eclampsia, Int. J. Gynaecol. Obstet. 100 (2008) 216–220.
[21] H.P. Robinson, J.E. Fleming, A critical evaluation of sonar "crown-rump length" measurements, Br. J. Obstet. Gynaecol. 82 (1975) 702–710.
[22] R.J. Snijders, K.H. Nicolaides, Fetal biometry at 14–40 weeks' gestation, Ultrasound Obstet. Gynecol. 4 (1994) 34–48.
[23] P. Muntner, D. Shimbo, R.M. Carey, J.B. Charleston, T. Gaillard, S. Misra, et al., Measurement of blood pressure in humans: A scientific statement from the American Heart Association, Hypertension 73 (2019) e35–e66.
[24] K. Clark, O. Snowball, D. Nzelu, P. Kay, N.A. Kametas, Validation of the Microlife WatchBP Home blood pressure device in pregnancy for medium and large arm circumferences, Blood Press. Monit. 23 (2018) 171–174.
[25] M. Sarno, A. Wright, N. Vieira, I. Sapantzoglou, M. Charakida, K.H. Nicolaides, Ophthalmic artery Doppler in combination with other biomarkers in prediction of pre-eclampsia at 35–37 weeks' gestation, Ultrasound Obstet. Gynecol. 57 (2021) 600–606.
[26] F. Figueras, E. Gratacós, Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol, Fetal Diagn. Ther. 36 (2014) 86–98.
[27] K. Hecher, C.M. Bilardo, R.H. Stigter, Y. Ville, B.J. Hackelöer, H.J. Kok, et al., Monitoring of fetuses with intrauterine growth restriction: a longitudinal study, Ultrasound Obstet. Gynecol. 18 (2001) 564–570.
[28] N. Melamed, A. Baschat, Y. Yinon, A. Athanasiadis, F. Mecacci, F. Figueras, et al., FIGO (international Federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction, Int. J. Gynaecol. Obstet. 152 (Suppl 1) (2021) 3–57.
[29] K.H. Nicolaides, D. Wright, A. Syngelaki, A. Wright, R. Akolekar, Fetal Medicine Foundation fetal and neonatal population weight charts, Ultrasound Obstet. Gynecol. 52 (2018) 44–51.
[30] E.R. DeLong, D.M. DeLong, D.L. Clarke-Pearson, Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach, Biometrics 44 (1988) 837–845.
[31] P.K. Aggarwal, N. Chandel, V. Jain, V. Jha, The relationship between circulating endothelin-1, soluble fms-like tyrosine kinase-1 and soluble endoglin in preeclampsia, J. Hum. Hypertens. 26 (2012) 236–241.
[32] S. Verlohren, I. Herraiz, O. Lapaire, D. Schlembach, H. Zeisler, P. Calda, et al., New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia, Hypertension 63 (2014) 346–352.
[33] A. Tsiakkas, N. Duvdevani, A. Wright, D. Wright, K.H. Nicolaides, Serum placental growth factor in the three trimesters of pregnancy: effects of maternal characteristics and medical history, Ultrasound Obstet. Gynecol. 45 (2015) 591–598.
[34] A. Tsiakkas, N. Duvdevani, A. Wright, D. Wright, K.H. Nicolaides, Serum soluble fms-like tyrosine kinase-1 in the three trimesters of pregnancy: effects of maternal characteristics and medical history, Ultrasound Obstet. Gynecol. 45 (2015) 584–590.
[35] A. Khalil, N. Maiz, R. Garcia-Mandujano, J.M. Penco, K.H. Nicolaides, Longitudinal changes in maternal serum placental growth factor and soluble fms-like tyrosine kinase-1 in women at increased risk of pre-eclampsia, Ultrasound Obstet. Gynecol. 47 (2016) 324–331.
[36] X. Bian, A. Biswas, X. Huang, K.J. Lee, T.K. Li, H. Masuyama, et al., Short-term prediction of adverse outcomes using the sFlt-1 (Soluble fms-Like Tyrosine Kinase 1)/PlGF (placental growth factor) ratio in Asian women with suspected preeclampsia, Hypertension 74 (2019) 164–172.
[37] S. Rana, S. Salahuddin, A. Mueller, A.H. Berg, R.I. Thadhani, S.A. Karumanchi, Angiogenic biomarkers in triage and risk for preeclampsia with severe features, Pregnancy Hypertens. 13 (2018) 100–106.
[38] L.A. Dröge, F.H. Perschel, N. Stütz, A. Gafron, L. Frank, A. Busjahn, et al., Prediction of preeclampsia-related adverse outcomes with the sFlt-1 (soluble fms-Like tyrosine kinase 1)/PlGF (placental growth factor)-ratio in the clinical routine: A real-world study, Hypertension 77 (2021) 461–471.
[39] H. Zeisler, E. Llurba, F.J. Chantraine, M. Vatish, A.C. Staff, M. Sennström, et al., Soluble fms-like tyrosine kinase-1 to placental growth factor ratio: ruling out pre-eclampsia for up to 4 weeks and value of retesting, Ultrasound Obstet. Gynecol. 53 (2019) 367–375.
[40] Xu B, Charlton F, Makris A, Hennessy A. Antihypertensive drugs methyldopa, labetalol, hydralazine, and clonidine improve trophoblast interaction with endothelial cellular networks in vitro. *J. Hypertens.* 32 (2014) 1075–1083; discussion 83.
[41] D.B. Carr, L.T. Tran, D.A. Brateng, C. Kawamura, J.B. Shofer, S.A. Karumanchi, et al., Hemodynamically-directed atenolol therapy is associated with a blunted rise in maternal sFLT-1 levels during pregnancy, Hypertens. Pregnancy 28 (2009) 42–55.
[42] Y. Wang, J. Bao, M. Peng, Effect of magnesium sulfate combined with labetalol on serum sFlt-1/PlGF ratio in patients with early-onset severe pre-eclampsia, Exp. Ther. Med. 20 (2020) 276.
[43] K.G. Lau, M. Baloi, D. Dumitrascu-Biris, K.H. Nicolaides, N.A. Kametas, Changes in ophthalmic artery Doppler during acute blood-pressure control in hypertensive pregnant women, Ultrasound Obstet. Gynecol. 59 (2022) 185–191.