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RESEARCH ARTICLE

Maternal Medicine

Ophthalmic artery peak systolic velocity ratio distinguishes pre-eclampsia from chronic and gestational hypertension: A prospective cohort study

Katherine G. Y. Lau[1,2] | **Allan Wright**[3] | **Emmanouil Kountouris**[1] | **Kypros H. Nicolaides**[2] | **Nikos A. Kametas**[1,2]

[1]Antenatal Hypertension Clinic, King's College Hospital, London, UK

[2]Harris Birthright, Research Centre for Fetal Medicine, King's College Hospital, London, UK

[3]Institute of Health Research, University of Exeter, Exeter, UK

Correspondence
Nikos A. Kametas, Antenatal Hypertension Clinic, Fetal Medicine Research Institution, King's College Hospital, 16–20 Windsor Walk, London SE5 8BB, UK.
Email: nick.kametas@kcl.ac.uk

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Abstract

Objective: To examine whether the ophthalmic artery peak systolic velocity ratio (OA PSV-ratio) is higher in women with pre-eclampsia compared with gestational hypertension (GH) and chronic hypertension (CH), after controlling for confounding variables.

Design: Prospective cohort.

Setting: Specialist hypertension clinic in a tertiary referral centre.

Population: Singleton pregnancies presenting between 32^{+0} and 36^{+6} weeks of gestation with pre-eclampsia ($n = 50$), GH ($n = 54$) and CH ($n = 56$).

Methods: Paired measurements of maternal mean arterial pressure (MAP) and OA PSV-ratio were performed by trained sonographers. Multiple linear regression was fitted to the OA PSV-ratio, including maternal characteristics and medical history, GH, pre-eclampsia and MAP and use of antihypertensive medication.

Main Outcome Measure: Whether pre-eclampsia is independently associated with higher OA PSV-ratio.

Results: MAP was significantly higher in both GH ($p = 0.0015$) and pre-eclampsia ($p = 0.008$) than in CH pregnancies. There was no significant difference between pre-eclampsia and GH (0.670). The OA PSV-ratio was significantly higher in pre-eclampsia than CH ($p = 0.0008$) and GH ($p = 0.015$). There was no significant difference between the OA PSV-ratio in CH and GH ($p = 0.352$). Multiple linear regression modelling showed that the OA PSV-ratio was influenced by maternal weight ($p = 0.005$), maternal age ($p = 0.014$), antihypertensive medications ($p = 0.007$) and MAP ($p < 0.0001$). After controlling for these variables, the OA PSV-ratio was still significantly higher in those with pre-eclampsia ($p = 0.0002$).

Conclusions: The OA PSV-ratio is influenced by maternal weight, age, antihypertensive medications and MAP. Pre-eclampsia is an independent predictor of OA PSV-ratio, which therefore may be a useful point-of-care test when assessing women presenting with hypertension.

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This article includes Author Insights, a video abstract available at: https://vimeo.com/bjog/authorinsights17061.

This article has a Video Abstract presented by Katherine Lau.

KEYWORDS
hypertension in pregnancy, ophthalmic artery, point-of-care test, pre-eclampsia, screening

Tweetable Abstract: Ophthalmic artery peak systolic velocity ratio is higher in pre-eclampsia compared with gestational or chronic hypertension.

1 | INTRODUCTION

Hypertensive disorders of pregnancy complicate 8–10% of pregnancies[1,2] and pre-eclampsia is one of the leading causes of maternal and perinatal morbidity and mortality worldwide.[3,4] Screening for pre-eclampsia in low-risk populations aims at pre-eclampsia prevention[5] and has been shown to be effective using a combination of maternal characteristics, clinical, ultrasound and biochemical markers.[6] More recently, the ophthalmic artery (OA) Doppler peak systolic velocity ratio (PSV-ratio) has been shown to be promising in screening for pre-eclampsia in low-risk populations, adding a similar power as anti-angiogenic markers to multivariate prediction models.[7,8] Conversely, at the point of overt disease, screening has a principal focus of risk stratification. By identifying women who have or are at risk of developing pre-eclampsia from those with uncomplicated hypertension, the need for hospital admission, frequency of follow-up visits, timing and location of delivery and treatment can be determined. Hence, risk stratification of hypertensive women at the time of presentation allows for individualisation of patient care and increased efficiency by optimising resource utilisation, as well as reducing the risk of adverse perinatal events.[9]

Blood pressure and dipstick urinalysis are the two traditional point-of-care tests used in the detection and classification of severity of hypertension at presentation but they are subject to both user and machine variation[10–12] and have a low predictive value for pre-eclampsia.[13,14] Anti-angiogenic factors have recently gained attention[15] but they can be costly or necessitate complex laboratory processes that may not be available in under-resourced settings.[16] Ophthalmic artery Doppler uses a simple and safe ultrasound technique and can be measured with standard ultrasound equipment within an outpatient obstetric setting. The measurements are quick to obtain, provide good inter-observer and intra-observer variability, change minimally with gestational age[17,18] and are not affected by maternal adiposity.[17] These qualities allow the OA Doppler ultrasound to be an ideal tool for point-of-care assessment of maternal haemodynamics, providing real-time risk stratification and an objective aide to guide appropriate management.

Previous studies investigating the use of the OA PSV-ratio in established disease have shown an increased ratio in women with pre-eclampsia versus controls[19–22] and an increase in severe versus mild pre-eclampsia.[19,20,22] There is scanty information regarding the performance of the OA PSV-ratio in triaging women at presentation with new-onset or deteriorating hypertension. Therefore, in this study we aim to determine whether the OA PSV-ratio can distinguish pre-eclampsia within a hypertensive cohort at the point of presentation.

2 | METHODS

2.1 | Study population

This is a prospective study conducted in the Antenatal Hypertension Clinic at King's College Hospital, London. According to local protocols, pregnant women with hypertension, pre-existing or newly identified during routine antenatal care, are referred to this dedicated clinic for the management of their pregnancy. The inclusion criteria for this study were singleton pregnancies with chronic hypertension (CH), gestational hypertension (GH) or pre-eclampsia presenting in the clinic between July 2019 and March 2021 and consenting to participate in the study. The hospital visit included recording of maternal demographic characteristics and medical history, ultrasound examination for fetal anatomy and growth, measurement of blood pressure using a standardised protocol[23] and automated device validated for use in pregnancy and pre-eclampsia,[24] and assessment of flow velocity waveforms from the maternal OA. This study received a favourable opinion from the Office of Research Ethics Committee Northern Ireland (REC reference 18/NI/0013, IRAS ID 237936).

Diagnosis of CH, GH and pre-eclampsia was made according to the International Society of Hypertension Guidelines.[25] Hypertension was defined by the presence of systolic blood pressure 140 mmHg or more or diastolic blood pressure 90 mmHg or more. In CH, the onset of high blood pressure is before or within the first 19 weeks of pregnancy. In GH and pre-eclampsia the onset of hypertension is at or after 20 weeks of gestation with at least two episodes of high blood pressure, at least 4 hours apart. In GH there is no proteinuria, maternal organ dysfunction or fetal growth restriction. In pre-eclampsia there is evidence of maternal organ dysfunction with significant proteinuria (protein creatinine ratio 30 mg/mmol or more or 24-h urinary protein 300 mg or more) or other maternal organ dysfunction, including acute kidney injury (creatinine 90 μmol/l or more), liver impairment (alanine aminotransferase or aspartate aminotransferase more than 40 IU/l), haematological complications (thrombocytopenia with platelet count less than 150 000/μl, disseminated intravascular coagulation or haemolysis) or neurological complications (eclampsia, altered mental status, visual

disturbances or severe headaches). Pre-eclampsia can be new onset or super-imposed on CH. Mean arterial pressure (MAP) was calculated as (systolic blood pressure + 2 * diastolic blood pressure)/3.

2.2 | Ophthalmic artery Doppler

A standard protocol as previously described was used for the measurement of the OA Doppler assessment.[7] The mother was placed in the supine position for at least 5 minutes, a 7.5-MHz linear transducer (GE ML6-15-D Matrix Linear Probe, GE Healthcare Ultrasound) was then placed transversely and gently over her closed upper eyelid after application of conduction gel. Colour flow was used to identify the ophthalmic artery, which is found superior and medially to the hypoechoic band representing the optic nerve. Pulsed wave Doppler was then used to record three to five similar waveforms; the angle of insonation was kept at less than 20°, the sample gate was 2 mm, the depth was 3.0–4.5 cm, the high-pass filter was 50 Hz, and the pulse repetition frequency was 125 kHz. To reduce any discomfort or adverse effects, a customised preset with a maximal mechanical index of 0.3 was used to reduce output power and measurement duration was kept to less than 1 minute.[26] To reduce intra-observer variability only three trained sonographers performed the measurements. Waveforms were obtained in sequence from the right eye, left eye, and again right and then left eye. The first peak systolic velocity (PSV1) was obtained automatically by the ultrasound machine, the second PSV systolic velocity (PSV2) was measured manually. The peak systolic velocity ratio was calculated as PSV2/PSV1. The average of the four ratios (two from the left eye and two from the right eye) was used for statistical analysis.

2.3 | Statistical analysis

Data were expressed as median (interquartile range) for continuous variables and *n* (%) for categorical variables. The Mann–Whitney *U* test and chi-square test or Fisher's exact test were used for comparing outcome groups for continuous and categorical data, respectively.

Multiple of the Median (MoM) values for MAP and difference from the median (Delta) values for the ratio were calculated according to the Fetal Medicine Foundation reference ranges.[7,8,27] The effect of CH on each of the markers was not corrected for. The distribution of the markers in CH, GH and pre-eclampsia was examined via boxplots. We have shown evidence in previous studies that both MAP and the ratio are significantly raised in women who develop pre-eclampsia.[7,8,27]

A multiple linear regression model was fitted to the ratio, including maternal characteristics (age and weight at 12 weeks of gestation) and medical history, GH, pre-eclampsia and MAP MoM and use of antihypertensive medication. Maternal age and weight were centred at the median maternal age and weight at 12 weeks of gestation. Backwards elimination was used for variable selection. The aim of this model fitting was to determine whether, after allowing for MAP and maternal characteristics, the ratio distinguished between CH, GH and pre-eclampsia.

The statistical software package R was used for data analyses.[28]

3 | RESULTS

3.1 | Study participants and pregnancy outcomes

The study population of 160 pregnancies contained 50 with pre-eclampsia, 56 with CH and 54 with GH. Maternal and pregnancy characteristics of the study population and pregnancy outcomes are summarised in Table 1. Women of black racial origin appeared more highly represented in the CH group over the pre-eclampsia group and women with CH seemed generally heavier than those with pre-eclampsia and GH. Women with pre-eclampsia delivered smaller babies, had a higher number of admissions to the neonatal unit and had increased rates of severe hypertension compared with women with CH or GH.

3.2 | Ophthalmic artery Doppler and mean arterial pressure

Median and interquartile ranges of OA PSV-ratio and MAP in pregnancies with CH, GH and pre-eclampsia are illustrated in Figure 1 and summarised in Table 1. There was a positive correlation between MAP and OA PSV-ratio for the total cohort (Figure S1, $r = 0.4$). In all three hypertensive disorders the OA PSV-ratio and MAP were increased compared with previously published values in normotensive pregnancies.[7,8,27] The median MAP was significantly higher in both GH ($p = 0.0015$) and pre-eclampsia ($p = 0.008$) than in CH pregnancies; there was no significant difference between pre-eclampsia and GH (0.670). Ophthalmic artery PSV-ratio was significantly higher in pre-eclampsia than in both CH ($p = 0.0008$) and GH ($p = 0.015$); there was no significant difference between CH and GH ($p = 0.352$).

Table 2 shows a multiple linear regression model fitted to the OA PSV-ratio. After taking into account MAP MoM, maternal weight, age and treatment with antihypertensive drugs, the OA PSV-ratio was significantly raised in pre-eclampsia pregnancies over CH or GH pregnancies. Chronic hypertension was taken as the reference group and terms were tested for both pre-eclampsia and GH. There was found to be no evidence of a difference between the GH and CH groups and so the term for GH was removed from the model as part of the backwards elimination procedure. These results suggest that the PSV-ratio independently helps us to distinguish pre-eclampsia from CH or GH over MAP alone.

TABLE 1 Maternal characteristics of the study population, pregnancy outcomes and haemodynamic variables

	Chronic hypertension (n = 56)	Gestational hypertension (n = 54)	Pre-eclampsia (n = 50)
Maternal characteristics			
Maternal age (years)	35.2 (32.8–38.3)	35.3 (30.9–37.9)	32.9 (29.9–35.6)
Maternal weight (kg)	80.0 (68.0–95.3)	73.0 (63.0–89.5)	77.0 (65.3–91.3)
Maternal height (cm)	166 (162–171)	165 (162–172)	165 (162–169)
Body mass index (kg/m^2)	28.3 (24.6–34.0)	25.4 (22.9–32.7)	27.6 (24.1–33.0)
Gestational age (weeks)	34.5 (32.0–35.8)	36.0 (35.0–36.7)	35.3 (33.6–36.1)
Racial origin			
White	21 (37.5)	36 (66.6)	28 (56.0)
Black	28 (50.0)	13 (24.1)	16 (32.0)
South Asian	5 (8.9)	1 (1.9)	4 (8.0)
East Asian	1 (1.8)	2 (3.7)	1 (2.0)
Mixed	1 (1.8)	2 (3.7)	1 (2.0)
Diabetes mellitus	4 (7.1)	1 (1.9)	4 (8.0)
Smoker	1 (1.8)	0 (0.0)	1 (2.0)
Family history of pre-eclampsia	2 (3.6)	7 (13.0)	4 (8.0)
Method of conception			
Natural	53 (94.6)	48 (88.9)	47 (94.0)
In vitro fertilisation	3 (5.4)	6 (11.1)	3 (6.0)
Parity			
Nulliparous	22 (39.3)	29 (53.7)	32 (64.0)
Parous, no previous pre-eclampsia	27 (48.2)	21 (38.9)	15 (30.0)
Parous, previous pre-eclampsia	7 (12.5)	4 (7.4)	3 (6.0)
Interpregnancy interval (years)	2.8 (1.9–7.2)	2.3 (1.7–5.1)	3.2 (1.7–6.2)
Antihypertensive drugs	39 (69.6)	24 (44.4)	27 (54.0)
Pregnancy outcome			
Birthweight centile median	25.7 (2.5–52.5)	34.5 (12.7–74.7)	8.54 (2.5–51.7)
Delivery by emergency caesarean section	18 (32.1)	22 (40.7)	20 (40)
Admission to neonatal unit	8 (14.3)	8 (14.8)	12 (24)
Severe hypertension[c]	14 (25)	10 (18.5)	15 (30)
Haemodynamic variables			
OA PSV-ratio delta[a]	0.13 (0.09–0.17)	0.13 (0.10–0.16)	0.22 (0.18–0.27)
MAP MoM[b]	1.12 (1.09–1.15)	1.18 (1.13–1.22)	1.20 (1.17–1.24)

Note: Numerical variables are shown as median (interquartile range) and categorical variables as n (%).

[a]Ophthalmic artery peak systolic velocity ratio delta.

[b]Mean arterial pressure Multiples of the Median.

[c]Severe hypertension defined as systolic blood pressure of 160 mmHg or more and/or diastolic blood pressure of 110 mmHg or more.

4 | DISCUSSION

4.1 | Main findings

This study has demonstrated that maternal OA PSV-ratio can differentiate between pre-eclampsia and uncomplicated GH and CH at the point of presentation. The OA PSV-ratio was found to be significantly raised in those with pre-eclampsia, despite MAPs being similar in both the pre-eclampsia and GH groups. Linear regression modelling showed that maternal weight, age and antihypertensive medication influenced the OA PSV-ratio, so future studies should control for these variables. Development of pre-eclampsia was an independent predictor of the OA PSV-ratio.

4.2 | Interpretation of findings

The OA is the first branch of the internal carotid artery[29] and has a time–velocity waveform with two systolic peaks, a dicrotic notch and a subsequent end-diastolic wave (Figure 2).[30] The first systolic wave (PSV1) is created by cardiac systole,[31]

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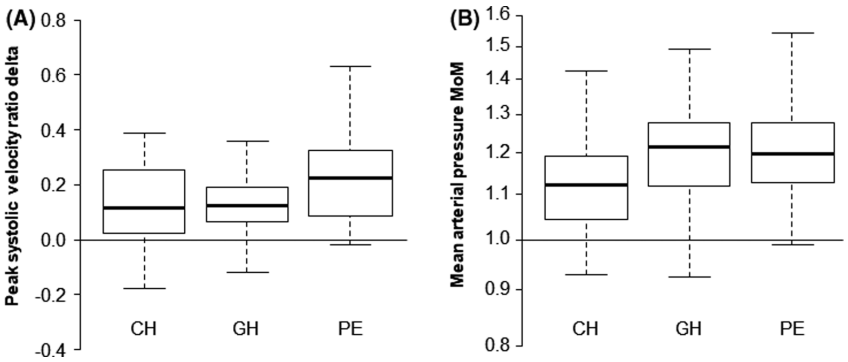

FIGURE 1 Median and 95% confidence intervals for (A) ophthalmic artery peak systolic velocity ratio delta in pregnancies with CH, GH and pre-eclampsia; (B) mean arterial pressure MoM in pregnancies with CH, GH and pre-eclampsia

TABLE 2 Multiple linear regression model fitted to the ophthalmic artery peak systolic velocity ratio

	Estimate (95% confidence interval)	*p*-value
Intercept	0.65175 (0.60572–0.69778)	<0.0001
$\log_{10}$(MAP MoM)	0.97593 (0.58515–1.36672)	<0.0001
Pre-eclampsia	0.08276 (0.04092–0.12459)	0.0002
Maternal weight in kg – 69[a]	−0.00165 (−0.00279, −0.00052)	0.005
Maternal age in years – 35[a]	0.00455 (0.00095–0.00815)	0.014
Antihypertensive medication	0.05467 (0.01527–0.09406)	0.007

Note: The independent predictors of the ophthalmic artery PSV-ratio are presented, with the corresponding regression co-efficients (95% confidence interval) and *p*-values.

Based on the above regression model, the PSV ratio can be calculated with the following equation: PSV ratio = 0.65175 + 0.97593 * $\log_{10}$(MAP MoM) + 0.08276 * pre-eclampsia − 0.00165 * (Maternal weight in kg − 69) + 0.00455 * (Maternal age in years − 35) + 0.05467 * Antihypertensive medication.

For example, the PSV ratio in a 38-year-old woman with a booking weight of 80 kg, a MAP MoM of 1.5, who is on antihypertensive medication and has been diagnosed with pre-eclampsia. the following calculation would be used: PSV ratio = 0.65175 + 0.97593 * $\log_{10}$(1.5) + 0.08276 * 1 − 0.00165 * (80 − 69) + 0.00455 * (38 − 35) + 0.05467 * 1 = 0.65175 + 0.17185 + 0.08276 − 0.01815 + 0.01365 + 0.05467 = 0.95653.

On the contrary, if the patient was 25 years old, with a booking weight of 70 kg, a MAP MoM of 1.0, was not diagnosed with pre-eclampsia and was not on antihypertensive medications, the PSV ratio would be calculated as: PSV ratio = 0.65175 + 0.97593 * $\log_{10}$(1.0) + 0.08276 * 0 − 0.00165 * (70 − 69) + 0.00455 * (25 − 35) + 0.05467 * 0 = 0.65175 + 0 + 0 − 0.00165 − 0.0455 + 0 = 0.6046.

[a]Maternal age and weight were centred at the median maternal age and weight at 12 weeks of gestation.

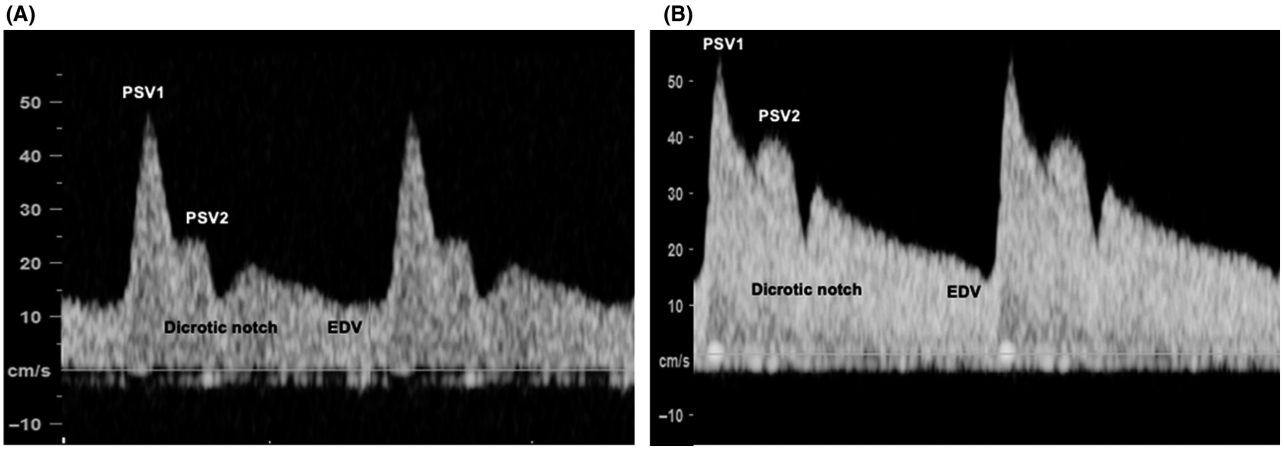

FIGURE 2 Doppler sonogram with demonstration of the ophthalmic artery waveform by pulse-wave Doppler. The first systolic velocity peak (PSV1), second systolic velocity peak (PSV2), dicrotic notch and the end-diastolic velocity (EDV) are shown in: (A) a woman with no hypertensive disease in pregnancy, and (B) a woman with pre-eclampsia. Note that the PSV2 is higher in pre-eclampsia, compared with normotensive women

with the opening of the aortic valve and ejection of blood into the aorta, whereas 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 the second systolic peak (PSV2).[32,33] In this way, PSV2 is most influenced by peripheral arterial compliance and resistance, whereas PSV1 is more affected by cardiac output.[31,32] Therefore, an increase in OA PSV-ratio (the ratio between PSV2 and PSV1) could represent either an increase in peripheral vascular resistance and/or a reduction in cardiac output.[34] Research on maternal haemodynamics has suggested that GH is characterised by a hyperdynamic profile with high cardiac output and low peripheral resistance, whereas clinically evident pre-eclampsia has a vasoconstricted profile with low cardiac output and high peripheral resistance.[35,36] It is therefore not surprising that the OA PSV-ratio distinguishes pre-eclampsia from GH, but MAP does not, as pre-eclampsia is associated with higher peripheral resistance and lower cardiac output than GH. The fact that the median CH values for the OA PSV-ratio were similar to those with GH probably reflects the fact that these women have had their blood pressure controlled since early pregnancy and hence their peripheral resistance is artificially reduced by vasodilatory therapy.

The finding that the OA PSV-ratio is influenced by MAP and antihypertensive medication is also logical. In our previous work[37] we assessed longitudinal changes in OA PSV-ratio with antihypertensive treatment, and we found that MAP is strongly correlated with the OA PSV-ratio before instigation of antihypertensive medications but this relationship is lost when blood pressure is controlled to levels of 140/90 mmHg or more. We hypothesised that this probably reflected the reduction of PSV2 due to vasodilatory therapy. Similarly, in the current study, higher MAP was associated with higher values of OA PSV-ratio. The fact that the use of antihypertensive medications was also associated with greater values of OA PSV-ratio is probably a selection bias, because the women who were treated before their first clinic appointment had the highest blood pressure values and would necessitate urgent treatment. There are no studies describing the relationship between age or weight with OA Doppler indices in pregnancy. Outside of pregnancy, age has been shown to correlate positively with OA PSV-ratio, mainly because of an increase in PSV2,[38] and also with the OA resistance index, suggesting an increase in vascular resistance with age.[39] In view of the above evidence, controlling for these cofounders in our regression model, we ensured a robust independent association between the OA PSV-ratio and pre-eclampsia.

4.3 | Clinical implications

Hypertensive disorders of pregnancy encompass a spectrum of conditions with different risks of adverse pregnancy outcomes – pre-eclampsia being the most severe and GH being milder. Pre-eclampsia, compared with GH, has a 1.5 times higher risk of fetal death and three times higher risk for preterm and very preterm delivery, neonatal intensive care unit admission for 7 or more days and neonatal death.[40] Similarly, in CH, superimposed pre-eclampsia compared with uncomplicated CH has a three-fold increase in the risk of preterm and very preterm birth, admission to neonatal unit and fetal growth restriction.[41] It is known that planned delivery for pre-eclampsia reduces maternal morbidity, but this must be balanced against the complications of iatrogenic preterm delivery.[42,43] Therefore, being able to select women with potentially poorer outcomes may allow earlier delivery, while for the remaining ones it will guide decisions regarding hospital admission, antihypertensive medication administration and frequency and location of follow up.

Existing prediction models incorporate blood test results, which are not available instantaneously.[9,44] So far, the only point-of-care tests in practice are blood pressure, dipstick urinalysis for proteinuria and angiogenic factors. Severity of hypertension has been used as a method for triaging those with new-onset hypertension and for determining the need for antihypertensive therapy. However, validation studies of automated blood pressure devices have shown that they are subject to great variation, with underestimation of blood pressure with automated devices leading to underdiagnoses and undertreatment, particularly in overweight individuals.[12] Dipstick urinalysis has been shown to have a poor positive predictive value when testing for significant proteinuria in comparison with the reference standard of 24-hour urine collection,[14,45] and was shown to only detect severe pre-eclampsia in 36% of cases and is therefore not a reliable bedside test for pre-eclampsia.[14] More recently, anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 and serum placental growth factor (PlGF) have been advocated as a triage tool in women presenting with pregnancy hypertension.[46–49] However, these tests are still not widely used and definitely not in developing countries[16] because they are expensive, require complex laboratory processes, laboratory equipment and reagents and regular quality control testing. The 'Triage PlGF-test' is billed as a bedside test with a turnaround time of 15 minutes; however, this still requires laboratory equipment with a centrifuge.[47] The OA Doppler is a bedside test that can be performed in all units with an ultrasound machine and only requires a vascular probe used in general ultrasonography. Studies have shown low inter-operator variability with the OA[18,50] and as it is non-invasive, it is not affected by adiposity or a gravid uterus (unlike the uterine arteries) and is simple to measure, taking less than 5 minutes per patient, it therefore provides a promising method of point-of-care testing for those with suspected pre-eclampsia that warrants further exploration.

4.4 | Strengths and limitations

Strengths of this study include prospective data collection by only two trained sonographers (KL, EK), reducing measurement variability, the balance across the three hypertensive groups and strict protocols for disease monitoring, classification and outcome collection. Limitations

include the fact that not all women were treatment naive at their first presentation, as those with more severe hypertension would have started with treatment on an emergency out-of-hours visit to hospital. However, this was the reason for controlling for the use of antihypertensive medications in our regression model. Furthermore, a limitation of the study is lack of longitudinal data to clarify whether the disparity of OA PSV-ratio between women with and without pre-eclampsia pre-exists the disease or persists throughout gestation and the lack of data investigating the relationship between the OA PSV-ratio and anti-angiogenic markers.

4.5 | Conclusions

The OA PSV-ratio is significantly higher in women presenting with pre-eclampsia, compared with GH and CH, even after controlling for confounding variables. Further work is needed to clarify the clinical impact of its use in disease stratification and management protocols.

CONFLICT OF INTERESTS

None declared. Completed disclosure of interests form available to view online as supporting information.

AUTHOR CONTRIBUTIONS

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

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 22 January 2018 (REC reference 18/NI/0013, IRAS ID 237936).

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

Nikos A. Kametas https://orcid.org/0000-0002-7992-6038

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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