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Relationship between ophthalmic artery Doppler and maternal cardiovascular function

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CONTRIBUTION

What are the novel findings of this work?
This study of 2853 unselected pregnancies at 19–23 weeks' gestation found that the ophthalmic artery second to first peak of systolic velocity ratio (PSV ratio), which provides useful prediction of subsequent development of pre-eclampsia (PE), had very weak associations with indices of maternal cardiovascular function, but, in the subgroup that developed PE, there was a moderately strong association with left ventricular mass indexed for body surface area.

What are the clinical implications of this work?
The ophthalmic artery second systolic wave is a reflective one, and its increase, relative to the first systolic wave, is indicative of increased peripheral vascular resistance. The association between PSV ratio and left ventricular mass in women who develop PE suggests that cardiac structural changes are likely to be the result of the increase in peripheral vascular resistance.

ABSTRACT

Objective *In mid-gestation, the finding of an increase in the ophthalmic artery second to first peak of systolic velocity ratio (PSV ratio) provides useful prediction of subsequent development of pre-eclampsia (PE). The objective of this study of an unselected population at 19–23 weeks' gestation was to gain a better understanding of the factors that influence ophthalmic artery Doppler by examining the possible association between the PSV ratio and maternal cardiovascular function.*

Methods *This was a prospective observational study in women attending for a routine hospital visit at 19 + 1 to 23 + 3 weeks' gestation. This visit included assessment of flow velocity waveforms from the maternal ophthalmic arteries and assessment of maternal cardiovascular function. The following nine cardiovascular indices were examined: E/A ratio; E/e′ ratio; myocardial performance index; global longitudinal systolic strain; left ventricular ejection fraction; peripheral vascular resistance; left ventricular cardiac output; left ventricular mass indexed for body surface area; and mean arterial pressure. The ophthalmic artery PSV ratio and the nine cardiovascular indices were converted to either* $\log_{10}$ *multiples of the median (MoM) values or deviations from the median (deltas) values after adjustment for maternal characteristics and elements of medical history. Regression analysis was then used to examine the significance of the association between PSV ratio delta and MoM or delta values of each cardiovascular index in the total population and in the subgroup that developed PE.*

Results *The study population of 2853 pregnancies contained 76 (2.7%) that developed PE. In the total population, there were significant but weak associations between the PSV ratio and most of the cardiovascular indices, with* r*-values of* < 0.1*, except for mean arterial pressure with* $r = 0.178$*. In the subgroup that developed PE, a moderately strong association between the PSV ratio and left ventricular mass indexed for body surface area was noted* ($r = 0.308$).

Conclusions *The findings of this study suggest that Doppler assessment of PSV ratio in the ophthalmic artery provides information about peripheral vascular status. The increase in PSV ratio in women who develop PE is associated with increased afterload and an increase in left ventricular thickness.* © *2021 International Society of Ultrasound in Obstetrics and Gynecology.*

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INTRODUCTION

The ophthalmic artery, which is the first branch of the internal carotid artery, is an easily accessible vessel for Doppler assessment that provides information on the less accessible intracranial circulation. In women with pre-eclampsia (PE), compared to normotensive pregnant women, there is a decrease in impedance to flow and an increase in velocity in the waveforms from the ophthalmic arteries[1–12]. There is also evidence that an increase in velocity in this vessel precedes the development of PE and may be apparent from as early as the first trimester of pregnancy[13–16]. The waveform from the ophthalmic artery is characterized by two peaks in systole. In two recent screening studies, we examined 2853 unselected singleton pregnancies at 19–23 weeks' gestation and 2287 pregnancies at 35–37 weeks; we found that the ratio of the second to first peak of systolic velocity (PSV ratio) was increased in those pregnancies that subsequently developed PE and that the PSV ratio improved the prediction of PE provided by maternal factors alone and combinations of maternal factors with other biomarkers[15,16].

The objective of this study of an unselected population at 19–23 weeks' gestation was to gain a better understanding of the factors that influence ophthalmic artery Doppler by examining the possible association between the PSV ratio and maternal cardiovascular function.

METHODS

Study design and participants

This was a prospective observational study in women attending for a routine hospital visit at 19 + 1 to 23 + 3 weeks' gestation at King's College Hospital, London, UK, between August 2019 and April 2020. This visit included recording of maternal demographic characteristics and medical history, ultrasound examination for fetal anatomy and growth, assessment of maternal cardiovascular function and assessment of flow velocity waveforms from the maternal ophthalmic arteries. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[17,18]. 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 delivering a non-malformed liveborn or stillborn neonate. We excluded pregnancies with aneuploidy or major fetal abnormality. The same dataset was used in two previous publications on the prediction of PE from ophthalmic artery Doppler and cardiovascular function[15,19].

Ophthalmic artery Doppler

The mother was in the supine position for the routine 19 + 1 to 23 + 3-week scan, and, at the end of this procedure, a 7.5-MHz linear transducer (Canon Aplio i900 PLT-704SBT Linear Probe, Canon Medical Systems Europe BV, Zoetermeer, The Netherlands) 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 medial to the hypoechoic band representing the optic nerve[20]. Pulsed-wave Doppler was then used to record three to five similar waveforms; the angle of insonation was kept at $< 20°$, 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 set at 125 kHz. In order to minimize any potential adverse effects on the eyes, the duration of the examination was always less than 1 min and a special preset was used with significant reduction in output power and the maximum mechanical index was 0.4.

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 without technical difficulties in any of the patients. Waveforms were obtained in sequence from the right eye, left eye and again from the right and then left eye. The first and second peaks of systolic velocity were measured and the PSV ratio was calculated. The first peak of systolic velocity was obtained automatically by the machine and the second peak of systolic velocity was measured manually.

Maternal cardiovascular assessment

All participants were studied using two-dimensional and Doppler transthoracic echocardiography at rest in the left lateral decubitus position, and data were acquired during unforced expiration. The protocol included standard parasternal and apical views acquired using a Canon Aplio i900 scanner (Canon Medical Systems Europe BV) as per the American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines[21,22]. Echocardiography was performed by seven fetal medicine fellows who were trained in acquisition and analysis of echocardiograms. In a previous study, we reported excellent interobserver reproducibility of measurement of various cardiac indices[23].

The following nine cardiovascular indices were examined: E/A ratio; E/e′ ratio; myocardial performance index; global longitudinal systolic strain; left ventricular ejection fraction; peripheral vascular resistance; left ventricular cardiac output; left ventricular mass indexed for body surface area; and mean arterial pressure. Cardiac output was calculated from stroke volume (derived from the left ventricular outflow tract velocity time integral) multiplied by heart rate. Left atrial area was calculated in end-systole from the four-chamber view. Left ventricular mass was calculated with the Devereux formula using measurements of the anatomical M-mode applied in the parasternal long axis. The mitral peak early (E) and late (A) diastolic flow velocities were measured, and the E/A ratio was calculated. Pulsed tissue Doppler recordings

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were obtained at the septal and lateral aspects of the basal left ventricle at the junction with the mitral valve annulus in the apical four-chamber view. The E/e′ ratio was calculated using the mean value between the septal and lateral peak e′ waves. Speckle tracking was employed to assess global longitudinal systolic strain of the left ventricle. Mean arterial pressure was measured using validated automated devices and a standardized protocol[24].

Outcome measure

The outcome measure was delivery with PE. 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. This 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, 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 (for example, cerebral or visual symptoms); or pulmonary edema[25].

Statistical analysis

The ophthalmic artery PSV ratio and the nine cardiovascular indices were converted to either $\log_{10}$ multiples of the median (MoM) values or deviations from the median (deltas) values after adjustment for maternal characteristics and elements of medical history, as described previously[15,19]. Regression analysis was then used to

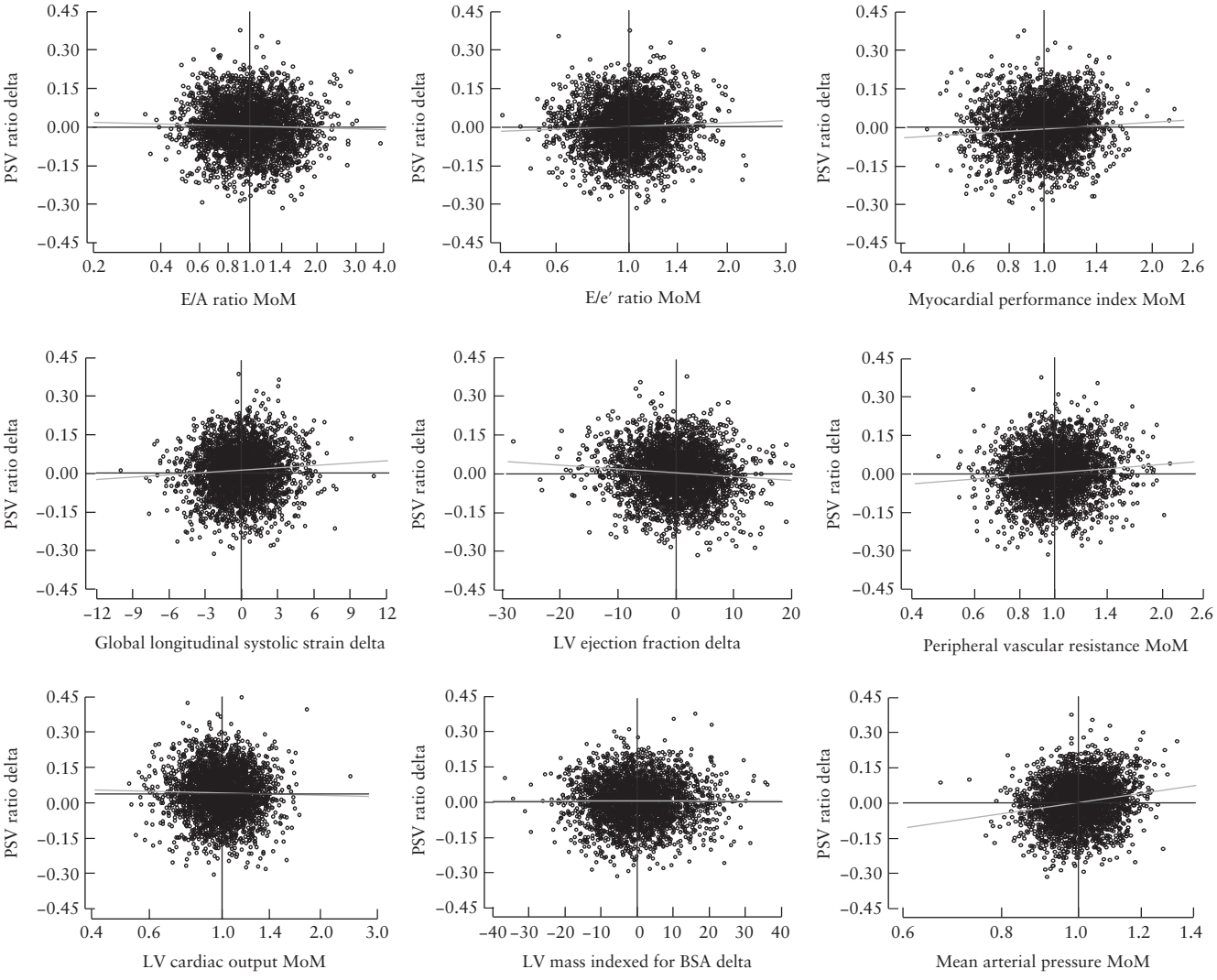

Figure 1 Relationship between ophthalmic artery second to first peak of systolic velocity ratio (PSV ratio) and cardiovascular indices in the total population. A, mitral peak late diastolic flow velocity; BSA, body surface area; E, mitral peak early diastolic flow velocity; e′, tissue Doppler early diastolic flow velocity; LV, left ventricular; MoM, multiples of the median.

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examine the significance of the association between PSV ratio delta and MoM or delta values of each cardiovascular index.

The statistical software package R was used for data analyses[26].

RESULTS

Study participants

The study population of 2853 pregnancies contained 76 (2.7%) that developed PE. Maternal and pregnancy characteristics of the study population are presented in our previous publications[15,19]; essentially, median gestational age was 21 weeks, median maternal age was 33 years, median body mass index was 25.5 kg/m^2, 74%, 14% and 12% of women were of white, black or other racial origin, respectively, conception was natural in 93% of cases and by assisted reproduction techniques in 7%, 54% of women were nulliparous and 46% were parous, 2% had chronic hypertension and 1% had diabetes mellitus.

Association between ophthalmic artery PSV ratio and cardiovascular indices

The association between ophthalmic artery PSV ratio delta and MoM or delta values of each of the nine cardiovascular indices in the total population and in the subgroup that developed PE are illustrated in Figures 1 and 2 and summarized in Table 1. In the total population,

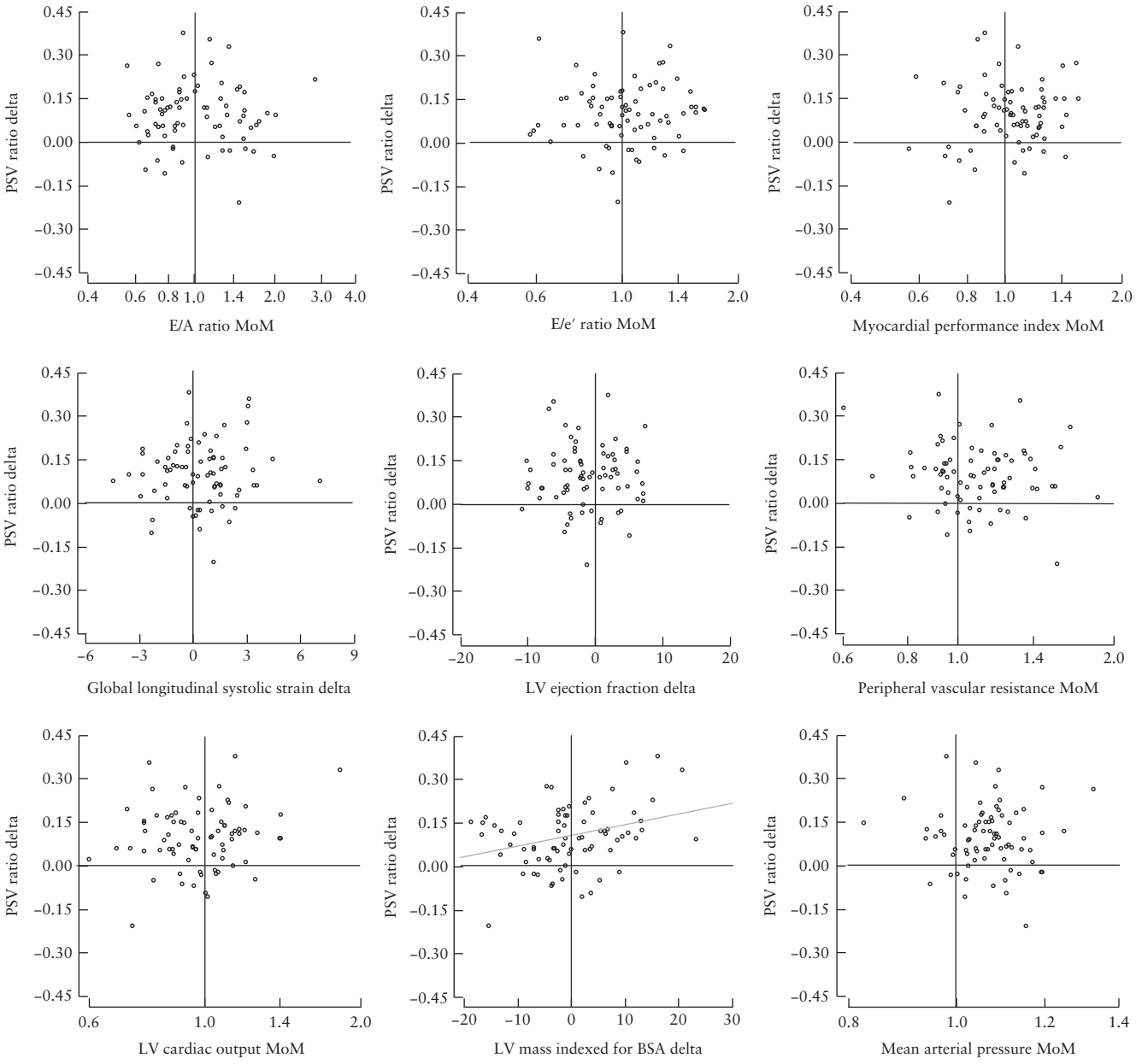

Figure 2 Relationship between ophthalmic artery second to first peak of systolic velocity ratio (PSV ratio) and cardiovascular indices in subgroup that developed pre-eclampsia. A, mitral peak late diastolic flow velocity; BSA, body surface area; E, mitral peak early diastolic flow velocity; e′, tissue Doppler early diastolic flow velocity; LV, left ventricular; MoM, multiples of the median.

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Table 1 Association between ophthalmic artery second to first peak of systolic velocity ratio and cardiovascular indices in total population and in subgroup that developed pre-eclampsia (PE)

Variable	*Correlation coefficient (95% CI)*
Total population	
E/A ratio MoM	−0.042 (−0.079 to −0.005)*
E/e′ ratio MoM	0.048 (0.012 to 0.085)*
MPI MoM	0.081 (0.045 to 0.118)*
GLS delta	0.072 (0.035 to 0.108)*
LV EF delta	−0.088 (−0.124 to −0.051)*
PVR MoM	0.099 (0.062 to 0.135)*
LV CO MoM	−0.024 (−0.061 to 0.013)
LV mass indexed for BSA delta	0.005 (−0.032 to 0.041)
MAP MoM	0.178 (0.143 to 0.214)*
Pre-eclampsia subgroup	
E/A ratio MoM	−0.018 (−0.242 to 0.208)
E/e′ ratio MoM	0.043 (−0.184 to 0.266)
MPI MoM	0.094 (−0.135 to 0.312)
GLS delta	0.085 (−0.143 to 0.305)
LV EF delta	−0.002 (−0.227 to 0.224)
PVR MoM	−0.136 (−0.350 to 0.093)
LV CO MoM	0.156 (−0.072 to 0.369)
LV mass indexed for BSA delta	0.308 (0.089 to 0.499)*
MAP MoM	−0.037 (−0.260 to 0.190)

*Significant association. A, mitral peak late diastolic flow velocity; BSA, body surface area; CO, cardiac output; E, mitral peak early diastolic flow velocity; e′, tissue Doppler early diastolic flow velocity; EF, ejection fraction; GLS, global longitudinal systolic strain; LV, left ventricular; MAP, mean arterial pressure; MoM, multiples of the median; MPI, myocardial performance index; PVR, peripheral vascular resistance.

there were significant but very weak associations between the PSV ratio and most of the cardiovascular indices. In the subgroup that developed PE, there was no significant association between the PSV ratio and any of the cardiovascular indices except left ventricular mass delta indexed for body surface area, for which there was a moderately strong association.

DISCUSSION

Principal findings of study

In this prospective screening study of an unselected population at 19–23 weeks' gestation, we assessed maternal ophthalmic artery Doppler and cardiovascular function. The data demonstrated that, first, in the total population, there were significant but very weak associations between the ophthalmic artery PSV ratio and cardiovascular indices, and, second, in pregnancies that subsequently developed PE, there was no significant association between the PSV ratio and any of the cardiovascular indices except left ventricular mass indexed for body surface area, for which there was a moderately strong association.

Interpretation of results and comparison with findings of previous studies

Several studies have reported consistently that, in women with established PE, compared to normotensive pregnancies, impedance to flow in the ophthalmic artery is reduced and systolic velocities are increased[1–12]. These findings suggest that PE is characterized by increased orbital and probably cerebral perfusion, and this is consistent with the hypothesis that PE is a hyperdynamic condition with increased cardiac output and compensatory vasodilation in both the cerebral and systemic circulation[3,6,27].

In our screening studies at 19–23 and 35–37 weeks' gestation, we found that, in pregnancies which subsequently developed PE, compared to those which remained normotensive, the ophthalmic artery pulsatility index was not significantly different but the PSV ratio was increased[15,16]. The first systolic component of an arterial waveform is produced by the contraction of the left ventricle, whereas the second systolic wave is a reflected one[28]. The observed increase in the velocity of the second compared to the first systolic waveform in the ophthalmic artery is not indicative of increased ophthalmic or cerebral perfusion but rather of increased peripheral resistance. This is consistent with our finding that the strongest associations of the PSV ratio were with mean arterial pressure and peripheral artery resistance.

Our finding that, at 20 weeks' gestation, in women who subsequently developed PE, there was a significant association between ophthalmic artery Doppler and left ventricular mass but no other indices of cardiovascular function, suggests that it is unlikely that higher blood pressure and increased PSV ratio are due to changes in cardiac function. We have reported previously that, at 20 weeks' gestation in women who subsequently developed PE, compared to those who remained normotensive, there were some differences in cardiovascular indices, but, after adjustment for maternal demographic characteristics and medical history, the only cardiovascular index that was affected significantly was peripheral vascular resistance[19]. We suggest that increased peripheral vascular resistance and changes in vascular tone are the primary changes in women with PE and these drive the cardiac alterations. As cardiac afterload increases, the structure of the heart is modified by increasing left ventricular thickness to maintain cardiac output; however, with prolonged exposure, functional cardiac alterations occur, with a decrease in diastolic and systolic indices, as demonstrated in our previous screening study at 35–37 weeks' gestation[29].

Strengths and limitations

The main strengths of this study are, first, prospective examination of a large unselected population of pregnant women attending for a routine ultrasound examination in mid-gestation, second, use of standardized techniques for maternal ophthalmic artery and cardiovascular assessment by appropriately trained research fellows, and, third, adjustment of the ophthalmic artery and cardiovascular indices for maternal characteristics and elements from the medical history known to be associated with an increased risk for PE. The main limitation of our

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study is the cross-sectional design which does not permit temporal associations to be evaluated.

Conclusions

The findings of our study suggest that assessment of the PSV ratio in the ophthalmic artery in pregnancy can provide useful information about peripheral vascular resistance. Considering that the PSV ratio in women who develop PE was associated with left ventricular mass, further studies are needed to demonstrate whether monitoring of the PSV ratio can also provide information about cardiac adaptations during pregnancy.

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