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Ophthalmic artery Doppler at 35–37 weeks' gestation in pregnancies with small or growth-restricted fetuses

S. ABDEL AZIM[1,2], M. SARNO[1,3], A. WRIGHT[4], N. VIEIRA[1], M. CHARAKIDA[1,5] and K. H. NICOLAIDES[1]

[1]*Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK;* [2]*Department of Obstetrics and Gynaecology, Medical University of Innsbruck, Innsbruck, Austria;* [3]*Department of Obstetrics and Gynecology, Federal University of Bahia (UFBA), Salvador-Bahia, Brazil;* [4]*Institute of Health Research, University of Exeter, Exeter, UK;* [5]*School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK*

KEYWORDS: Doppler; ophthalmic artery; small-for-gestational age

CONTRIBUTION

What are the novel findings of this work?
In the third trimester, women with small-for-gestational-age (SGA) fetuses in the absence of hypertensive disorders have increased peak systolic velocity (PSV) ratio in the ophthalmic artery on Doppler, mildly increased mean arterial pressure and decreased serum placental growth factor compared to women with uncomplicated pregnancy. Although the maternal arterial changes resemble those seen in hypertensive disorders of pregnancy, they differ in magnitude and physiology. Ophthalmic artery waveform analysis revealed that the predominant feature in pregnancies complicated by SGA is a reduction in the first systolic wave, whereas, in those with hypertensive disorders, there is an increase in the second systolic wave. There is a linear (inverse) association between PSV ratio and birth-weight *Z*-score in non-hypertensive pregnancies.

What are the clinical implications of this work?
The ophthalmic artery PSV ratio and derivative waveforms can provide information about maternal hemodynamics. The linear association between PSV ratio and birth-weight *Z*-score suggests the presence of a continuous physiological relationship between fetal size and cardiovascular response rather than a dichotomous relationship between high peripheral resistance and low cardiac output in small compared with non-small fetuses.

ABSTRACT

Objectives *First, to compare the ophthalmic artery peak systolic velocity (PSV) ratio at 35–37 weeks' gestation among women who delivered small-for-gestational-age (SGA) or growth-restricted (FGR) neonates in the absence of hypertensive disorders, women who developed pre-eclampsia (PE) or gestational hypertension (GH) and those without SGA, FGR, PE or GH. Second, to examine the association of PSV ratio with placental growth factor (PlGF) and mean arterial pressure (MAP). Third, to assess the associations of PSV ratio, PlGF and MAP with birth-weight Z-score and percentile.*

Methods *This was a prospective observational study in 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, and measurement of maternal ophthalmic artery PSV ratio, first (PSV1) and second (PSV2) peaks of systolic velocity, MAP and serum PlGF. The values of PSV ratio, MAP and PlGF were converted to multiples of the median (MoM) or delta values, and the median MoM or delta of these variables in the SGA, FGR, PE and GH groups were compared with those in the unaffected group. Regression analysis was used to examine the relationship of PSV ratio delta, PlGF MoM and MAP MoM with birth-weight Z-score after exclusion of PE and GH cases. Regression analysis was also used to examine the association of PSV ratio delta with $\log_{10}$ PlGF MoM and $\log_{10}$ MAP MoM.*

Results *The study population included 2287 pregnancies, of which 1954 (85.4%) were not affected by FGR, SGA, PE or GH, 49 (2.1%) were complicated by FGR in the absence of PE or GH, 160 (7.0%) had SGA in the absence of FGR, PE or GH, 60 (2.6%) had PE and 64 (2.8%) had GH. Compared with unaffected pregnancies, in both the FGR and SGA groups, the means of PSV ratio delta (0.042 (95% CI, 0.007–0.076) and 0.032 (95% CI, 0.016–0.049), respectively) and MAP*

Correspondence to: Prof. K. H. Nicolaides, Fetal Medicine Research Institute, King's College Hospital, 16–20 Windsor Walk, Denmark Hill, London SE5 8BB, UK (e-mail: kypros@fetalmedicine.com)

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MoM (1.028 (95% CI, 1.006–1.050) and 1.048 (95% CI, 1.035–1.060), respectively) were increased, while the mean of PlGF MoM was decreased (0.495 (95% CI, 0.393–0.622) and 0.648 (95% CI, 0.562–0.747), respectively). However, the magnitude of these changes was smaller than in the PE and GH groups. Ophthalmic artery waveform analysis revealed that the predominant feature of pregnancies complicated by SGA in the absence of hypertensive disorders was a reduction in PSV1, whereas, in those with hypertensive disorders, there was an increase in PSV2. In non-hypertensive pregnancies, there were linear inverse associations of PSV ratio delta and MAP MoM with birth-weight Z-score, with increased values in small neonates and decreased values in large neonates. There was a quadratic relationship between PlGF MoM and birth-weight Z-score, with low PlGF levels in small neonates and high PlGF levels in large neonates. There was a significant correlation of ophthalmic artery PSV ratio delta with both log_{10} MAP MoM (0.124 (95% CI, 0.069–0.178)) and log_{10} PlGF MoM (−0.238 (95% CI, −0.289 to −0.185)).

***Conclusion** Assuming that the ophthalmic artery PSV ratio is a reflection of the interplay between cardiac output and peripheral vascular resistance, the linear association between PSV ratio and birth-weight Z-score in non-hypertensive pregnancies suggests the presence of a continuous physiological relationship between fetal size and cardiovascular response rather than a dichotomous relationship between high peripheral resistance and low cardiac output in small compared with non-small fetuses.*

INTRODUCTION

The ophthalmic artery, which is the first branch of the internal carotid artery, has a Doppler velocity waveform with 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[1,2]. In this way, PSV2 is most influenced by peripheral arterial compliance and resistance, whilst PSV1 is more affected by cardiac output. Therefore, an increase in the ratio of PSV2 to PSV1 (PSV ratio) could represent an increase in peripheral vascular resistance and/or a reduction in cardiac output[3]. The association between ophthalmic artery PSV ratio and peripheral vascular resistance is supported by the findings of a study in hypertensive pregnancies, which reported a high correlation between PSV ratio and mean arterial pressure (MAP) and a decrease of both MAP and PSV ratio after the administration of antihypertensive drugs, such as nifedipine modified release and labetalol, which reduce peripheral resistance[4]. In two recent prospective observational studies, we examined 2853 unselected pregnancies at 19–23 weeks' gestation and 2287 unselected pregnancies at 35–37 weeks[5,6]. In both study groups, we found that PSV ratio was increased in pregnancies that subsequently developed pre-eclampsia (PE) and that it improved the prediction of PE provided by maternal factors alone and by combinations of maternal factors with other biomarkers[5,6].

Pregnancies complicated by small-for-gestational age (SGA) at birth in the absence of hypertensive disorders share features with PE, including impaired placentation and endothelial dysfunction, and are associated with an increased long-term risk of development of maternal cardiovascular disease[7–12]. There are limited data on ophthalmic artery Doppler in SGA pregnancies. A cross-sectional study of 60 pregnancies with SGA fetuses at 32–40 weeks' gestation and 60 normal controls reported that maternal ophthalmic artery PSV ratio in the SGA group was significantly higher than in the control group[13]. A prospective observational study involving 499 singleton pregnancies at 11–14 weeks' gestation reported that PSV ratio in the group of 27 women who delivered SGA neonates was slightly higher than in the non-SGA group[14].

The objectives of this study on 2287 unselected pregnancies at 35–37 weeks' gestation, which have been examined previously[6], were, first, to compare the ophthalmic artery PSV ratio among women who delivered SGA or growth-restricted (FGR) neonates in the absence of hypertensive disorders, women who developed PE or gestational hypertension (GH) and those unaffected by SGA, FGR, PE or GH, second, to examine the association between PSV ratio and the established biomarkers of PE, placental growth factor (PlGF) and MAP, and, third, to examine the association of PSV ratio, PlGF and MAP with birth-weight *Z*-score or percentile.

METHODS

Study design and participants

This was a prospective observational study in women attending for a routine hospital visit at 35 + 0 to 36 + 6 weeks' gestation at King's College Hospital, London, UK, between June 2019 and March 2020. This visit included, first, recording of maternal demographic characteristics and medical history, second, ultrasound examination for fetal anatomy and growth, third, two recordings of flow velocity waveforms from the left and right maternal ophthalmic arteries and calculating the average of the four measurements for PSV1, PSV2 and PSV ratio[15], fourth, measurement of MAP by validated automated devices following a standardized protocol[16], fifth, color flow imaging of the left and right uterine arteries (UtA) by transabdominal ultrasound and measurement of mean UtA pulsatility index (PI)[17], color flow imaging of the umbilical artery (UA) and fetal middle cerebral artery (MCA) and measurement of UA-PI and MCA-PI[18] and, sixth, measurement of serum concentration of

PlGF in pg/mL by 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[19,20]. 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 delivering a non-malformed liveborn neonate. We excluded pregnancies with aneuploidy or major fetal abnormalities and those with PE at the time of screening.

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. Outcome measures were delivery with SGA, FGR, PE or GH. Diagnosis of SGA in the absence of hypertensive disorders was made if birth weight was $< 10^{th}$ percentile of the The Fetal Medicine Foundation fetal and neonatal population weight charts[21] in the absence of PE or GH and in the presence of UtA-PI $\leq 95^{th}$ percentile, UA-PI $\leq 95^{th}$ percentile and MCA-PI $\geq 5^{th}$ percentile. Diagnosis of FGR in the absence of hypertensive disorders was made if birth weight was $< 10^{th}$ percentile in the absence of PE or GH and in the presence of UtA-PI $> 95^{th}$ percentile, UA-PI $> 95^{th}$ percentile or MCA-PI $< 5^{th}$ percentile. Diagnosis of GH was based on the finding of 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). Diagnosis of PE was based on the finding of new onset hypertension or chronic hypertension and at least one of the following: proteinuria (≥ 300 mg/24 h or protein-to-creatinine ratio ≥ 30 mg/mmol or $\geq 2+$ 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. Student's *t*-test and chi-square test or Fisher's exact test were used for comparing continuous and categorical data, respectively, between outcome groups.

The measured values of biomarkers were converted to multiples of the median (MoM) or delta to remove the effects of characteristics such as gestational age, weight, race, method of conception, medical conditions, obstetric history and characteristics of the instrument used for the measurement. The means with 95% CIs of ophthalmic artery PSV ratio delta, PSV1 MoM, PSV2 MoM, PlGF MoM and MAP MoM in SGA, FGR, PE and GH groups were compared with those in the unaffected group using *t*-test. Regression analysis was used to examine the relationship of PSV ratio delta, PlGF MoM and MAP MoM with birth-weight *Z*-score. Regression analysis was also used to examine the association of PSV ratio delta with $\log_{10}$ PlGF MoM and $\log_{10}$ MAP MoM. The statistical software package R was used for data analysis[23].

RESULTS

Study participants

The study population included 2287 pregnancies, of which 1954 (85.4%) were not affected by FGR, SGA, PE or GH, 49 (2.1%) were complicated by FGR in the absence of PE or GH, 160 (7.0%) had SGA in the absence of FGR, PE or GH, 60 (2.6%) had PE and 64 (2.8%) had GH. Maternal and pregnancy characteristics of the study population are summarized in Table 1. In the SGA group, compared with unaffected pregnancies, there was a lower median maternal weight and body mass index, and higher proportions of non-white and nulliparous women. In the PE and GH groups, compared with unaffected pregnancies, there was a higher median maternal weight and body mass index, and a higher rate of nulliparity and previous PE.

Distribution of biomarkers in SGA, FGR, PE, GH and unaffected pregnancies

The median (IQR) of PSV ratio delta and PSV1, PSV2, PlGF and MAP MoMs according to study group is shown in Figure 1 and the mean (95% CI) of each group compared with unaffected pregnancies is shown in Table 2. In both FGR and SGA groups in the absence of hypertensive disorders, the PSV ratio delta and MAP MoM were increased and PlGF MoM was decreased compared with unaffected pregnancies. However, the magnitude of these changes was smaller than in PE and GH groups. In addition, in the SGA group, PSV1 MoM was reduced, whereas, in pregnancies complicated by GH, both PSV1 MoM and PSV2 MoM were increased (Table 2).

The associations of PSV ratio delta, PlGF MoM and MAP MoM with birth-weight *Z*-score or percentile in all pregnancies after exclusion of PE and GH are shown in Figure 2 and the fitted regression models are presented in Table 3. There was a linear inverse association of PSV ratio delta and MAP MoM with birth-weight *Z*-score, with increased values in small neonates and decreased values in large neonates. There was a quadratic relationship between PlGF MoM and birth-weight *Z*-score, with lower PlGF levels in small neonates and higher PlGF levels in large neonates. There was a significant correlation of ophthalmic artery PSV ratio delta with $\log_{10}$ MAP MoM (0.124 (95% CI, 0.069–0.178)) and $\log_{10}$ PlGF MoM (−0.238 (95% CI, −0.289 to −0.185)).

Table 1 Maternal and pregnancy characteristics of the study population

Characteristic	*Unaffected* (n = *1954*)	*FGR** (n = *49*)	*SGA (no FGR)** (n = *160*)	*PE* (n = *60*)	*GH* (n = *64*)
Age (years)	33.6 (30.6–36.8)	31.0 (28.4–36.5)	33.9 (31.0–36.8)	34.0 (30.3–37.0)	34.6 (30.8–38.2)
Weight (kg)	78.0 (71.0–87.5)	79.7 (68.0–88.2)	73.0 (65.3–81.9)†	85.5 (76.0–93.4)†	83.7 (71.4–101.7)†
Height (cm)	167 (163–171)	165 (162–168)	164 (159–168)†	166 (163–171)	166 (163–168)
Body mass index (kg/m^2)	28.2 (25.7–31.3)	29.2 (25.4–31.8)	26.9 (24.6–30.5)†	30.6 (27.7–33.6)†	29.7 (26.5–36.5)†
Gestational age (weeks)	35.7 (35.6–36.0)	35.9 (35.4–36.0)	35.7 (35.4–36.0)	35.8 (35.6–36.0)	35.9 (35.6–36.1)
Racial origin					
White	1483 (75.9)	32 (65.3)	108 (67.5)†	45 (75.0)	48 (75.0)
Black	228 (11.7)	11 (22.4)	24 (15.0)	10 (16.7)	13 (20.3)
South Asian	104 (5.3)	4 (8.2)	17 (10.6)	1 (1.7)	0 (0)
East Asian	70 (3.6)	0 (0.0)	4 (2.5)	2 (3.3)	1 (1.6)
Mixed	69 (3.5)	2 (4.1)	7 (4.4)	2 (3.3)	2 (3.1)
Medical history					
Chronic hypertension	25 (1.3)	1 (2.0)	7 (4.4)	2 (3.3)	64 (100)
Diabetes mellitus	25 (1.3)	0 (0)	2 (1.3)	3 (5.0)	2 (3.1)
Smoker	7 (0.4)	0 (0)	2 (1.3)	1 (1.7)	0 (0)
Family history of PE	59 (3.0)	1 (2.0)	8 (5.0)	5 (8.3)	3 (4.7)
Method of conception					
Spontaneous	1853 (94.8)	46 (93.9)	148 (92.5)	54 (90.0)	58 (90.6)
In-vitro fertilization	94 (4.8)	3 (6.1)	10 (6.3)	6 (10.0)	6 (9.4)
Ovulation drugs	7 (0.4)	0 (0)	2 (1.3)	0 (0)	0 (0)
Parity					
Nulliparous	1003 (51.3)	29 (59.2)	104 (65.0)†	49 (81.7)†	39 (60.9)†
Parous, no previous PE	916 (46.9)	18 (36.7)	52 (32.5)	9 (15.0)	20 (31.3)
Parous, previous PE	35 (1.8)	2 (4.1)	4 (2.5)	2 (3.3)†	5 (7.8)†
Interpregnancy interval (years)	2.4 (1.6–4.1)	2.6 (1.4–5.0)	2.9 (1.9–6.7)	3.2 (2.0–5.6)	3.2 (2.2–5.2)

Data are given as median (interquartile range) or *n* (%). *In non-hypertensive pregnancies. †Significant difference compared with unaffected pregnancies. Outcome groups were compared using chi-square or Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. FGR, fetal growth restriction; GH, gestational hypertension; PE, pre-eclampsia; SGA, small-for-gestational age.

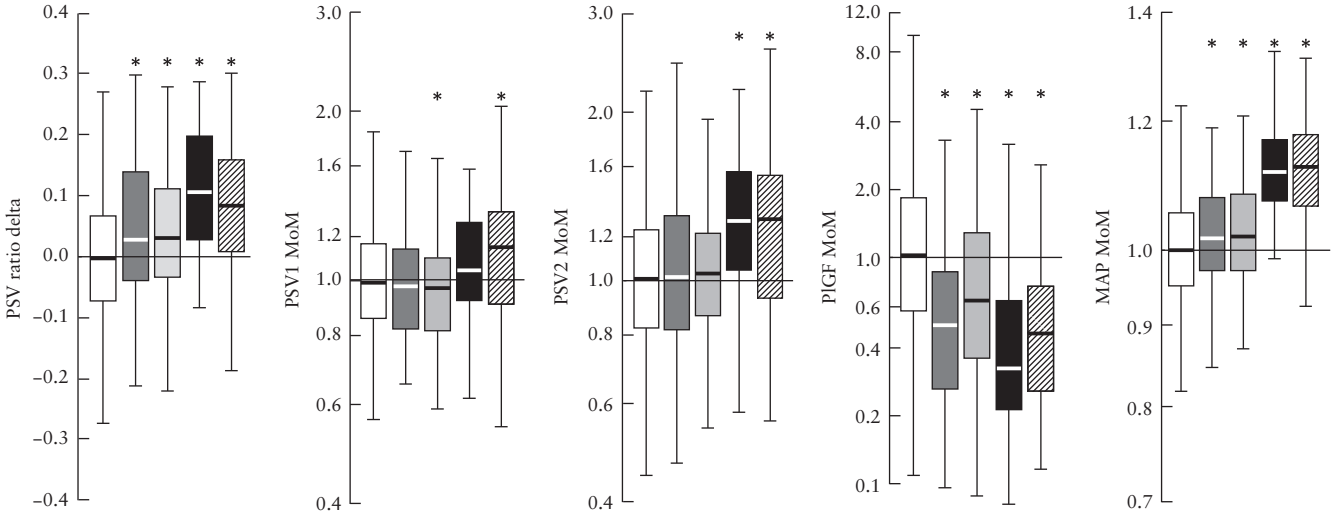

Figure 1 Box-and-whiskers plots of ophthalmic artery peak systolic velocity (PSV) ratio delta, first (PSV1) and second (PSV2) systolic velocities multiples of the median (MoM), placental growth factor (PlGF) MoM and mean arterial pressure (MAP) MoM in unaffected pregnancies (□), non-hypertensive pregnancies complicated by fetal growth restriction (FGR) (■) or by small-for-gestational age without FGR (▩) and pregnancies with pre-eclampsia (■) or gestational hypertension (▨). Boxes are median and interquartile range and whiskers are range. *Significant difference compared with unaffected pregnancies.

DISCUSSION

Principal findings of this study

This prospective non-interventional study of women attending for a routine hospital visit at 35–37 weeks has four main findings. First, in non-hypertensive pregnancies delivering SGA or FGR neonates, the ophthalmic artery PSV ratio and MAP are increased and serum PlGF is decreased compared with unaffected pregnancies, but the magnitude of these changes is smaller than in pregnancies complicated by PE or GH. Second, the predominant feature in non-hypertensive pregnancies delivering SGA or FGR neonates is a reduction in PSV1, whereas, in pregnancies complicated by PE or GH, the main feature

Table 2 Comparison of mean (95% CI) ophthalmic artery (OA) Doppler measurements, placental growth factor (PlGF) multiples of the median (MoM) and mean arterial pressure (MAP) MoM between adverse outcome groups and the unaffected group

Parameter	*Unaffected*	*FGR or SGA*	*FGR*	*SGA (no FGR)*	*PE*	*GH*
OA PSV ratio delta	0.000 (−0.005 to 0.005)	0.035 (0.020–0.050)*	0.042 (0.007–0.076)*	0.032 (0.016–0.049)*	0.114 (0.084–0.144)*	0.078 (0.051–0.106)*
OA PSV1 MoM	1.000 (0.990–1.010)	0.958 (0.928–0.988)*	0.971 (0.904–1.043)	0.954 (0.923–0.986)*	1.043 (0.983–1.107)	1.084 (1.024–1.147)*
OA PSV2 MoM	1.000 (0.987–1.013)	1.016 (0.979–1.054)	1.035 (0.935–1.146)	1.010 (0.972–1.051)	1.263 (1.172–1.360)*	1.224 (1.131–1.326)*
PlGF MoM	1.000 (0.964–1.038)	0.608 (0.537–0.689)*	0.495 (0.393–0.622)*	0.648 (0.562–0.747)*	0.366 (0.306–0.438)*	0.459 (0.376–0.559)*
MAP MoM	1.000 (0.997–1.003)	1.043 (1.032–1.054)*	1.028 (1.006–1.050)*	1.048 (1.035–1.060)*	1.122 (1.105–1.140)*	1.124 (1.104–1.144)*

*Significant difference compared with the unaffected group. FGR, fetal growth restriction; GH, gestational hypertension; PE, pre-eclampsia; PSV, peak systolic velocity; PSV1, first peak of systolic velocity; PSV2, second peak of systolic velocity; SGA, small-for-gestational age.

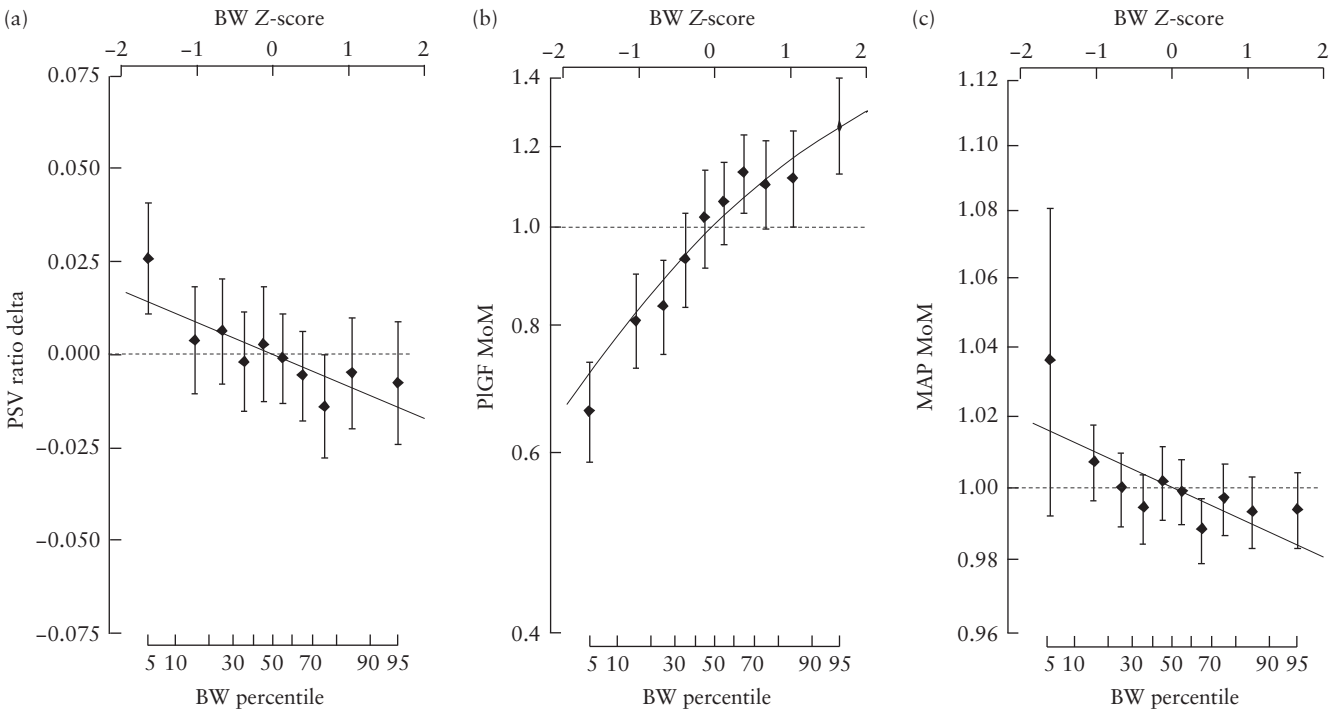

Figure 2 Association of ophthalmic artery peak systolic velocity (PSV) ratio delta (a), placental growth factor (PlGF) multiples of the median (MoM) (b) and mean arterial pressure (MAP) MoM (c) with birth-weight (BW) *Z*-score or percentile in non-hypertensive pregnancies.

is an increase in PSV2. Third, there is a significant correlation of ophthalmic artery PSV ratio with both MAP and PlGF. These findings highlight the presence of a close inter-relationship between placental function, systemic perfusion and maternal ophthalmic artery Doppler waveform. Fourth, there are linear (inverse) associations of PSV ratio delta and MAP MoM with birth-weight *Z*-score, whereby the values are increased in small neonates and decreased in large neonates, and a quadratic relationship between PlGF MoM and birth-weight *Z*-score, with low PlGF levels in small neonates and high PlGF levels in large neonates.

Interpretation of results

Pregnancies complicated by hypertensive disorders and those with a SGA fetus in the absence of hypertensive disorders are associated with suboptimal placentation[24,25], and this is reflected by our finding of reduced serum PlGF in these conditions. However, our study also highlights important differences between SGA and hypertensive disorders in maternal hemodynamic response. Although we did not perform direct assessment of cardiac output and peripheral vascular resistance, our data suggest that the ophthalmic artery PSV ratio can be used as an indirect marker of both. In both SGA and PE, the PSV ratio was increased, albeit to a greater degree in the latter; however, the difference in the component waves of PSV1 and PSV2 suggests that the predominant feature in SGA is reduced cardiac output, whereas the main feature of PE is increased peripheral vascular resistance. The finding of a linear relationship between birth-weight *Z*-score and PSV ratio is consistent with the results of a previous study in uncomplicated pregnancies, in which

Table 3 Regression models summarizing the relationship of ophthalmic artery peak systolic velocity (PSV) ratio, placental growth factor (PlGF) and mean arterial pressure (MAP) with birth-weight *Z*-score, in study population after exclusion of pregnancies with hypertensive disorders

	Estimate (95% CI)	P
PSV ratio delta		
Intercept	0.43764 (0.29319 to 0.58209)	< 0.0001
Birth-weight *Z*-score	−0.00872 (−0.01331 to −0.00414)	0.0002
GA at delivery (in weeks)	−0.01090 (−0.01452 to −0.00728)	< 0.0001
PlGF MoM		
Intercept	−1.92574 (−2.39866 to −1.45282)	< 0.0001
Birth-weight *Z*-score	0.07420 (0.05923 to 0.08917)	< 0.0001
(Birth-weight *Z*-score)^2	−0.01012 (−0.02012 to −0.00012)	0.047
GA at delivery (in weeks)	0.04807 (0.03625 to 0.05989)	< 0.0001
MAP MoM		
Intercept	0.11786 (0.04567 to 0.19005)	0.001
Birth-weight *Z*-score	−0.00424 (−0.00653 to −0.00195)	0.0003
GA at delivery (in weeks)	−0.00291 (−0.00472 to −0.00110)	0.002

GA, gestational age; MoM, multiples of the median.

we reported that cardiac output decreased and peripheral vascular resistance increased linearly with decreasing fetal weight[26]. Our finding of increased MAP not only in pregnancies with hypertensive disorders but also in those with SGA/FGR fetuses in the absence of hypertensive disorders is consistent with previous reports[27,28] and may explain the increased long-term risk of developing cardiovascular disease in affected women[10–12].

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[29–39], second, the 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 PlGF as a reflection of placentation and, fourth, presentation of results not only for pregnancies with SGA/FGR fetuses in the absence of hypertensive disorders but also for pregnancies with PE or GH to allow comparison between different placental pathologies.

We have demonstrated that the PSV ratio is reflective of maternal hemodynamic response, but we did not perform direct assessment of maternal cardiac output and peripheral vascular resistance to confirm our hypothesis. In addition, all our measurements were performed late in gestation; therefore, our observations may be reflective of the changes seen in term PE and late SGA but not representative of the physiology seen in early pregnancy or mid-gestation in association with early SGA or early PE.

Conclusions

Assuming that the ophthalmic artery PSV ratio is a reflection of the interplay between cardiac output and peripheral vascular resistance, the linear (inverse) association between the PSV ratio and birth-weight *Z*-score in non-hypertensive pregnancies suggests the presence of a continuous physiological relationship between fetal size and cardiovascular response rather than a dichotomous relationship between high peripheral resistance and low cardiac output in pregnancies with small compared with non-small fetuses.

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