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Changes in ophthalmic artery Doppler during acute blood-pressure control in hypertensive pregnant women

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KEYWORDS: blood-pressure control; hemodynamics; hypertension in pregnancy; ophthalmic artery; pre-eclampsia screening

CONTRIBUTION

What are the novel findings of this work?
Acute treatment of hypertension in pregnancy to achieve a blood pressure of < 140/90 leads to a significant reduction in the ophthalmic artery peak systolic velocity (PSV) ratio. The association between PSV ratio and mean arterial pressure in hypertensive women is mostly attributed to a significant relationship between PSV ratio and diastolic blood pressure.

What are the clinical implications of this work?
Ophthalmic artery Doppler could be used to tailor antihypertensive therapy in pregnant women in order to ensure that there is no disruption to cerebrovascular autoregulation.

ABSTRACT

Objective *To examine the changes in ophthalmic artery Doppler indices and their association with changes in mean arterial blood pressure (MAP) and systolic (SBP) and diastolic (DBP) blood pressure, following acute antihypertensive treatment in women with hypertensive disorders of pregnancy presenting with high blood pressure.*

Methods *This was a prospective cohort study of 31 pregnant women presenting at 30 + 0 to 39 + 6 weeks' gestation for management of their hypertension. Paired maternal blood-pressure and ophthalmic-artery-Doppler measurements were performed prior to and at 30 min and 60 min after starting antihypertensive medication. In patients who did not achieve blood-pressure control (i.e. when blood pressure was < 140/90 mmHg) by 60 min, paired readings were continued up to 120 min. If blood-pressure control was still not achieved at that point, patients were admitted to hospital. Univariate linear regression was performed to determine the association of ophthalmic artery peak systolic velocity (PSV) ratio with SBP, DBP and MAP before treatment and after blood-pressure control. The longitudinal changes in MAP, SBP, DBP and PSV ratio from pretreatment to 30 min and 60 min after commencement of antihypertensives were examined by repeated measure, multilevel, linear mixed-effects analysis.*

Results *Antihypertensive treatment was associated with a decrease in SBP, DBP, MAP and PSV ratio. At 60 min following antihypertensive treatment, the decrease in SBP, DBP, MAP and PSV ratio was 12.1 mmHg (95% CI, 9.0–15.1 mmHg;* $P < 0.0001$*), 9.1 mmHg (95% CI, 6.5–11.5 mmHg;* $P < 0.0001$*), 10.0 mmHg (95% CI, 7.6–12.4 mmHg;* $P < 0.0001$*) and 0.07 (95% CI, 0.03–0.11 mmHg;* $P < 0.001$*), respectively. From the total cohort, 20 (64.5%) women had achieved blood-pressure control at 60 min and another seven (22.6%) by 120 min from commencement of antihypertensive treatment. Four (12.9%) women did not achieve blood-pressure control during this period and were admitted to hospital. The relationship between PSV ratio and SBP, DBP and MAP was assessed before treatment* ($n = 31$) *and at the point of blood-pressure control in women in whom this was achieved by 120 min* ($n = 27$)*. Prior to treatment, there was a significant association between PSV ratio and MAP* ($P < 0.0001$, $R^2 = 0.39$)*. This was primarily due to the association of PSV ratio with DBP* ($P < 0.0001$, $R^2 = 0.39$) *and less so due to its association with SBP* ($P = 0.02$, $R^2 = 0.16$)*. At the point of achieving blood-pressure control, there was no significant association between PSV ratio and MAP* ($P = 0.7$)*, DBP* ($P = 0.5$) *or SBP* ($P = 0.7$)*.*

Conclusions *Acute blood-pressure control in pregnancy is associated with a concomitant reduction in blood pressure and ophthalmic artery PSV ratio. In hypertensive pregnant women, there is a significant association of PSV ratio with MAP, SBP and DBP, which disappears after*

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blood pressure is reduced to < 140/90 mmHg following antihypertensive treatment. © *2021 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Outside of pregnancy, hypertension is one of the main determinants of stroke and dementia[1]. Increasing peripheral blood pressure has short- and long-term detrimental effects on the brain by impairing cerebral autoregulation[2]. This realization led to intracerebral hemodynamics being utilized to assess not only cerebral autoregulation in cardiovascular disease[3–5] but also the severity of peripheral vascular disease[6–8] and response to antihypertensive treatment[2,9]. In the previous two decades, the anterior and the middle cerebral artery (MCA) were the main vessels interrogated in cardiovascular research[10]. More recently, the ophthalmic artery, which is the first branch of the internal carotid artery, has attracted attention because it is an easily accessible vessel that provides non-invasive and reproducible information on intracerebral hemodynamics[11,12]. There are three components to the arterial waveform from the ophthalmic artery: first, the systolic wave comprising the first (PSV1) and second (PSV2) peaks of systolic velocity; second, a dicrotic notch; and third, a diastolic wave (Figure 1). The ratio between PSV2 and PSV1 (PSV ratio) has been suggested to be the primary indicator of vascular changes associated with orbital hyperperfusion[13].

In pregnancy, there is evidence that development of pre-eclampsia (PE) is preceded by alterations in the ophthalmic artery waveform[14]. Two recent screening studies examined 2853 unselected singleton pregnancies at 19–23 weeks and 2287 pregnancies at 35–37 weeks, respectively, and found that the PSV ratio was increased in pregnancies that subsequently developed PE and that the PSV ratio improved the prediction of PE provided by maternal factors alone or in combination with other biomarkers[15,16]. However, although there are emerging data incorporating ophthalmic artery Doppler in screening for PE, there is no current literature on the hemodynamic changes of the ophthalmic artery with acute treatment of blood pressure in hypertensive pregnant women.

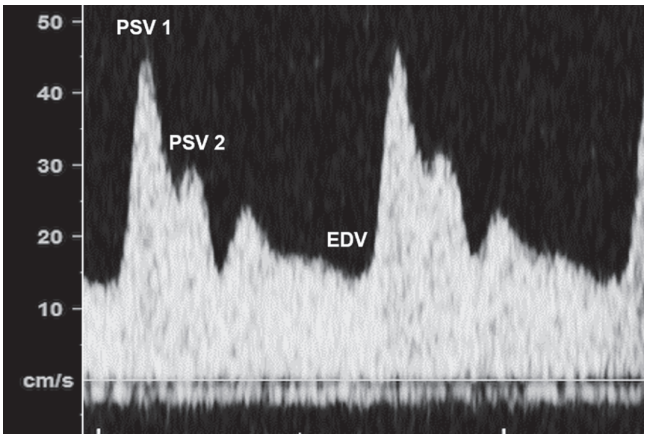

Figure 1 Flow velocity waveform from ophthalmic artery obtained by pulsed-wave Doppler, showing first (PSV1) and second (PSV2) peaks of systolic velocity and end-diastolic velocity (EDV).

The objective of this study in women with hypertensive disorders of pregnancy presenting with high blood pressure, was to examine the changes in ophthalmic artery Doppler indices and their association with changes in mean arterial blood pressure (MAP) and systolic (SBP) and diastolic (DBP) blood pressure, following acute antihypertensive treatment.

METHODS

Study population

This was a prospective cohort study of 31 pregnant women presenting at 30 + 0 to 39 + 6 weeks' gestation to a dedicated maternal–fetal medicine clinic at King's College Hospital, London, UK, between July 2019 and March 2020, for management of their hypertension. Women with a hypertensive disorder of pregnancy, such as chronic or new-onset hypertension, are referred to this clinic to exclude secondary causes of hypertension and optimize blood-pressure control. None of the women was receiving antihypertensive treatment at presentation to the clinic.

At presentation, maternal demographic characteristics and medical history were recorded and ultrasound examination was carried out for fetal anatomy, growth and fetal and ophthalmic artery Doppler studies. Blood pressure was measured using an automated device (Microlife® 'WatchBP Home', MicrolifeCorporation, Taipei, Taiwan) validated for use in pregnancy and PE[17], using the standardized protocol of the American Heart Association[18]. Antihypertensive medication was given based on our previously described methodology on individualization of antihypertensive treatment based on the maternal hemodynamic profile[19,20]. Medication of choice included labetalol or nifedipine modified release (MR), and the dose was titrated aiming at a target DBP of < 85 mmHg[21]. All participants were treated with oral medication and monitored for 60 min after medication administration. The period of 60 min was chosen to ensure adequate blood-pressure control prior to discharge, whilst also allowing time for peak plasma levels of labetalol[22] and nifedipine MR[23] to be achieved. If blood-pressure control was not achieved within 60 min, the duration of monitoring was extended to 120 min, after which time the patient was admitted to hospital if high blood pressure persisted.

This study was approved by the Office of Research Ethics Committee Northern Ireland (REC reference 18/NI/0013; IRAS ID 237936). The Office of Research Ethics Committee has adopted a centralized process whereby an online application is reviewed by any ethics committee in the UK that has available capacity. This system has been put in place in order to speed up the process.

Ophthalmic artery Doppler

Doppler assessment of the ophthalmic artery was performed by two trained fetal medicine fellows using a standardized procedure, as described previously[16]. Briefly, the mother was placed in the supine position and, after a 5-min period of rest, a 7.5-MHz linear transducer was placed transversely and gently over her closed upper eyelid after application of conduction gel. The optic nerve was visualized as a hypoechoic band, before using color flow to identify the ophthalmic artery which lies superior and medial to the optic nerve. Three to five waveforms were then recorded using pulsed-wave Doppler. Measurements were performed with the insonation angle kept $< 20°$, sample gate 2 mm and depth of 3.0–4.5 cm. The high-pass filter was set at 50 Hz with pulse-repetition frequency at 125 kHz. In order to minimize any discomfort or adverse effects, the duration of the measurement was kept to less than 1 min and a customized preset for the ultrasound was used to reduce output power, with a maximal mechanical index of 0.3[24]. The measurements were taken in sequence, from the right eye, the left eye and then again from each eye. The average of two cycles from each eye was used for final analysis.

The following four indices were used for analysis: PSV1, PSV2, PSV ratio and pulsatility index (PI). PSV1 and PI were obtained automatically by the machine, PSV2 was measured manually and the PSV ratio was calculated as PSV2/PSV1. Paired maternal blood-pressure and ophthalmic-artery-Doppler measurements were performed prior to and at 30 and 60 min after starting antihypertensive medication or up to 120 min until blood-pressure control ($< 140/90$ mmHg).

Definitions

The 2018 criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP) were used for the definition of chronic hypertension, gestational hypertension and PE[25]. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. Chronic hypertension was diagnosed in the presence of hypertension before or in the first 19 weeks of pregnancy. Gestational hypertension was diagnosed when there was new-onset hypertension at ≥ 20 weeks' gestation on two occasions, at least 4 h apart, in the absence of proteinuria or maternal organ dysfunction. The diagnosis of PE was made in the presence of gestational hypertension plus either proteinuria (protein-to-creatinine ratio ≥ 30 mg/mmol or 24-h urinary protein ≥ 300 mg) or other maternal organ dysfunction, including acute kidney injury (creatinine ≥ 90 μmol/L), liver impairment (alanine aminotransferase or aspartate aminotransferase > 40 IU/L), hematological complications (thrombocytopenia with platelet count $< 150\,000$/μL, disseminated intravascular coagulation or hemolysis) or neurological complications (eclampsia, altered mental status, visual disturbances or severe headaches). MAP was calculated as $(SBP + (2 \times DBP))/3$.

Statistical analysis

Normality of the data was assessed using the Kolmogorov–Smirnov test. Normally and non-normally distributed data were expressed as mean ± SD or median (interquartile range), respectively. The longitudinal changes of MAP, SBP, DBP and PSV ratio across the three timepoints (pretreatment, and 30 min and 60 min after antihypertensive treatment) were examined by a repeated measure, linear mixed-effects model. The likelihood ratio test was used to define the best multilevel model comparing the base model to either the random intercept or random intercept and slope. The estimated marginal means of each hemodynamic variable at each timepoint were presented. Univariate linear regression was performed to determine the association of PSV ratio with SBP, DBP and MAP before treatment and when acute blood-pressure control was achieved for each subject (up to 120 min).

As there was no previous literature with repeat measures over time for the ophthalmic artery Doppler, the power calculation was based on the required sample size for the paired-samples *t*-test to detect a 10-mmHg difference between pretreatment MAP and MAP at 60 min after administration of antihypertensive medication[26]. For the blood-pressure measurement at 60 min after treatment, we arbitrarily set the target of 135/85 (MAP = 102 mmHg). Our previous work informed on the average MAP at presentation and SD of the differences[19,20]. The power calculation showed that, for an α-level of 0.01 and power of 99% (beta 0.01), 28 pregnant women would be needed to prove statistical significance of a 10-mmHg decline in MAP (from 112 mmHg to 102 mmHg) for a SD of the differences of 10 mmHg.

Statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows 2015, version 26.0; IBM Corp, Armonk, NY, USA) and STATA (STATACorp. 2019, release 16; STATACorp. LLC, College Station, TX, USA).

RESULTS

The demographic characteristics of the 31 women included in the study are summarized in Table 1. The diagnosis at presentation to the hypertension clinic was PE in 17 (54.8%) cases, gestational hypertension in 11 (35.5%) and chronic hypertension in three (9.7%). At presentation, all cases had SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.

Figure 2 illustrates the change in MAP, SBP, DBP and ophthalmic artery PSV ratio with antihypertensive medication. The results of the linear mixed-effects model demonstrating the change in the abovementioned variables from pretreatment (reference) to 30 min and 60 min after commencement of antihypertensive medication are shown in Table S1 and the estimated marginal means of each model in Table 2. Antihypertensive treatment was associated with a decrease in SBP, DBP, MAP and ophthalmic artery PSV ratio, which was most marked at 60 min. There was no significant change in ophthalmic

artery PSV1, PSV2 or PI following administration of antihypertensive medication (data not presented). From the total cohort, 20 (64.5%) women had achieved blood-pressure control at 60 min and another seven (22.6%) by 120 min from commencement of antihypertensive treatment. Four (12.9%) women did not achieve blood-pressure control during this period and were admitted to hospital.

Table 1 Demographic characteristics, hemodynamic parameters at presentation and pregnancy outcomes of 31 women with hypertensive disorder of pregnancy included in study

Parameter	*Value*
Age (years)	35.6 (29.5–38.4)
Body mass index (kg/m^2)	26.7 (24.4–29.4)
Nulliparous	18 (58.1)
Racial origin	
White	16 (51.6)
Black	10 (32.3)
South Asian	4 (12.9)
Mixed	1 (3.2)
Gestational age at examination (weeks)	36.1 (34.7–37.9)
Mean arterial pressure (mmHg)	112.6 ± 7.2
Systolic blood pressure (mmHg)	148.3 ± 11.1
Diastolic blood pressure (mmHg)	94.8 ± 7.2
Ophthalmic artery Doppler	
PSV 1 (cm/s)	35.3 (30.6–48.1)
PSV 2 (cm/s)	25.6 (22.4–40.9)
PSV ratio*	0.78 ± 0.1
Pulsatility index	1.5 (1.2–1.7)
Diagnosis at presentation	
Pre-eclampsia	17 (54.8)
Gestational hypertension	11 (35.5)
Chronic hypertension	3 (9.7)
Gestational age at delivery (weeks)	38.5 (37.1–39.4)
Birth-weight percentile	27.2 (8.5–52.2)

Categorical data are presented as *n* (%). Numerical data are presented as mean ± SD or median (interquartile range), if normally or non-normally distributed, respectively. *Ophthalmic artery peak systolic velocity (PSV) ratio was calculated as ratio of second peak (PSV2) to first peak (PSV1) of systolic velocity.

We assessed the relationship of PSV ratio with MAP, SBP and DBP before treatment ($n = 31$) and at the point of blood-pressure control (< 140/90) in women in whom this was achieved by 120 min after commencement of treatment ($n = 27$). Prior to treatment, there was a significant association between PSV ratio and MAP (PSV ratio $= -0.59 + (0.01 \times \text{MAP})$; $P < 0.0001$; $R^2 = 0.39$) (Figure 3). This was primarily due to the association between PSV ratio and DBP (PSV ratio $= -0.39 + (0.01 \times \text{DBP})$; $P < 0.0001$; $R^2 = 0.39$) and less so due to the association between PSV ratio and SBP (PSV ratio $= 0.02 + (0.005 \times \text{SBP})$; $P = 0.02$; $R^2 = 0.16$). At the point of achieving blood-pressure control, there was no significant association between PSV ratio and MAP ($P = 0.7$), DBP ($P = 0.5$) or SBP ($P = 0.7$) (Figure 4). The values of MAP, DBP and PSV ratio were not normally distributed and were transformed by raising the values to the cubic power (values in Figures 2–4 appear back-transformed to facilitate appreciation by the reader). In addition, the ophthalmic artery PI was transformed to the $\log_{10}$ power.

DISCUSSION

Main findings

This study has demonstrated that, during acute treatment of hypertension in pregnancy, the decrease in SBP, DBP and MAP is accompanied by a concomitant reduction in PSV ratio. Prior to treatment, there was a significant association between PSV ratio and MAP, which was primarily due to the association of PSV ratio with DBP and less so due to its association with SBP. When blood-pressure control was achieved, the association of PSV ratio with MAP, SBP and DBP was no longer significant.

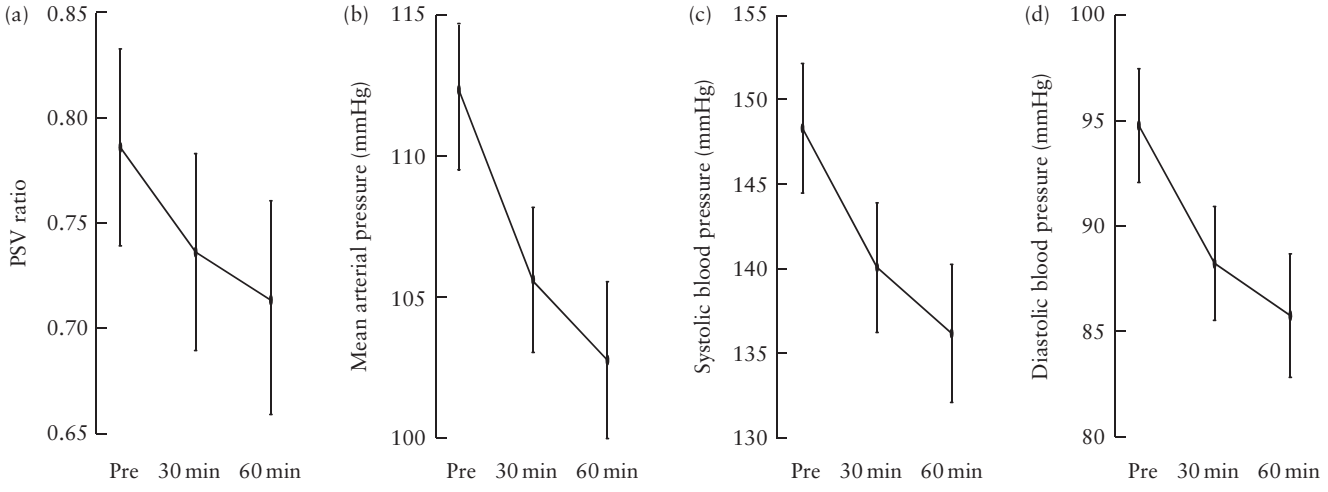

Figure 2 Estimated marginal means, with 95% CI, from linear mixed models for ophthalmic artery peak systolic velocity (PSV) ratio (a), mean arterial pressure (b), systolic blood pressure (c) and diastolic blood pressure (d) before treatment (Pre) and at 30 min and 60 min after commencement of antihypertensive treatment, in 31 women with hypertensive disorder of pregnancy. The values for mean arterial pressure, diastolic blood pressure and PSV ratio are back-transformed to facilitate appreciation by the reader.

Table 2 Estimated marginal means (95% CI) of hemodynamic parameters in 31 women with hypertensive disorder of pregnancy, at presentation and at 30 min and 60 min after commencement of antihypertensive treatment

		After treatment	
Parameter	*Before treatment*	*30 min*	*60 min*
PSV ratio	0.78 (0.74–0.83)	0.74 (0.69–0.78)	0.71 (0.66–0.76)
MAP (mmHg)	112.6 (109.9–114.3)	105.5 (102.8–108.2)	102.6 (100.6–105.5)
SBP (mmHg)	148.3 (144.4–152.1)	140.0 (136.2–143.9)	136.2 (132.1–140.2)
DBP (mmHg)	94.8 (92.1–97.5)	88.2 (85.5–90.9)	85.7 (82.8–88.7)

DBP, diastolic blood pressure; MAP, mean arterial pressure; PSV, ophthalmic artery peak systolic velocity; SBP, systolic blood pressure.

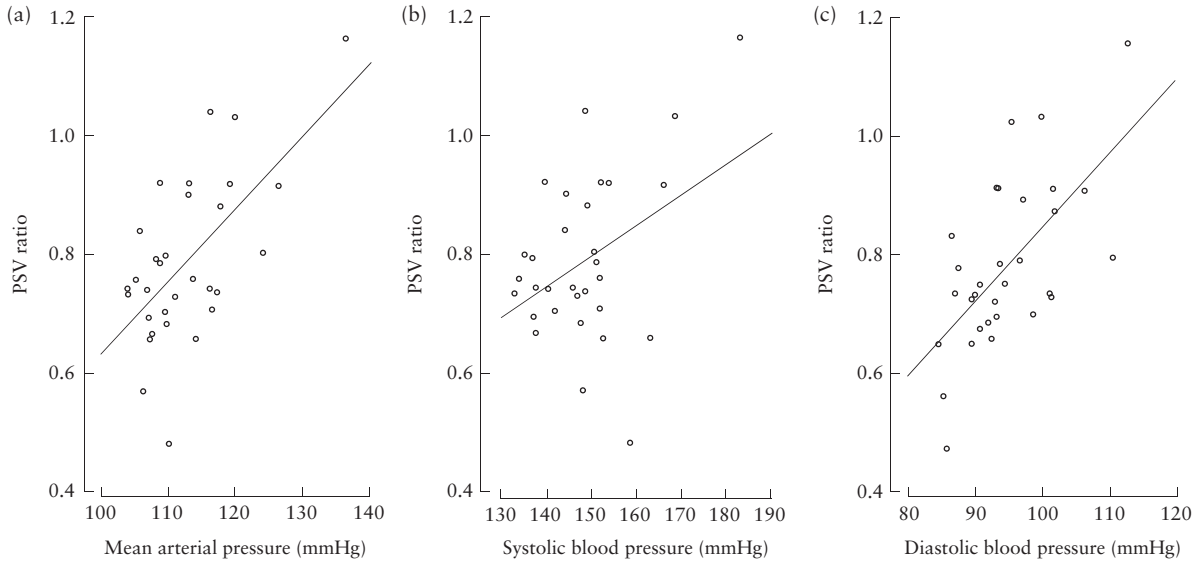

Figure 3 Scatterplots showing relationship between peak systolic velocity (PSV) ratio and mean arterial pressure (a), systolic blood pressure (b) and diastolic blood pressure (c), in 31 women with hypertensive disorder of pregnancy before commencement of treatment. Regression lines are shown. The values for mean arterial pressure, diastolic blood pressure and PSV ratio are back-transformed to facilitate appreciation by the reader.

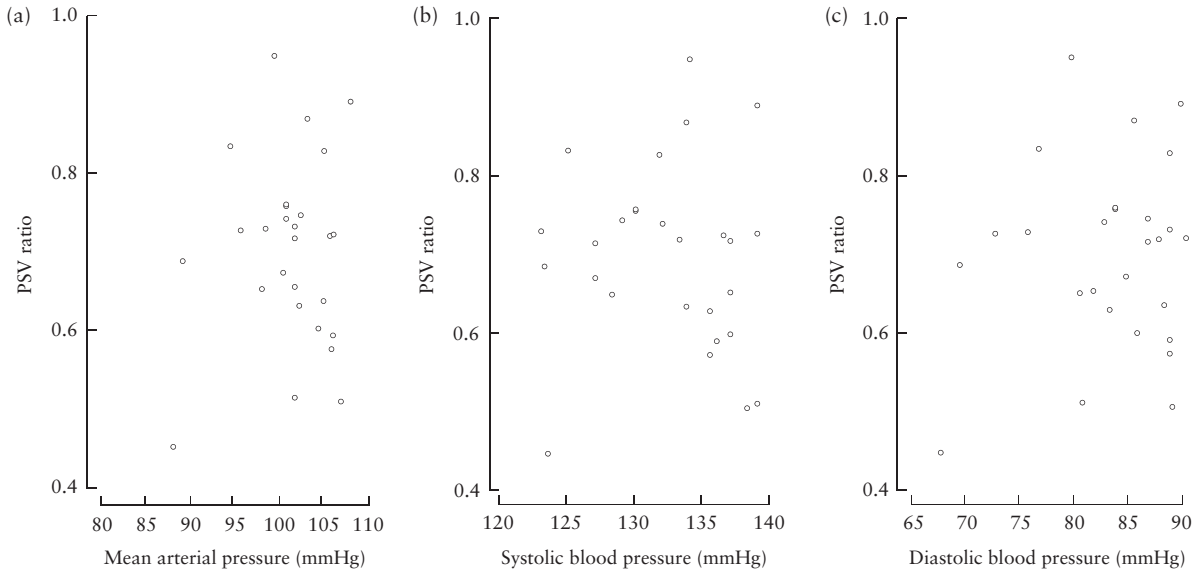

Figure 4 Scatterplots showing relationship between peak systolic velocity (PSV) ratio and mean arterial pressure (a), systolic blood pressure (b) and diastolic blood pressure (c) at the time of blood-pressure control (i.e. blood pressure < 140/90), in 27 women with hypertensive disorder of pregnancy in whom this was achieved by 120 min after commencement of treatment. The values for mean arterial pressure, diastolic blood pressure and PSV ratio are back-transformed to facilitate appreciation by the reader.

Interpretation of findings

The PSV ratio is the interplay between PSV1 and PSV2. PSV1 is created by cardiac systole, generating a rapid upstroke to reach systolic peak pressure[27], whereas, PSV2 is created by reflection of the systolic wave as it encounters the higher resistance of smaller arterioles[28]. Specifically, the wave is reflected back towards the aortic arch, where a fraction is diverted cranially to the cerebral circulation as a forward wave, to create the second systolic peak (PSV2)[28]. In our data, there was a trend for PSV1 to increase and PSV2 to decrease after administration of antihypertensive medication, although the changes did not reach statistical significance (Figure S1). We have demonstrated previously that acute control of blood pressure during pregnancy is associated with an increase in cardiac output, secondary to reduction of afterload[19]. Therefore, the trend for increase in PSV1 reflects the increase in cardiac output due to a more efficient pump function of the left ventricle. The progressive decline with time in PSV2 reflects reduction in peripheral vascular resistance (PVR) secondary to vasodilatation caused by antihypertensive treatment. Nifedipine MR, a calcium-channel blocker, causes peripheral vasodilatation via vascular smooth muscle relaxation[23]. Labetalol, has not only alpha and beta adrenergic blocking effects but also direct vasodilatory action, over and above that caused via alpha adrenergic blocking[29]. Therefore, this peripheral vasodilatation leads to a more compliant arterial tree, with a subsequent reduction in the reflected systolic wave. It is obvious that the PSV ratio is more sensitive than its constituents and demonstrates better than the individual measurements the reduction in peripheral resistance.

An interesting observation arising from our findings is the strong relationship of PSV ratio with MAP and DBP, and less so with SBP. MAP is the average pressure within a blood vessel during a cardiac cycle and, since two-thirds of the cycle is spent in diastole and one-third in systole, MAP is largely influenced by the DBP[30]. The SBP corresponds to the peak pressure in the aorta during systole and is directly related to left ventricular contraction and stroke volume[30]. On the contrary, DBP is the minimum aortic pressure when the ventricles are relaxing and filling, and is directly related to total PVR[30]. Since the PSV ratio is mirroring the changes in PSV2, which is related to PVR, it is not surprising that it correlates better with DBP and, therefore, MAP, than with SBP. Controlling blood pressure with agents exhibiting strong vasodilatory action leads to a loss of this relationship between DBP, MAP and PSV ratio when blood-pressure control is achieved.

Comparison with previous studies

Outside of pregnancy, previous studies have assessed the effect of blood-pressure control on cerebral hemodynamics. Short-term (1–2 weeks) and long-term (3–4 months) antihypertensive treatment with losartan/hydrochlorthiazide is associated with reduction in blood pressure and cerebrovascular resistance index of the MCA but no change in cerebral blood flow velocity, suggestive of maintenance of autoregulation during blood-pressure control[31]. Furthermore, an increase in blood pressure following administration of nicotine resulted in increase in ophthalmic artery PSV1 when compared with placebo[32], whilst vasodilatation via nitric oxide donors resulted in a significant decrease in the ophthalmic artery PSV ratio and PSV2[33].

During pregnancy, one previous study has investigated the effect of antihypertensive treatment on the ophthalmic artery waveform[34]. Treatment with transdermal isosorbide dinitrate in 10 women with PE revealed, 7 days after treatment, a significant reduction in the PSV ratio, MAP, SBP and DBP. Three studies examining MCA changes in hypertensive pregnant women following treatment reported conflicting results, possibly because a proportion of the cohorts were already on antihypertensive medications[35–37]. In eight women with PE who were treated with 200 mg of labetalol, a significant fall in MCA cerebral perfusion pressure was seen, whilst cerebral blood flow velocity, resistance index and PSV1 were unchanged at 180 min post-treatment[35]. Conversely, in a study of eight women with severe hypertension, there was no change in cerebral perfusion pressure despite a significant reduction in MAP at 30 min post-treatment with intravenous labetalol[37]. However, in the same study, when oral nifedipine was given in another group of eight women, a significant fall in cerebral perfusion pressure was observed. Administration of 10 mg of a bitten nifedipine capsule in women with hypertension in pregnancy showed a reduction in all velocities of the MCA (PSV1 and mean velocity) and increased PI at 45 min post-treatment. Similar changes, albeit weaker, were seen after 48 h of treatment with methyldopa[36].

Strengths and limitations

This is the first study investigating the dynamic effects of oral antihypertensive therapy and subsequent effect of normalization of blood pressure on the ophthalmic artery waveform. Strengths of the study include its prospective design, the repeat measures over time in the same individual, the standardized protocol for measurement of blood pressure, ophthalmic artery indices and antihypertensive treatment and that only two experienced fetal–medicine sonographers performed the measurements, reducing the variability of results. A limitation of the study is that it was not powered to inform on changes over time in less sensitive indices, such as ophthalmic artery PSV1, PSV2 and PI.

Conclusions

Acute blood-pressure control in pregnancy is associated with a significant reduction in the ophthalmic artery PSV ratio. In hypertensive pregnant women, there is a significant association between PSV ratio and MAP, SBP and DBP which disappears after reducing blood pressure to $< 140/90$. Larger studies should address whether ophthalmic artery Doppler can be

used in tailoring antihypertensive therapy, so that cerebrovascular hemodynamics can be maintained within the autoregulatory range.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Multilevel linear mixed-effects models for ophthalmic artery peak systolic velocity (PSV) ratio, mean arterial pressure, and systolic and diastolic blood pressure, before treatment and at 30 min and 60 min after commencement of antihypertensive medication in 31 women with hypertensive disorder of pregnancy

Figure S1 Linear mixed models: estimated marginal means, with 95% CI, for ophthalmic artery peak systolic velocity 1 (a) and peak systolic velocity 2 (b) before treatment (Pre) and at 30 min and 60 min after commencement of antihypertensive treatment, in 31 women with hypertensive disorder of pregnancy.

