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Longitudinal changes in maternal hemodynamics in a population at risk for pre-eclampsia

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KEYWORDS: augmentation index; blood pressure; maternal hemodynamics; pre-eclampsia; pregnancy screening; pulse wave velocity

ABSTRACT

Objective *To investigate longitudinal changes in maternal hemodynamics from the first trimester onward in women who develop pre-eclampsia (PE) or gestational hypertension (GH).*

Methods *This was a prospective longitudinal study of singleton pregnancies identified by screening at 11 + 0 to 13 + 6 weeks' gestation as being at high risk for PE. Measurements of augmentation index (AIx), pulsed wave velocity (PWV) and aortic systolic blood pressure (SBPao) were taken every 4 weeks until delivery. Values were compared between women who developed preterm PE requiring delivery before 37 weeks, term PE or GH, and those who remained normotensive.*

Results *A total of 1198 observations were recorded in 245 women, including 181 who were normotensive, 22 with preterm PE, 22 with term PE and 20 with GH. In the normotensive group, there was a U-shaped relationship between AIx and gestational age with a trough at 25 weeks' gestation, whereas changes in levels of PWV or SBPao were minimal, with a mild increase from 25 and 30 weeks' gestation onward, respectively. In the GH and preterm PE groups, compared to the normotensive group, SBPao was higher and the difference did not change significantly with gestational age. In the term PE group, SBPao did not differ significantly from that in the normotensive group. In the preterm PE group compared to the normotensive group, PWV and AIx were significantly higher from 16–17 weeks' gestation onward and the difference increased with gestational age in both cases. In the term PE and GH groups, PWV and AIx did not differ significantly from normal.*

Conclusion *This study describes temporal changes in AIx, PWV and SBPao in normotensive pregnant women and in women who develop PE or GH.* *Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Pre-eclampsia (PE), a major cause of maternal and fetal complications, is associated with increased arterial stiffness[1–4]. Previous studies reported higher indices of arterial stiffness, both at the time of and prior to clinical diagnosis of PE[4–9]. These changes have been described as early as 11 weeks' gestation and several months after the index pregnancy[5,6,8,10–12]. Women who develop PE are at increased risk for cardiovascular disease and stroke in subsequent decades[13–16]. Furthermore, studies have suggested that maternal predisposition to cardiovascular disease, manifested as high levels of pulsed wave velocity (PWV) and blood pressure, is a prepregnancy risk factor for PE[17,18]. Large epidemiological studies have clearly demonstrated that arterial stiffness is a reliable predictor of cardiovascular mortality and morbidity in both low- and high-risk non-pregnant populations[19–27].

Evidence is accumulating that indices of arterial stiffness can identify women who will later develop PE[4–8]. However, most of these studies have focused on specific gestational age windows, commonly 11–13 and 20–24 weeks' gestation[4–8].

The aim of this study was to investigate longitudinal changes in maternal hemodynamics from the first trimester onward in women who subsequently develop PE or gestational hypertension (GH) and those who remain normotensive.

METHODS

At University College London Hospitals, the risk of developing PE was routinely assessed at 11 + 0 to 13 + 6 weeks' gestation, using a combination of maternal history, uterine artery Doppler mean pulsatility index, mean arterial pressure and serum pregnancy-associated plasma protein A (PAPP-A)[28]. Women considered to be at high risk for early PE were followed at a specialist hypertension

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clinic in which augmentation index (AIx), PWV and aortic systolic blood pressure (SBPao) were measured (TensioMed Ltd., Budapest, Hungary) every 4 weeks until delivery using the arteriograph (TensioMed Ltd.). The study took place between December 2009 and May 2012. Written informed consent was obtained from all women participating in the study which was approved by the London-Surrey Borders Research Ethics Committee. None of these pregnancies was complicated by aneuploidy or major fetal structural abnormalities.

Recorded patient characteristics included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian or mixed), method of conception (spontaneous or assisted, requiring ovulation-inducing drugs), smoking status during pregnancy, history of chronic hypertension or pre-existing diabetes mellitus, family history of PE in the mother of the patient and obstetric history including parity (parous or nulliparous if no previous pregnancies at or after 24 weeks) and previous pregnancy with PE. Maternal weight and height were also measured and the body mass index (kg/m^2) was calculated.

All measurements of AIx, PWV and SBPao were performed in a temperature-controlled room (22°C) with participants in a semi-recumbent position. The arteriograph cuff was applied to the left arm over the brachial artery for estimation of SBPao (mmHg), PWV (m/s) and AIx (%) as previously described[29]. The accuracy of SBPao, PWV and AIx determination has been validated against invasive monitoring[30]. All recordings were made by doctors appropriately trained in use of the arteriograph. Results of PWV, AIx or SBPao determination were not given to the women or their doctors and did not influence subsequent management of the pregnancies.

Data on pregnancy outcomes were collected from hospital maternity records. Obstetric records of women with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was chronic hypertension, PE or GH. The diagnosis of PE and GH was made according to the guidelines of the International Society for the Study of Hypertension in Pregnancy[31]. In the case of GH, systolic BP should be ≥ 140 mmHg and/or diastolic BP should be ≥ 90 mmHg on at least two occasions 4 hours apart and should develop after 20 weeks' gestation in a previously normotensive woman in the absence of significant proteinuria. In the case of PE, there should be GH with proteinuria ≥ 300 mg within 24 hours, or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In the case of PE superimposed on chronic hypertension, significant proteinuria (as defined above) should develop after 20 weeks' gestation in women with known chronic hypertension (history of hypertension before conception or presence of hypertension at the booking visit before 20 weeks' gestation in the absence of trophoblastic disease).

Statistical analysis

Maternal baseline characteristics were compared using chi-square or Fisher's exact tests for categorical variables and the Kruskal–Wallis test for continuous variables, and comparisons between outcome groups were done using the Mann–Whitney *U*-test with post-hoc Bonferroni correction for multiple comparisons. Data are presented as median and interquartile range for continuous variables and as *n* (%) for categorical variables.

PWV, SBPao and AIx values were made Gaussian after logarithmic transformation. In the case of AIx, normality was achieved using the formula $\log_{10}(\text{AIx} + 50)$, where 50 was added to avoid negative values. Analysis of repeated measures with multilevel mixed-effects linear models (fixed effects and random effects) was performed. The fixed-effect component included up to third-order polynomial terms of gestational age, hypertensive disorders (PE or GH) and first-order interaction between gestational age and each hypertensive disorder. The random-effect component included the intercept and linear effects of gestational age. Repeated measurements at different weeks of gestation in the same woman constituted level 1 and each individual constituted level 2. Prior to regression analysis, continuous variables were centered by subtracting the mean from each measured value (70 from maternal weight in kg, 164 from maternal height in cm, 32 from maternal age in years and 75 from heart rate in beats per min).

The software used for statistical analysis was MLwiN 2.28 (Centre for Multilevel Modelling, University of Bristol, Bristol, UK) and IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA) .

RESULTS

A total of 1198 observations were recorded in 245 women, with a median of three (range, 1–9) measurements for each. The 245 pregnant women included 181 who remained normotensive, 20 who developed GH, 22 who developed PE requiring delivery after 37 weeks (term PE) and 22 who developed PE requiring delivery at or before 37 weeks (preterm PE).

Maternal characteristics of each outcome group are summarized in Table 1. Median maternal age was significantly lower in women who subsequently developed term PE or preterm PE, while median weight was higher in women who developed term PE, and height was lower in women who developed term PE or preterm PE. There were no significant differences in racial origin ($P = 0.126$), mode of conception ($P = 0.387$), parity ($P = 0.861$) or smoking status ($P = 0.560$) between outcome groups.

A total of 1061 SBPao observations were recorded in 214 women, with a median of three (range, 1–9) measurements for each. Among these women, 164 remained normotensive, 15 developed GH, 18 developed term PE and 17 developed preterm PE. Log_{10} SBPao increased significantly with maternal weight, East Asian racial origin and heart rate (Table 2), but was not significantly affected by maternal age ($P = 0.987$), height ($P = 0.204$), parity ($P = 0.629$), smoking status ($P = 0.249$), mode of conception ($P = 0.139$) or chronic hypertension ($P = 0.071$).

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Table 1 Maternal characteristics according to outcome group

	Outcome			
Characteristic	*Normal (n = 181)*	*Gestational hypertension (n = 20)*	*Term pre-eclampsia (n = 22)*	*Preterm pre-eclampsia (n = 22)*
Age (years)	33.5 (29.5–36.5)	34.5 (30.5–38.0)	28.5 (25.5–32.5)**	28.5 (27.5–35.5)*
Weight (kg)	70.0 (60.0–80.0)	70.0 (64.9–77.1)	82.0 (68.4–95.0)**	68.0 (59.0–81.0)
Height (cm)	165.0 (160.0–169.0)	165.0 (162.6–169.0)	162.0 (157.0–167.6)**	159.0 (152.8–167.0)**
Racial origin				
Caucasian	128 (70.7)	11 (55.0)	13 (59.1)	10 (45.5)
Afro-Caribbean	24 (13.3)	7 (35.0)	4 (18.2)	6 (27.3)
South Asian	16 (8.8)	2 (10.0)	3 (13.6)	5 (22.7)
East Asian	9 (5.0)	0	2 (9.1)	0
Mixed	4 (2.2)	0	0	1 (4.5)
Parous	53 (29.3)	5 (25.0)	6 (27.3)	8 (36.4)
Cigarette smoker	8 (4.4)	1 (5.0)	0	0
Mode of conception				
Spontaneous	171 (94.5)	18 (90.0)	20 (90.9)	21 (95.5)
Ovulation induction	7 (3.9)	2 (10.0)	1 (4.5)	0
In-vitro fertilization	3 (1.7)	0	1 (4.5)	1 (4.5)
Chronic hypertension	3 (1.7)	0	2 (9.1)	2 (9.1)
GA at delivery (weeks)	39.7 (38.8–40.6)	39.9 (38.1–41.1)	39.3 (38.3–40.1)	32.5 (29.4–35.8)

Data are given as median (interquartile range) or *n* (%). Outcome groups were compared using chi-square and Fisher's exact tests for categorical variables and the Kruskal–Wallis test for continuous variables; each unfavorable outcome group and the normal outcome group were compared using the Mann–Whitney *U*-test with post-hoc Bonferroni correction. $*P < 0.005$. $**P < 0.001$. GA, gestational age.

In the normotensive group, there was a cubic relationship of $\log_{10}$ SBPao with gestational age, with minimal change up to 30 weeks' gestation and mild increase thereafter (Table 2, Figure 1). In the GH and preterm PE groups, compared to the normotensive group, SBPao was higher and the difference did not change significantly with gestational age (Table 2, Figure 2). In the term PE group, SBPao did not differ significantly from the normotensive group ($P = 0.052$).

A total of 1000 PWV observations were recorded in 205 women, with a median of three (range, 1–9) measurements for each. The 205 pregnant women included 158 who remained normotensive, 14 who developed GH, 16 who developed term PE and 17 who developed preterm PE. Log_{10} PWV increased significantly with maternal weight, age and heart rate (Table 2), but was not significantly affected by height ($P = 0.535$), ethnic origin ($P = 0.409$), parity ($P = 0.308$), smoking status ($P = 0.079$), mode of conception ($P = 0.645$) or chronic hypertension ($P = 0.574$).

In the normotensive group, there was a quadratic relationship of $\log_{10}$ PWV with gestational age, with minimal change up to 25 weeks and mild increase thereafter (Table 2, Figure 3). In the preterm PE group, compared to the normotensive group, PWV was significantly higher at between 16 and 35 weeks' gestation and the difference increased with gestational age (Table 2, Figure 4). In the term PE and GH groups, PWV was not significantly different from that in the normotensive group.

A total of 999 AIx measurements were recorded in 205 women, with a median of three (range 1–9) for each. The 205 pregnant women included 158 who remained normotensive, 14 who developed GH, 16 who developed term PE and 17 who developed preterm PE. Log_{10} AIx increased significantly with maternal age and chronic hypertension, and decreased with maternal heart rate (Table 2), but was not significantly affected by maternal weight ($P = 0.892$), height ($P = 0.388$), ethnic origin ($P = 0.183$), parity ($P = 0.842$), smoking status ($P = 0.427$) or mode of conception ($P = 0.615$).

In the normotensive group, there was a U-shaped relationship between $\log_{10}$ AIx and gestational age with a trough at *c.* 25 weeks (Table 2, Figure 5). In the preterm PE group, AIx was significantly higher than that in the normotensive group from 17 weeks onward and the difference increased with gestational age (Table 2, Figure 6). In women who subsequently developed GH or term PE, $\log_{10}$ AIx did not differ significantly from that in those who remained normotensive.

A summary of changes in SBPao, PWV and AIx in pregnancies complicated by PE or GH is given in Table S1.

DISCUSSION

This study demonstrates that in women who were identified as being at high risk for PE following first-trimester screening, but who remained normotensive, there is a U-shaped relationship between AIx and gestational age, with a trough at 25 weeks, whereas the changes with gestation in PWV and SBPao are minimal, with a slight increase after 25 and 30 weeks' gestation, respectively. In the preterm PE group, compared to the normal group, AIx, PWV and SBPao are significantly higher starting at an early stage in pregnancy, with the difference from normal in AIx and PWV increasing, but that for SBPao not changing with gestational age. In the term PE group, AIx, PWV and SBPao do not differ significantly from those values in the normotensive group. In GH, SBPao is higher, but AIx and PWV do not significantly differ from those values in the normotensive group.

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Table 2 Summary of multilevel linear mixed-effects models for log_{10} aortic systolic blood pressure, log_{10} pulsed wave velocity and log_{10} augmentation index

	Log_{10} aortic systolic blood pressure			*Log_{10} pulsed wave velocity*			*Log_{10} augmentation index*		
Variable	*Estimate*	*SE*	P	*Estimate*	*SE*	P	*Estimate*	*SE*	P
Fixed part									
Intercept	1.940718	0.049919	< 0.001	0.893507	0.021688	< 0.001	1.888146	0.022263	< 0.001
GH	0.020561	0.006934	0.003	0.090551	0.077273	0.242	−0.007779	0.028958	0.789
Term PE	0.012272	0.006280	0.052	−0.036472	0.070486	0.605	0.026767	0.025963	0.304
Preterm PE	0.034541	0.006710	< 0.001	−0.179960	0.076287	0.019	−0.061264	0.028484	0.033
GA (weeks)	0.014248	0.006623	0.032	−0.006868	0.001844	< 0.001	−0.010156	0.001892	< 0.001
GA (weeks)^2	−0.000666	0.000276	0.016	0.000166	0.000037	< 0.001	0.000198	0.000038	< 0.001
GA (weeks)^3	0.000010	0.000004	0.007						
Interaction:									
GH with GA (weeks)				−0.006962	0.006588	0.291	0.000383	0.001189	0.748
GH with GA (weeks)^2				0.000136	0.000133	0.304			
Term PE with GA (weeks)				0.004445	0.005986	0.743	−0.000940	0.001048	0.371
Term PE with GA (weeks)^2				−0.000090	0.000119	0.448			
Preterm PE with GA (weeks)				0.017569	0.006796	0.010	0.005228	0.001232	< 0.001
Preterm PE with GA (weeks)^2				−0.000310	0.000144	0.032			
Weight (−70)*	0.000520	0.000113	< 0.001	0.000489	0.000163	0.003			
Heart rate (−75)†	0.000860	0.000115	< 0.001	0.002645	0.000156	< 0.001	−0.000805	0.000156	< 0.001
Racial origin									
Caucasian									
Afro-Caribbean	−0.001141	0.005117	0.824						
South Asian	0.008097	0.005982	0.177						
East Asian	0.022211	0.008064	0.006						
Mixed	0.014086	0.013411	0.295						
Maternal age (−32)‡				0.001837	0.000496	< 0.001	0.001445	0.000536	0.008
Chronic hypertension							0.041378	0.017124	0.016
Random part									
Level 2									
Variance (const)	0.001127	0.000568	0.047	0.002699	0.001053	0.010	0.001338	0.001155	0.247
Variance (GA)	0.000002	0.000001	0.013	0.000005	0.000002	0.003	0.000003	0.000002	0.094
Covariance (const, GA)	−0.000044	0.000022	0.041	−0.000103	0.000041	0.012	−0.000049	0.000044	0.267
Level 1									
Residual	0.001822	0.000103	< 0.001	0.002847	0.000172	< 0.001	0.003931	0.000230	< 0.001

*Subtracted from maternal weight in kg. †Subtracted from maternal heart rate in bpm. ‡Subtracted from maternal age in years. const, constant; GA, gestational age; GH, gestational hypertension; PE, pre-eclampsia; SE, standard error.

Major strengths of this study are the large number of observations performed in a prospective longitudinal manner, a well-defined methodology, appropriately trained doctors for taking measurements and a robust statistical approach that takes into account not only the difference in marker levels in outcome groups but also the change with gestational age. This approach differs from the calculation of trends across gestation derived from large numbers of cross-sectional and unrelated measurements.

A limitation of the study is the lack of prepregnancy data to establish whether the women had cardiovascular predisposition to development of hypertensive disorders during pregnancy. As the study population was identified as being at increased risk for PE following first-trimester screening, the results might not be generalizable to low-risk pregnancies.

Normal pregnancy is associated with marked cardiovascular adaptation, with increase in cardiac output and decrease in systemic vascular resistance evident from as early as 6 weeks' gestation[32–34].

Our finding in normotensive women of a U-shaped relationship between AIx and gestational age, with a trough at 25 weeks, is compatible with the results of several previous longitudinal and cross-sectional studies in normal pregnancies[9,31,35–37]. Similarly, our finding of minimal change with gestational age in PWV and SBPao and a small increase during the third trimester are in agreement with previous reports[9,35,37]. These findings could be attributed, firstly, to changes in the levels of vasoactive substances such as progesterone and relaxin, and secondly, to plasma volume expansion during pregnancy[38–40].

Concerning the same cohort, we previously reported in the normotensive group a U-shaped relationship between mean arterial pressure (MAP) and gestational age, with a nadir at *c.* 24 weeks[41]. It is notable that the changes in SBPao we report here seem to differ from those previously reported in peripheral (brachial) blood pressure[41]. However, this is consistent with studies in non-pregnant patients which found that central and peripheral blood pressures are not synonymous[42]. Similar to the results of our large screening study at 11–13 weeks' gestation involving over 6000 singleton pregnancies, AIx was independently associated with maternal age and heart rate, PWV with age and weight and SBPao with weight[29].

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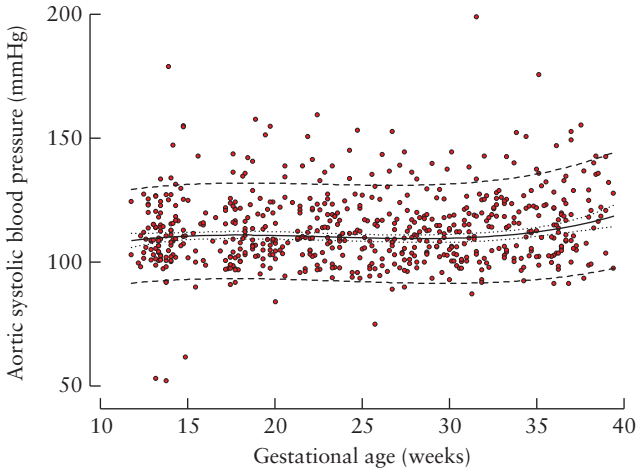

Figure 1 Aortic systolic blood pressure in pregnancies with normal outcome. ——, mean; - - - -, 5th and 95th centiles; ·····, 95% CI of mean.

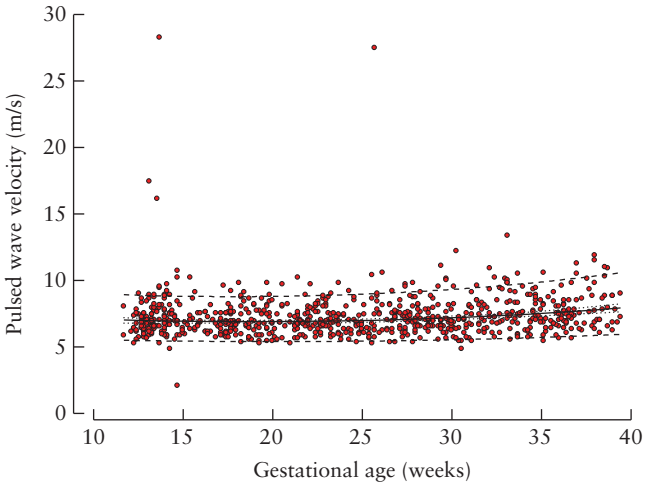

Figure 3 Pulsed wave velocity in pregnancies with normal outcome. ——, mean; - - - -, 5th and 95th centiles; ·····, 95% CI of mean.

PWV is considered to be the gold standard measure of arterial stiffness[43,44]. AIx is also a measure of arterial stiffness but is influenced by wave reflections from the arterial vessel tree[43,45] which makes it likely to depend on the diameter and elasticity of the small muscular arteries/arterioles at the major sites of pressure wave reflection. Thus, it will be affected by alterations in muscular smooth muscle tone, affecting mainly the small muscular arteries but not the elastic aorta. AIx is considered to be an indicator of increased work by the left ventricle during systole and may be a more direct measure of vasoconstriction than PWV[43,46,47].

Our study is the first to report longitudinal changes in maternal hemodynamics in women who later developed PE. In preterm PE, but not in term PE, AIx, PWV and SBPao are significantly increased from an early stage in pregnancy onward and the difference from normal in AIx and PWV increases with gestational age. Previous studies examined maternal hemodynamics either before or during established PE. A screening study at 11–13 weeks' gestation reported that, in pregnancies subsequently complicated by PE, compared to those with no hypertensive complications, there was an increase in AIx, PWV and SBPao by 12%, 6% and 9%, respectively[8].

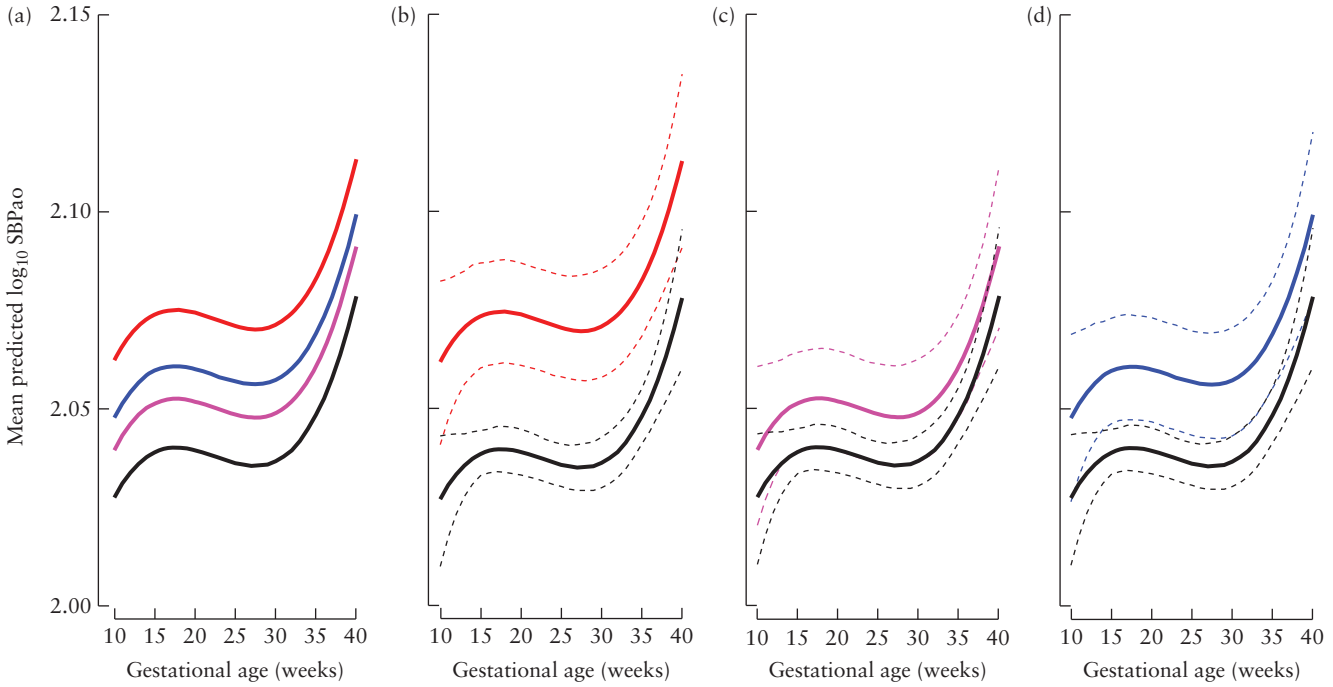

Figure 2 (a) Mean predicted $\log_{10}$ aortic systolic blood pressure (SBPao) in pregnancies with normal outcome (——) and in pregnancies complicated with preterm pre-eclampsia (PE) (——), term PE (——) and gestational hypertension (GH) (——). (b–d) Mean SBPao values with 95% CI (dashed lines) in preterm PE (b), term PE (c) and GH (d) groups, with normal outcome group values repeated for comparison.

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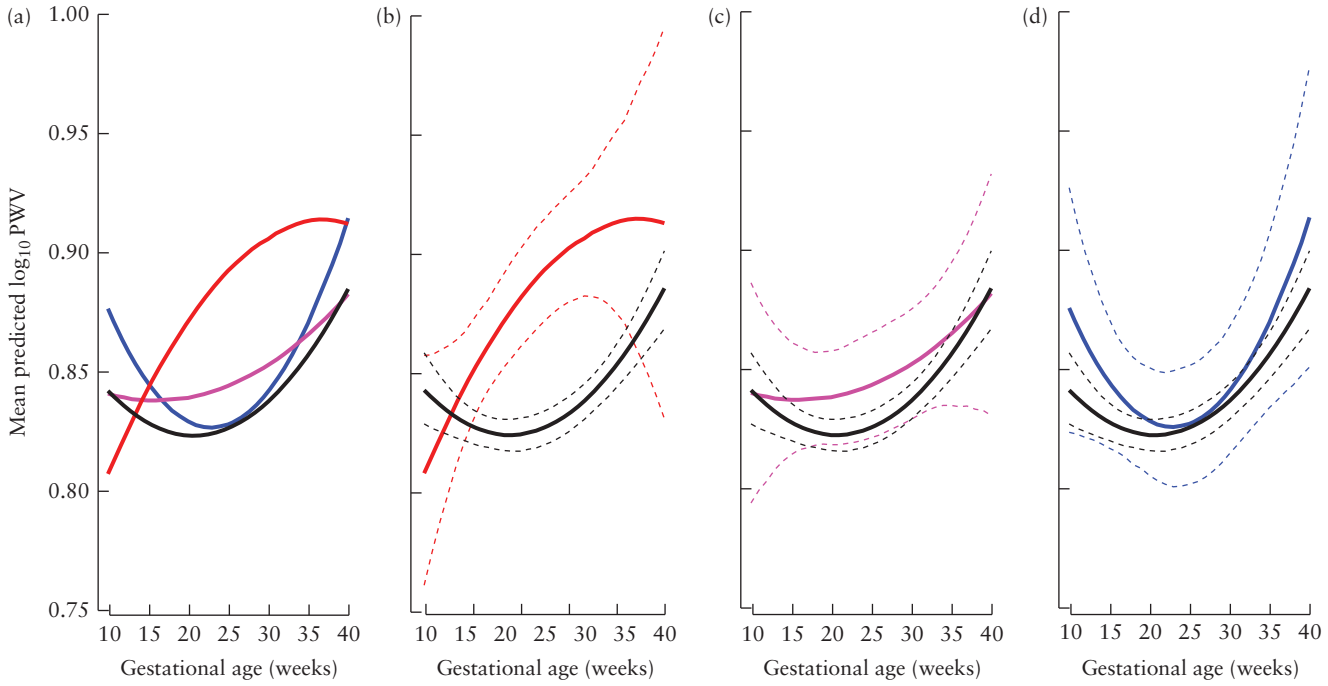

Figure 4 (a) Mean predicted $\log_{10}$ pulsed wave velocity (PWV) in pregnancies with normal outcome (——) and in pregnancies complicated with preterm pre-eclampsia (PE) (——), term PE (——) and gestational hypertension (GH) (——). (b–d) Mean PWV values with 95% CI (dashed lines) in preterm PE (b), term PE (c) and GH (d) groups, with normal outcome group values repeated for comparison.

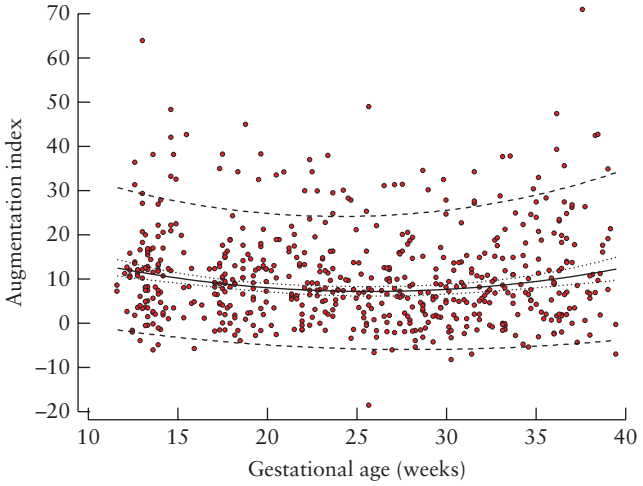

Figure 5 Augmentation index in pregnancies with normal outcome. ——, mean; - - - -, 5th and 95th centiles; ·····, 95% CI of mean.

Another study measured PWV at 22–24 weeks' gestation and reported that values were 17% higher in women who subsequently developed PE, compared to those who remained normotensive[7]. A study in pregnancies with established PE reported that the increase in AIx was much higher than that in PWV (838% vs. 10% in early PE requiring delivery before 34 weeks' gestation and 734% vs. 7% in late PE, respectively)[9]. These findings suggest that, in pregnancies complicated by PE, there is more vasoconstriction than arterial stiffness. In our cohort of women at high risk following first-trimester screening, after adjusting for potential confounders, women who developed preterm PE showed an increase of *c.* 6% in AIx at 34 weeks' gestation. This increase was similar to that seen in PWV at the same gestational age (7%). The difference between our findings and those of previous studies could be explained by the different study population and the lack of adjustment to maternal characteristics or gestational age in some studies.

In our cohort, AIx, PWV and SBPao were significantly higher in the preterm PE group, but not in the term PE group, which might be related to the severity of disease reflected in the gestational age at delivery. It is also plausible that women who develop preterm PE, but not term PE, have a prepregnancy predisposition that is unmasked by the pregnancy in the form of PE. However, it is also possible that preterm PE and term PE have a different pathogenesis. Preterm PE is often associated with intrauterine fetal growth restriction while term PE is usually not. SBPao was significantly higher in the preterm PE and GH groups than in the normotensive group, and this difference did not change with advancing gestational age. However, SBPao did not differ in the term PE group. When compared to our previous results in the same cohort, MAP was significantly higher from the first trimester onward in the PE and GH groups as compared to the normotensive group, and the difference increased with gestational age in the term PE and GH groups[41]. According to these results, MAP would be a better candidate than SBPao in this high-risk cohort for further testing during pregnancy to optimize accuracy in predicting hypertensive disorders. In screening for PE, the benefit of SBPao obtained in the first trimester is not improved with advancing gestational age, whereas AIx and PWV measurements during the second and third trimesters are likely to improve predictive accuracy and reduce the false-positive rate.

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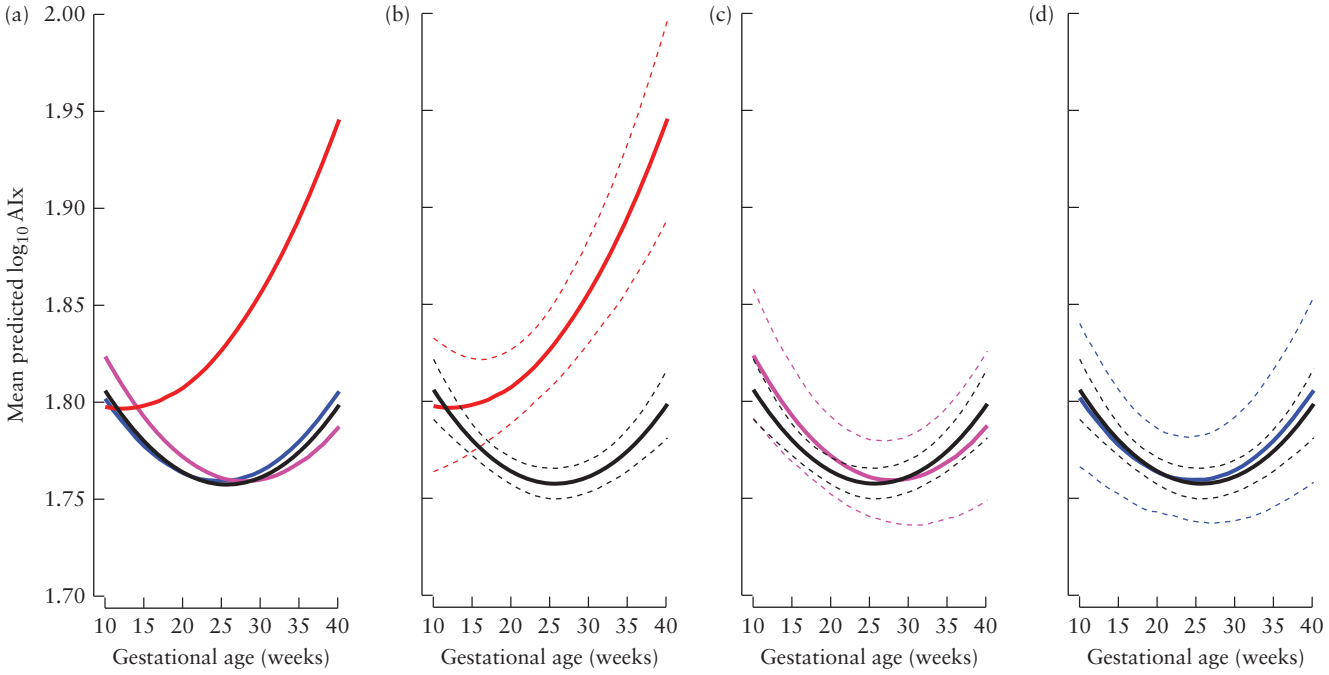

Figure 6 (a) Mean predicted $\log_{10}$ augmentation index (AIx) values in pregnancies with normal outcome (—) and in pregnancies complicated with preterm pre-eclampsia (PE) (—), term PE (—) and gestational hypertension (GH) (—). (b–d) Mean AIx values with 95% CI (dashed lines) in preterm PE (b), term PE (c) and GH (d) groups, with normal outcome group values repeated for comparison.

This study describes longitudinal changes in maternal hemodynamics in women at high risk, identified following first-trimester screening, who remained normotensive and those who developed GH or PE. These results are likely to benefit continuing efforts to improve accuracy in predicting PE.

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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 Summary of changes in maternal hemodynamics in women who developed gestational hypertension or pre-eclampsia.

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