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Maternal hemodynamics at 11–13 weeks' gestation and risk of pre-eclampsia

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KEYWORDS: arterial stiffness; hypertension; pre-eclampsia; pregnancy; pulse wave velocity

ABSTRACT

Objective *Women who develop pre-eclampsia are at increased risk of cardiovascular disease and stroke in the subsequent decades. Individuals with cardiovascular disorders have increased central aortic systolic blood pressure (SBP_{Ao}) and arterial stiffness, as assessed by pulse wave velocity (PWV) and augmentation index (AIx). The aim of this study was to examine the potential value of assessment of SBP_{Ao}, PWV and AIx at 11–13 weeks' gestation in identifying women who subsequently develop pre-eclampsia.*

Methods *This was a screening study for pre-eclampsia in singleton pregnancies at 11 + 0 to 13 + 6 weeks' gestation. Maternal history and characteristics were recorded and PWV, AIx (adjusted to a heart rate of 75 beats per min (AIx-75)) and SBP_{Ao} measured. We compared these parameters in women who developed pre-eclampsia (*n = *181) with those in unaffected controls (*n = *6766) and examined their performance in screening for pre-eclampsia.*

Results *In the pre-eclampsia group, compared to unaffected controls, there was an increase in AIx-75 (1.13 vs. 1.00 multiples of the median (MoM);* $P < 0.0001$*), PWV (1.06 vs. 1.00 MoM;* $P < 0.0001$*) and SBP_{Ao} (1.09 vs. 1.00 MoM;* $P < 0.0001$*). In screening for pre-eclampsia by a combination of maternal variables and $\log_{10}$AIx-75 MoM, $\log_{10}$PWV MoM and $\log_{10}SBP_{Ao}$ MoM, the estimated detection rate was 56.9% at a false-positive rate of 10%.*

Conclusion *Compared with women who remain normotensive, women who develop pre-eclampsia have higher SBP_{Ao} and arterial stiffness, which is apparent from the first trimester of pregnancy. Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Pre-eclampsia (PE), which is associated with an increased risk of perinatal and maternal morbidity and mortality[1,2], may be the common phenotypic expression of two distinct mechanisms. These are maternal predisposition to cardiovascular disease, which under the stress of physiological changes in pregnancy manifests as PE, and impairment of the physiological process of trophoblastic invasion of the maternal spiral arteries leading to placental hypoxia and the release of inflammatory factors that cause endothelial cell activation and the clinical manifestation of PE[3–5]. Evidence for increased maternal predisposition to PE is provided by studies that report that first, there is a significant association between the risk of developing PE and prepregnancy levels of cardiovascular risk factors such as high levels of triglycerides, cholesterol and low-density lipoprotein and high blood pressure[6], and second, women who develop PE are at increased risk of cardiovascular disease and stroke in the subsequent decades[7–10]. Biophysical and biochemical markers of impaired placentation include increased uterine artery (UtA) pulsatility index (PI) and reduced maternal serum pregnancy-associated plasma protein-A (PAPP-A)[11,12].

Cardiovascular disease is associated with increased arterial stiffness and central aortic systolic blood pressure (SBP_{Ao})[13–16]. Arterial stiffness can be assessed non-invasively by a simple technique that provides reproducible measurements within a few minutes and the values of SBP_{Ao}, pulse wave velocity (PWV) and augmentation index (AIx) have been validated against invasive monitoring[17]. In women with established PE there is an increase in the values of PWV and AIx, which are measures of arterial stiffness[18].

The aim of this screening study was to examine the potential value of assessment of arterial stiffness and SBP_{Ao} at 11–13 weeks' gestation in identifying women

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who subsequently develop PE, and to examine the association between the markers of arterial stiffness and UtA-PI and serum PAPP-A.

METHODS

This was part of a screening study for adverse obstetric outcomes in women attending for their routine first-trimester (11 + 0 to 13 + 6 weeks' gestation) ultrasound scan at University College Hospital and King's College Hospital, London, UK, between December 2009 and February 2011. At this visit we recorded maternal characteristics and medical history, and performed combined screening for aneuploidies by measurement of fetal crown–rump length, nuchal translucency thickness and maternal serum PAPP-A and free β-human chorionic gonadotropin levels[19,20]. We also used transabdominal color Doppler ultrasonography to visualize the left and right UtAs, measured the PI in each vessel and calculated the mean PI[11]. The Arteriograph (TensioMed Ltd, Budapest, Hungary) was used to measure the AIx, PWV and SBP_{Ao}. Written informed consent was obtained from all women agreeing to participate in the study, which was approved by the London–Surrey Borders Research Ethics Committee.

Data on pregnancy outcomes were collected from the hospital maternity records or the women's general practitioners. The obstetric records of all women with pre-existing or pregnancy-induced hypertension were examined to determine if the condition was chronic hypertension, PE or gestational hypertension (GH).

The inclusion criteria for this study were women with a singleton pregnancy and a live fetus identified at the 11 + 0 to 13 + 6-week scan. We excluded pregnancies with major fetal abnormalities and those ending in termination, miscarriage or fetal death before 24 weeks' gestation.

Maternal history and characteristics

The women were asked to complete a questionnaire on their age, racial origin (Caucasian, African, South Asian, East Asian or mixed), method of conception (spontaneous or assisted requiring the use of ovulation-inducing drugs), cigarette smoking during pregnancy (yes or no), history of chronic hypertension (yes or no), family history of PE in the mother of the patient (yes or no) and obstetric history including parity (parous or nulliparous if no previous pregnancies delivering at or after 24 weeks) and previous pregnancy with PE (yes or no). The questionnaire was then reviewed by a doctor together with each woman. Maternal weight and height were measured and BMI calculated.

Outcome measures

Diagnosis of PE and GH was made according to the criteria of the International Society for the Study of Hypertension in Pregnancy[21]. GH is characterized by systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least two occasions 4 h apart developing after 20 weeks' gestation in previously normotensive women in the absence of significant proteinuria. PE is characterized by GH with proteinuria of ≥ 300 mg in 24 h, or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection is available. PE superimposed on chronic hypertension is characterized by significant proteinuria (as defined above) developing after 20 weeks' gestation in women with known chronic hypertension (a history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks in the absence of trophoblastic disease).

Arteriograph measurements

All measurements were performed in a temperature-controlled room (22°C) with participants in the supine position. The Arteriograph cuff was then applied to the left arm over the brachial artery for estimation of SBP_{Ao} (mmHg), PWV (m/s) and AIx (%) as previously described[22]. All recordings were made by doctors who had received appropriate training in the use of the Arteriograph. The results of PWV, AIx and SBP_{Ao} were not given to the women or their doctors and did not influence the subsequent management of their pregnancies.

Statistical analysis

Comparison between the outcome groups was by χ^2-test or Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Data are presented as median and interquartile range (IQR) for continuous data and as *n* (%) for categorical variables.

The distributions of AIx, PWV and SBP_{Ao} were made Gaussian after logarithmic transformation. The normality of distributions was tested using histograms and probability plots after excluding outliers outside three SDs. Each value in the PE, GH and unaffected groups was expressed as a multiple of the median (MoM) after adjustment for those characteristics found to provide a substantial contribution to the log-transformed value in the multiple regression analysis, as previously described[22]. As there was a linear relationship between AIx and heart rate, AIx was adjusted to a heart rate of 75 beats per minute (AIx-75). Similarly, the measured values of PAPP-A and UtA-PI in each of the outcome groups were adjusted for maternal characteristics as previously described[23]. Pearson correlation analysis was used to examine the intercorrelation between $\log_{10}$AIx-75 MoM, $\log_{10}$PWV MoM, $\log_{10}SBP_{Ao}$ MoM, $\log_{10}$PAPP-A MoM and $\log_{10}$UtA-PI MoM.

Multivariate logistic regression analysis was used to examine which of the maternal characteristics provided a significant contribution to predicting the subsequent development of PE. The predicted probabilities based on maternal characteristics were then logarithmically transformed to derive the patient-specific *a-priori* risks based on maternal factors. Logistic regression analysis was then used to determine whether $\log_{10}$AIx-75 MoM, $\log_{10}$PWV MoM and $\log_{10}SBP_{Ao}$ MoM provided a significant

contribution to predicting PE and whether they improved the performance of screening that was achieved by maternal factors alone. In the case of the vascular-derived risk for PE (combination of $\log_{10}$AIx-75 MoM, $\log_{10}$PWV MoM and $\log_{10}SBP_{Ao}$ MoM) there was no significant association with gestational age at delivery in the PE group whereas the increase in UtA-PI and decrease in PAPP-A were more marked in early PE, requiring delivery before 34 weeks' gestation, compared to late PE (see Results). Multivariate logistic regression analysis was used to examine the value of the combined risk (*a-priori* risk based on maternal factors and vascular-derived risk) together with $\log_{10}$UtA-PI MoM and $\log_{10}$PAPP-A MoM in the prediction of early PE and late PE. The detection and false positive rates (FPR) were calculated as the respective proportions of PE (detection rate) and unaffected pregnancies (FPR) and the performance of screening was determined by receiver–operating characteristics (ROC) curve analysis. The performance of different methods of screening was compared by the areas under the ROC curves (AUC)[24].

The statistical software package SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

Study population

Maternal PWV, AIx and SBP_{Ao} were successfully recorded in 7653 singleton pregnancies. We excluded 569 (7.4%) because they had missing outcome data ($n = 449$), the pregnancy resulted in fetal death or miscarriage before 24 weeks' gestation ($n = 60$) or the pregnancy was terminated for fetal abnormalities or social reasons ($n = 60$). In the remaining 7084 cases, 181 (2.6%) developed PE, including 21 with PE superimposed on chronic hypertension, 137 (1.9%) developed GH and 6766 (95.5%) were unaffected by PE or GH.

The maternal characteristics of each outcome group are given in Table 1. In the PE group, compared with the unaffected group, women were heavier, more were of African origin, had had PE in a previous pregnancy, had a family history of PE, had had assisted conception, had chronic hypertension and delivered neonates with a lower birth weight percentile. In the GH group, compared with the unaffected group, women were heavier, more were of African origin and had had PE in a previous pregnancy.

Hypertensive disorders

In the pregnancies that subsequently developed PE, compared with the unaffected group, there was a significant increase in AIx-75, PWV, SBP_{Ao} and UtA-PI, and a decrease in serum PAPP-A. In those who subsequently developed GH, compared with unaffected controls, there was no significant difference in UtA-PI, PAPP-A or PWV, but AIx-75 and SBP_{Ao} were increased (Table 2, Figure 1).

In the study group, 68 women had chronic hypertension, including 21 who subsequently developed

Table 1 Characteristics of the three outcome groups

Characteristic	*Unaffected group* (n = *6766*)	*Pre-eclampsia group* (n = *181*)	*Gestational hypertension group* (n = *137*)
Maternal characteristics			
Age (years)	32.0 (28.0–35.4)	32.8 (27.9–37.1)	31.7 (28.5–35.5)
Weight (kg)	64.0 (57.6–72.0)	70.0 (63.1–80.9)*	70.0 (60.7–83.2)*
Height (m)	1.65 (1.60–1.69)	1.64 (1.60–1.68)	1.64 (1.60–1.69)
Body mass index (kg/m^2)	23.5 (21.3–26.5)	26.4 (23.5–29.7)*	26.5 (23.2–29.8)*
Ethnicity			
Caucasian	4898 (72.4)	94 (51.9)*	84 (61.3)
African	1005 (14.9)	67 (37.0)*	37 (27.0)*
South Asian	416 (6.1)	13 (7.2)	10 (7.3)
East Asian	271 (4.0)	3 (1.7)	4 (2.9)
Mixed	176 (2.6)	4 (2.2)	2 (1.5)
Parity			
Nulliparous	3665 (54.2)	109 (60.2)	84 (61.3)
Parous: no previous pre-eclampsia	2933 (43.3)	42 (23.2)*	34 (24.8)*
Parous: previous pre-eclampsia	168 (2.5)	30 (16.6)*	19 (13.9)*
Cigarette smoker	413 (6.1)	11 (6.1)	3 (2.2)
Family history of pre-eclampsia	310 (4.6)	23 (12.7)*	5 (3.6)
Conception			
Spontaneous	6486 (95.9)	166 (91.7)	129 (94.2)
Ovulation drugs	280 (4.1)	15 (8.3)*	8 (5.8)
Chronic hypertension	47 (0.7)	21 (11.6)*	0 (0.0)
Fetal characteristics			
Gestational age at recruitment (weeks)	12.6 (12.3–13.1)	12.7 (12.3–13.1)	12.7 (12.2–13.1)
Crown–rump length at recruitment (mm)	62.3 (57.5–67.6)	62.4 (57.7–67.1)	62.3 (56.9–68.4)
Gestational age at delivery (weeks)	40.0 (39.0–40.9)	38.6 (36.8–40.1)*	40.1 (38.9–41.0)
Birth-weight percentile	47.0 (26.5–67.9)	20.8 (4.7–50.9)*	44.9 (20.5–70.4)

Data are given as median (interquartile range) or *n* (%). Each outcome group was compared with controls by χ^2 test and Fisher exact test for categorical variables and Mann–Whitney test with *post hoc* Bonferroni correction for continuous variables. *$P < 0.025$.

Table 2 Augmentation index, pulse wave velocity, central aortic systolic blood pressure, uterine artery pulsatility index and pregnancy associated plasma protein-A in unaffected pregnancies and those that subsequently developed pre-eclampsia and gestational hypertension

Variable	*Unaffected group* (n = *6766*)	*Pre-eclampsia group* (n = *181*)	*Gestational hypertension group* (n = *137*)
Augmentation index			
%	10.6 (5.4–16.7)	13.2 (7.0–21.6)	12.2 (5.8–19.4)
MoM	1.00 (0.87–1.16)	1.13 (0.96–1.33)*	1.07 (0.90–1.33)*
Pulse wave velocity			
m/s	6.55 (5.82–7.41)	7.47 (6.60–8.14)	6.99 (6.23–8.20)
MoM	1.00 (0.90–1.12)	1.06 (0.97–1.17)*	1.03 (0.92–1.16)
Central systolic blood pressure			
mmHg	108 (101–117)	122 (113–133)	119 (111–130)
MoM	1.00 (0.94–1.08)	1.09 (1.02–1.20)*	1.08 (1.02–1.16)*
Uterine artery pulsatility index			
Unit	1.72 (1.40–2.08)	2.10 (1.66–2.50)	1.84 (1.27–2.18)
MoM	1.00 (0.82–1.21)	1.20 (0.97–1.44)*	1.10 (0.76–1.28)
Pregnancy associated plasma protein-A			
mIU/mL	2.80 (1.83–4.34)	2.59 (1.55–3.84)	2.79 (1.74–4.27)
MoM	1.00 (0.69–1.42)	0.92 (0.63–1.25)*	1.03 (0.68–1.43)

Data are presented as median (interquartile range). Each outcome group was compared with controls by Mann–Whitney test with *post hoc* Bonferroni correction. *$P < 0.025$. MoM, multiples of the median.

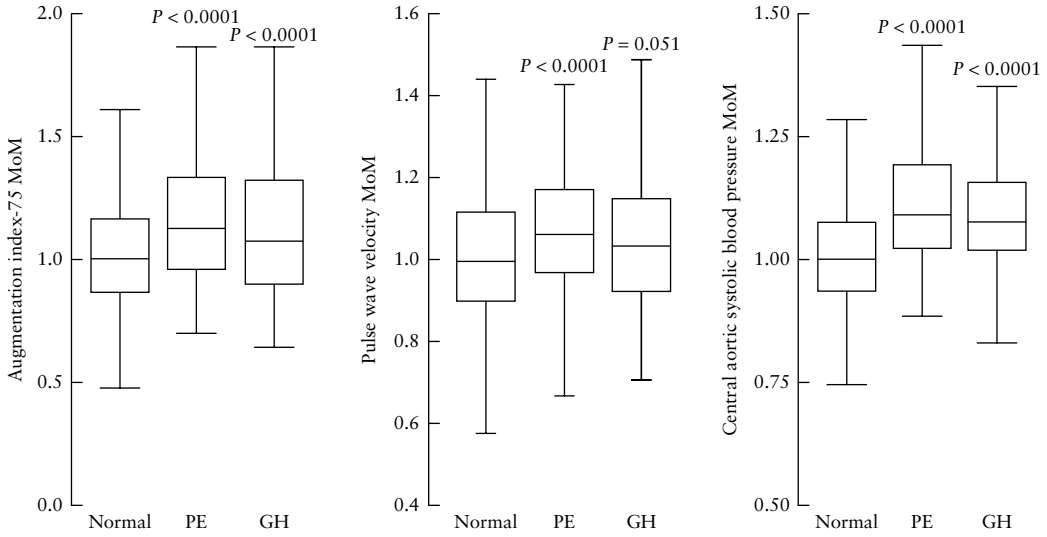

Figure 1 Box-and-whisker plots of augmentation index-75 multiples of the median (MoM), pulse wave velocity MoM and central systolic blood pressure MoM in unaffected controls and in those who developed pre-eclampsia (PE) or gestational hypertension (GH). The horizontal line in the box represents the median, the box represents the interquartile range and the whiskers indicate the minimum and maximum values.

superimposed PE and 47 who did not. In the group with chronic hypertension, in those who developed PE, compared to those who did not, the SBP_{Ao} (1.29 vs. 1.15 MoM; $P = 0.001$) was increased but there was no significant difference in PWV (1.02 vs.1.00 MoM; $P = 0.921$) or AIx-75 (1.37 vs. 1.21 MoM; $P = 0.104$), UtA-PI (1.04 vs. 1.07 MoM; $P = 0.738$) or PAPP-A (0.92 vs. 0.84 MoM; $P = 0.268$). In the total population, after exclusion of women with chronic hypertension, in those who developed PE compared to those who did not there was a significant increase in AIx-75 (1.09 vs. 1.00 MoM; $P < 0.0001$), PWV (1.08 vs. 1.00 MoM; $P < 0.0001$), SBP_{Ao} (1.08 vs. 1.00; $P < 0.0001$) and UtA-PI (1.21 vs. 1.00 MoM; $P < 0.0001$), and a decrease in serum PAPP-A (0.92 vs. 1.00; $P = 0.006$).

In the PE group, there was no significant association of $\log_{10}$AIx-75 MoM, $\log_{10}$PWV MoM and $\log_{10}SBP_{Ao}$ MoM with $\log_{10}$UtA-PI MoM or $\log_{10}$PAPP-A MoM (Table 3). Similarly, there was no significant association of $\log_{10}$AIx-75 MoM, $\log_{10}$PWV MoM and $\log_{10}SBP_{Ao}$ MoM with gestational age at delivery ($P = 0.728$, 0.188 and 0.722, respectively). However, there were significant associations between $\log_{10}$UtA-PI MoM ($r = -0.334$, $P < 0.0001$) and $\log_{10}$PAPP-A MoM ($r = 0.357$, $P < 0.0001$) and gestational age at delivery.

Table 3 Intercorrelations between log_{10}augmentation index-75 (AIx-75) multiples of the median (MoM), log_{10}pulse wave velocity (PWV) MoM, log_{10}central systolic blood pressure (SBP_{Ao}) MoM, log_{10}uterine artery pulsatility index (UtA-PI) MoM and log_{10}pregnancy associated plasma protein-A (PAPP-A) MoM in pregnancies destined to develop pre-eclampsia

Variable	*PWV MoM*	*SBP_{Ao} MoM*	*UtA-PI MoM*	*PAPP-A MoM*
Alx-75 MoM				
Pearson correlation (*r*)	0.209	0.630	−0.101	0.052
P	0.005	< 0.0001	0.186	0.498
PWV MoM				
Pearson correlation (*r*)		0.028	0.026	−0.022
P		0.705	0.737	0.769
SBP_{Ao} MoM				
Pearson correlation (*r*)			−0.095	0.075
P			0.213	0.326
UtA-PI MoM				
Pearson correlation (*r*)				−0.249
P				0.001

Table 4 Performance of screening for pre-eclampsia by maternal factors (history), augmentation index-75 (AIx-75), pulse wave velocity (PWV), central systolic blood pressure (SBP_{Ao}), uterine artery pulsatility index (UtA-PI), pregnancy associated plasma protein-A (PAPP-A), and by their combinations

		Detection rate (95% CI) for:		
Screening test	*AUC (95% CI)*	*5% FPR*	*10% FPR*	P
History	0.801 (0.792–0.811)	33.7 (26.9–41.1)	47.0 (39.5–54.5)	
History plus vascular-derived risk	0.835 (0.826–0.843)	43.7 (36.3–51.2)	56.9 (49.4–64.2)	0.005*
History plus vascular-derived risk, UtA-PI and PAPP-A	0.846 (0.837–0.855)	46.4 (38.7–54.3)	61.9 (54.1–69.3)	0.001*

*Comparison with performance of screening based on maternal factors only. AUC, area under receiver–operating characteristics curve; FPR, false-positive rate.

Performance of screening for pre-eclampsia

We used logistic regression analysis to calculate the contribution of various maternal factors to the prediction of PE. This demonstrated that, in the prediction of PE, there were significant contributions from log_{10}AIx-75 MoM (odds ratio (OR) $11.7E^{-02}$ (95% CI, $2.1E^{-02}$ to $65.2E^{-02}$); $P = 0.014$), log_{10}PWV MoM (OR 44.5 (95% CI, 5.7–348.6); $P < 0.0001$) and $log_{10}SBP_{Ao}$ MoM (OR $2.0E^{08}$ (95% CI, $5.6E^{07}$ to $7.0E^{09}$); $P < 0.0001$). These vascular parameters were used to calculate a vascular-derived risk and the patient-specific risk for PE was calculated from the formula: odds/(1+odds), where odds $= e^{Y}$ and Y was derived from multivariate logistic regression analysis ($R^2 = 0.102$, $P < 0.0001$).

The estimated detection rates of PE at a fixed FPR of 5% and 10% and their respective AUCs in screening by maternal factor-derived *a-priori* risk, log_{10}AIx-75 MoM, log_{10}PWV MoM and $log_{10}SBP_{Ao}$ MoM and by their combinations are shown in Table 4. The estimated detection rate of screening for PE by the combined test (maternal factor-derived *a-priori* risk and vascular-derived risk) was 56.9% at an FPR of 10%. The combination of maternal factors plus vascular-derived risk significantly improved the performance of screening compared to that provided by maternal factors alone (AUC 0.835 (95% CI, 0.826–0.843) vs. 0.801 (95% CI, 0.792–0.811); $P = 0.005$) (Table 4).

Multivariate logistic regression analysis demonstrated that in the prediction of early PE, there were significant contributions from the log_{10} combined maternal factors and vascular-derived risk (OR 14.57 (95% CI, 6.53–32.54); $P < 0.0001$), log_{10}UtA-PI MoM (OR 5.16 (95% CI, 1.68–15.88); $P = 0.004$) and log_{10}PAPP-A MoM (OR 0.03 (95% CI 0.01–0.13); $P < 0.0001$). The estimated detection rate of early PE at an FPR of 10% improved from 56.5% using the combined test alone to 71.4% with the addition of log_{10}UtA-PI MoM and log_{10}PAPP-A MoM.

In the prediction of late PE, addition of log_{10}UtA-PI MoM or log_{10}PAPP-A MoM did not significantly improve the performance of screening provided by the combination of maternal factors and vascular-derived risk alone (AUC 0.836 (95% CI, 0.803–0.869) vs. 0.841 (95% CI, 0.807–0.875); $P = 0.474$). The estimated detection rate of late PE was 60.5% at an FPR of 10%.

DISCUSSION

The findings of this study suggest that first, compared with women who remain normotensive, women who develop PE have greater arterial stiffness and higher SBP_{Ao}, which are evident from the first trimester of pregnancy and second, in these cases the mechanism of association with PE is not mediated by impaired placental perfusion and function.

The major strength of the study is the inclusion of a large number of patients within the narrow gestational range of 11–13 weeks, which is emerging as the optimal time for the first clinical visit in pregnancy for assessment of patient-specific risks for a wide range of pregnancy complications[25]. A limitation of the study is the lack of longitudinal data during pregnancy and assessment of the patients with PE after pregnancy to document whether, in those with increased arterial stiffness and SBP_{Ao}, there was persistence of these abnormalities. Although the validity of these vascular parameters for the prediction of cardiovascular disease has been established in non-pregnant individuals[17], they have not yet been validated in pregnancy.

The best of these indices for the prediction of PE was SBP_{Ao}. Current obstetric practice relies on the measurement of peripheral blood pressure. However, SBP_{Ao} may be more valuable in understanding cardiovascular pathophysiology and has been shown to relate more strongly to vascular hypertrophy, extent of atherosclerosis and cardiovascular events than does brachial blood pressure[14].

In normal pregnancies PWV, AIx-75 and SBP_{Ao} were related to certain maternal characteristics, including increase with maternal age for AIx-75 and PWV, decrease with maternal height for AIx-75 and increase with maternal weight for PWV and SBP_{Ao} and decrease for AIx-75[22]. The multiple regression models of the association of each parameter with maternal characteristics were used to derive MoM values before valid comparisons could be made between normal and pathological pregnancies.

The results of this screening study are consistent with those of our two previous smaller first-trimester studies[26,27]. In the first study we measured AIx-75 at 11–13 weeks' gestation in 210 pregnancies and found this index to be significantly increased in the 14 cases that subsequently developed PE[26]. Similarly, in a second study of 210 pregnancies, including 42 that developed PE, AIx-75 was higher in the PE group than in those that remained normotensive[27].

The mechanism linking these abnormal findings and PE may be analogous to that of gestational diabetes mellitus, in which women destined to develop type 2 diabetes mellitus in their 40s or 50s often present with gestational diabetes mellitus in their 20s or 30s[28,29]. Previous studies have reported increased arterial stiffness in women with clinically established PE[18]; in women who had developed PE in pregnancy, several months after delivery[30,31]; in healthy non-pregnant individuals who subsequently developed cardiovascular disease[32–34]; and in hypertensive patients at increased risk of subsequent death[35,36]. It is, therefore, likely that the abnormal cardiovascular findings in early pregnancy in women who subsequently develop PE may actually predate conception. This is well recognized for patients with chronic hypertension but, as demonstrated in our study, the same may also be true for women who at the beginning of their pregnancy are normotensive.

The effectiveness of screening for PE by maternal hemodynamics was unrelated to the gestational age at delivery. In contrast, increased UtA-PI and reduced serum PAPP-A, reflecting impaired placentation, were more marked in those developing early rather than late PE. These results are compatible with the concept that PE may be the common phenotypic expression of two distinct and unrelated processes, one based on a predisposition to cardiovascular disease that under the physiologic stress of pregnancy manifests as either early or late PE, the other resulting in early PE as a consequence of impaired trophoblastic invasion of the maternal spiral arteries.

Recent evidence suggests that the prophylactic use of low-dose aspirin starting in early pregnancy can potentially halve the rate of PE[37]. In the UK, The National Institute for Health and Clinical Excellence recommends that all pregnant women should be routinely screened in the first trimester for the risk of PE based on maternal characteristics and previous history, and those at high risk should be treated with aspirin[38]. We have previously demonstrated that the best approach to estimating a maternal factor-based risk is to incorporate the various characteristics into a combined algorithm derived by multivariate analysis[12]. In this study we found that such a maternal factor-based method of screening identifies around 45% of cases that develop PE, at an FPR of 10%. The detection rate was improved by combining maternal factors with the vascular parameters at 11–13 weeks' gestation. The extent to which such combined testing, undertaken before conception and thus allowing for earlier administration of aspirin, could result in further reduction in the prevalence of PE merits further investigation.

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