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Longitudinal changes in uterine artery Doppler and blood pressure and risk of pre-eclampsia

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KEYWORDS: blood pressure; gestational hypertension; pre-eclampsia; pregnancy screening; uterine artery Doppler

ABSTRACT

Objective *To investigate longitudinal changes in the uterine artery mean pulsatility index (UtA-PI) and mean arterial pressure (MAP) in women who develop pre-eclampsia (PE) and 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 UtA-PI and MAP were taken every 4 weeks until delivery and were compared in women who developed preterm PE, requiring delivery before 37 weeks, term PE and GH with those in women who remained normotensive.*

Results *In the normal outcome group, UtA-PI decreased with gestational age and MAP decreased between 12 and 24 weeks and then increased. In the preterm PE group, as compared to the normal group, UtA-PI and MAP were higher from early pregnancy onward and the difference for both increased with gestational age. In the term PE group, UtA-PI was significantly increased only from 33 weeks onward and MAP was increased from 12 weeks onward but the difference from normal did not increase with gestation. In GH, UtA-PI did not differ significantly from normal but MAP was higher from 12 weeks onward.*

Conclusion *The study describes temporal changes in UtA-PI and MAP in normal pregnancies and in women who develop PE and GH.* *Copyright © 2013 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Pre-eclampsia (PE), which affects 2–3% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality[1–3]. Maternal predisposition for cardiovascular disease, manifesting as elevated blood pressure, and impairment in the physiological process of trophoblastic invasion of the maternal spiral arteries, manifesting as an increased uterine artery pulsatility index (UtA-PI), have been proposed to play key roles in the pathogenesis of PE[4–7].

Several studies have demonstrated that women who will later develop PE can be predicted on the basis of mean arterial pressure (MAP) and UtA-PI but these studies have focused on specific gestational age windows, commonly 11–13, 20–24 and 30–33 weeks[7–14]. The aim of this study was to investigate longitudinal changes in UtA-PI and MAP from the first trimester onward in women who subsequently develop PE and gestational hypertension (GH).

METHODS

At University College London Hospital, the risk of developing of PE was routinely assessed at 11 + 0 to 13 + 6 weeks' gestation using a combination of maternal history, UtA-PI, MAP and serum pregnancy-associated plasma protein A[9]. Those considered to be at high risk for early PE were followed in a specialist hypertension clinic in which UtA-PI and MAP were measured every 4 weeks until delivery. 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 structural abnormalities.

Recorded patient characteristics included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian or mixed), method of conception (spontaneous

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or assisted, requiring the use of ovulation drugs), smoking status during pregnancy, history of chronic hypertension or pre-existing diabetes mellitus, history of PE in the patient's mother 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 calculated in kg/m^2.

Color Doppler was used transabdominally to visualize in turn the left and right uterine arteries on either side of the cervix before 14 weeks' gestation[8] and at the apparent crossover with the external iliac arteries after 14 weeks[15]. Pulsed-wave Doppler was then used to obtain waveforms, and, when three similar consecutive waveforms were obtained, the PI was measured and the mean PI of the two vessels was calculated. All sonographers had obtained the Fetal Medicine Foundation Certificate of Competence in Doppler.

MAP was measured by automated devices (3BTO-A2; Microlife, Taipei, Taiwan) that were calibrated before and at regular intervals during the study[16]. Recordings were made by doctors who had received appropriate training in the use of these machines. Women were in the sitting position, their arms supported at the level of the heart and either a small (< 22 cm), normal (22–32 cm) or large (33–42 cm) adult cuff was used, depending on mid-arm circumference. After rest for 5 min, two recordings of blood pressure (BP) were made in both arms simultaneously. We calculated final MAP and systolic and diastolic BP as the average of the four measurements[17].

Data on pregnancy outcome were collected from hospital maternity records. Obstetric records of women with pre-existing or pregnancy-associated hypertension were examined to determine whether the condition was chronic hypertension, PE or GH. The diagnosis of PE and GH was made according to guidelines of the International Society for the Study of Hypertension in Pregnancy[18]. In the case of GH systolic BP should be $\geq$ 140 mmHg and/or diastolic BP should be $\geq$ 90 mmHg on at least two occasions 4 hours apart, after 20 weeks' gestation in previously normotensive women in the absence of significant proteinuria. In the case of PE there should be GH with proteinuria of $\geq$ 300 mg/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) would 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 Fisher's exact or chi-square 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 data and as *n* (%) for categorical variables.

UtA-PI and MAP values were made Gaussian after logarithmic transformation. Analysis of repeated measures with a multilevel mixed-effects linear model (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 includes the intercept as well as linear effects of gestational age. Repeat measurements at different weeks of gestation in the same woman constituted level 1 and each individual constituted level 2. Prior to performing 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 and 32 from maternal age in years).

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

RESULTS

A total of 1198 observations were recorded for 245 women, with a median of three (range, 1–9) measurements for each. Among these women, 181 had a normal outcome, 20 developed GH, 22 developed PE requiring delivery after 37 weeks (term PE) and 22 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 or preterm PE. Median weight was higher in women who developed term PE and height was lower in women who developed term 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 the outcome groups.

For UtA-PI, 1139 observations were recorded in 241 women, with a median of three (range, 1–9) measurements for each woman. Among these women, 178 had a normal outcome, 19 developed GH, 22 developed term PE and 22 developed preterm PE. Log_{10} UtA-PI decreased significantly with maternal weight and chronic hypertension (Table 2) but was not significantly affected by maternal age ($P = 0.095$), height ($P = 0.306$), racial origin ($P = 0.237$), parity ($P = 0.483$), smoking status ($P = 0.910$) or mode of conception ($P = 0.947$).

In the normal outcome group, there was a cubic decrease in $\log_{10}$ UtA-PI with gestational age (Table 2, Figure 1). In women who subsequently developed GH, $\log_{10}$ UtA-PI did not differ significantly from that in those who had a normal outcome (Table 2, Figures 2 and 3). In the term PE group, as compared to the normal

Table 1 Maternal characteristics according to outcome group

Characteristic	*Outcome*			
	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	3 (1.7)	0	1 (4.5)	0
Intrauterine insemination	4 (2.2)	2 (10.0)	0	0
IVF	3 (1.7)	0	1 (4.5)	1 (4.5)
Chronic hypertension	3 (1.7)	0	2 (9.1)	2 (9.1)
Gestational age 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. $*P < 0.005$. $**P < 0.001$. IVF, *in-vitro* fertilization.

Table 2 Summary of multilevel linear mixed-effects models for $\log_{10}$ uterine artery pulsatility index and $\log_{10}$ mean arterial pressure

Variable	*Log_{10} uterine artery pulsatility index*			*Log_{10} mean arterial pressure*		
	Estimate	*SE*	P	*Estimate*	*SE*	P
Fixed part						
Intercept	1.442376	0.108965	< 0.001	1.990190	0.008353	< 0.001
GH	−0.048600	0.047099	0.303	0.025714	0.012291	0.037
Term PE	−0.110726	0.042050	0.009	0.023331	0.011058	0.035
Preterm PE	−0.055166	0.047681	0.248	−0.025005	0.012486	0.046
GA (weeks)	−0.114558	0.014474	< 0.001	−0.005261	0.000680	< 0.001
GA (weeks)^2	0.003081	0.000605	< 0.001	0.000119	0.000013	< 0.001
GA (weeks)^3	−0.000030	0.000008	< 0.001			
Interaction between GH and GA	0.003337	0.001861	0.074	−0.000197	0.000419	0.638
Interaction between term PE and GA	0.005320	0.001651	0.001	−0.000347	0.000379	0.360
Interaction between preterm PE and GA	0.010002	0.002011	< 0.001	0.002953	0.000473	< 0.001
Weight (− 70)*	−0.000935	0.000357	0.009	0.000789	0.000115	< 0.001
Chronic hypertension	−0.067732	0.030171	0.026	0.035260	0.009648	< 0.001
Random part						
Level 2						
Variance (constant)	0.012191	0.003422	< 0.001	0.001065	0.000163	< 0.001
Variance (GA)	0.000018	0.000005	< 0.001	0.000001		
Covariance (constant, GA)	−0.000359	0.000124	0.004	−0.000018	0.000003	< 0.001
Level 1						
Residual	0.008949	0.000487	< 0.001	0.000579	0.000028	< 0.001

*Subtracted from maternal weight in kg. GA, gestational age; GH, gestational hypertension; PE, pre-eclampsia; SE, standard error.

group, UtA-PI was significantly lower in the first trimester but the decrease in PI with gestational age was less pronounced and the value became significantly higher from 33 weeks onward (Table 2, Figures 2 and 3). In the preterm PE group, UtA-PI was significantly increased from 12 weeks onward and the expected PI reduction throughout gestation was significantly less pronounced (Table 2, Figures 2 and 3).

For MAP, 1185 observations were recorded in 243 women, with a median of three (range, 1–9) measurements for each woman. Among these women, 179 had a normal outcome, 20 developed GH, 22 developed term PE and 22 developed preterm PE. Log_{10} MAP values decreased significantly with maternal weight and chronic hypertension (Table 2) but were not significantly affected by maternal age ($P = 0.370$), height ($P = 0.960$), racial

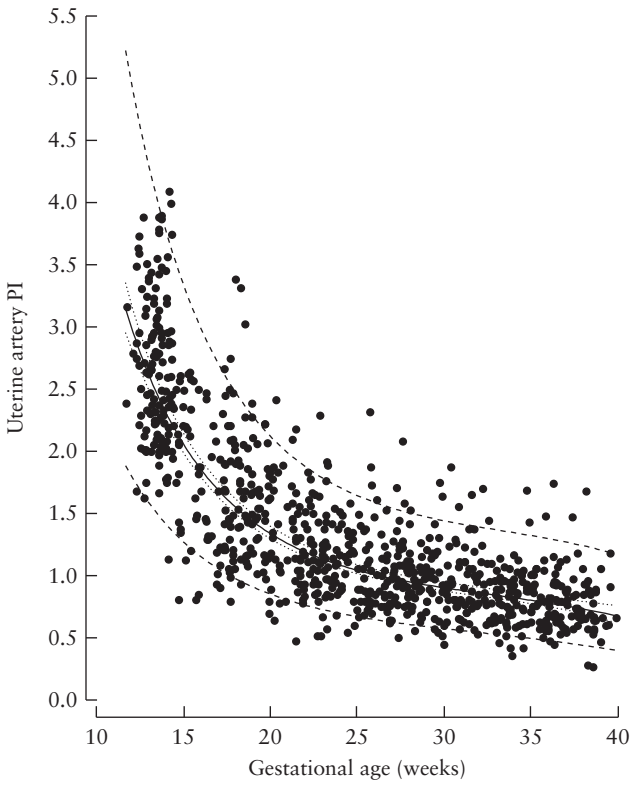

Figure 1 Uterine artery Doppler mean pulsatility index (PI) in pregnancies with normal outcome. ——, mean values; - - - -, 5th and 95th centiles; ·····, 95% CI of mean values.

origin ($P = 0.274$), parity ($P = 0.088$), smoking status ($P = 0.574$) or mode of conception ($P = 0.887$).

In the normal outcome group, there was a quadratic decrease in $\log_{10}$ MAP with gestational age (Table 2, Figure 4). In the GH and term PE groups, $\log_{10}$ MAP was significantly higher than that in the normal outcome group throughout pregnancy and the difference in MAP did not change significantly with gestational age (Table 2, Figures 5 and 6). In the preterm PE group, as compared to the normal group, MAP was significantly higher from 14 weeks onward and the difference increased significantly with gestational age (Table 2, Figures 5 and 6).

DISCUSSION

This study demonstrates that in the normal outcome group UtA-PI decreases with gestational age and MAP decreases between 12 and 24 weeks' gestation and then increases. In the preterm PE group, as compared to the normal group, UtA-PI and MAP are higher from early pregnancy onward and the difference for both increases with gestational age. In the term PE group, UtA-PI is significantly increased only from 33 weeks onward and MAP is increased from 12 weeks onward but the difference from normal does not increase with gestation. In the GH group, UtA-PI does not differ significantly from the normal group but MAP is increased from 12 weeks onward.

Major strengths of this study are the large number of observations made in a prospective longitudinal manner, a well-defined methodology, appropriately trained doctors for recording UtA-PI and MAP and a robust statistical approach that takes into account not only the difference in marker levels in the outcome groups but also the change with gestational age. This approach differs from the calculation of trends with gestation based on large numbers of cross-sectional and unrelated measurements. A limitation of the study is the lack of prepregnancy data to establish the existence of cardiovascular predisposition to development of hypertensive disorders in pregnancy.

In women who develop PE, UtA-PI is increased but in those with GH there is no significant difference as compared to women with normal pregnancies. In the preterm PE group the increase in UtA-PI is apparent from the first trimester and can be attributed to impaired trophoblastic invasion of the maternal spiral arteries. In the term PE group, significant increase in PI becomes apparent only during the third trimester, possibly as a consequence of vasoconstriction in uteroplacental circulation soon before clinical onset of the disease rather than impaired placentation.

The finding that in the preterm PE group UtA-PI was higher than in the normal group, and the difference increased with gestational age, is consistent with previous studies in which UtA-PI was measured in both the first and second trimesters. Plasencia *et al.* reported that the decrease in UtA-PI between the first and second trimesters was steeper in pregnancies with normal outcome than in those with PE; in women with normal pregnancies presenting with high UtA-PI at 11–13 weeks' gestation, PI normalized with advancing gestational age[19]. Similarly, Gomez *et al.* reported that in normal pregnancies the prevalence of abnormal UtA-PI decreased from 14% in the first trimester to 4% in the second trimester and persistence of high PI identified the group as having the greatest risk for adverse perinatal outcome[20]. A smaller study in high-risk pregnancies reported that, in all cases developing preterm PE, there was an increase in UtA-PI between the first and second trimesters. It was also shown that in pregnancies in which abnormal UtA-PI in the first trimester had become normal by the second, the risk of PE was similar to that in the group with normal PI in both trimesters[21].

In the normal outcome group, the initial decrease in MAP with gestational age to a nadir at 22–24 weeks is likely to be the consequence of progesterone-related vasodilation and decrease in systemic vascular resistance[22–24]. The subsequent increase in MAP with gestational age has been attributed to the different net effect of increased cardiac output, reduced vascular resistance and increased blood volume secondary to water retention. There are also cardiac changes, such as further increase in heart rate during the second trimester and increase in left atrial and left ventricular end-diastolic dimensions, suggesting an increase in venous return[25,26]. In the PE and GH groups, as compared to the normal group, MAP was higher from the first trimester onward; and in the preterm PE group, but not in the term PE or GH group, the difference increased with gestational age. These

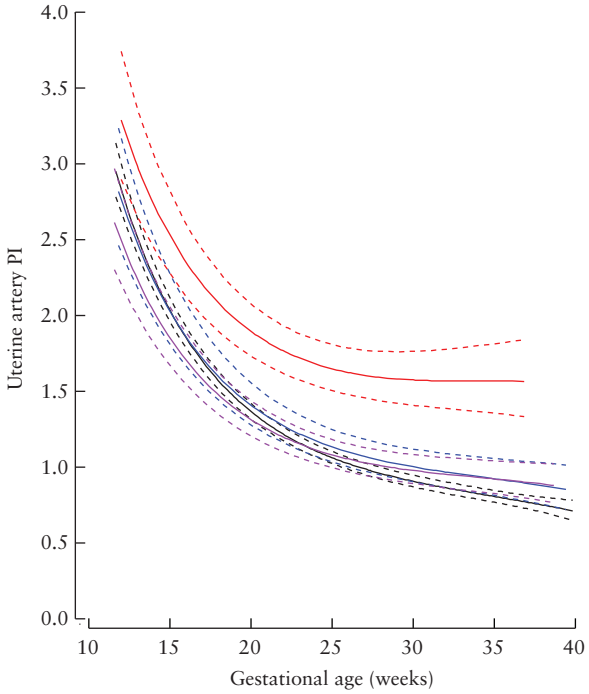

Figure 2 Uterine artery Doppler mean pulsatility index (PI) in pregnancies with normal outcome (——) and those complicated with preterm pre-eclampsia (PE) (——), term PE (——) and gestational hypertension (——). ——, mean values; - - - -, 95% CI of the mean values.

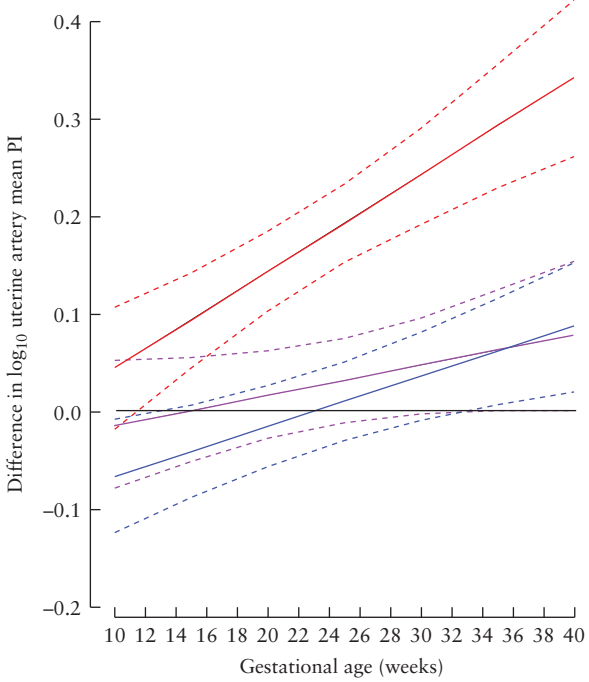

Figure 3 Difference in uterine artery Doppler mean pulsatility index (PI) between each outcome group and normotensive pregnancies. The difference was significant in preterm pre-eclampsia (PE) between 11 and 12 weeks' gestation and in term PE between 33 and 34 weeks' gestation. ——, Preterm PE; ——, term PE; ——, gestational hypertension. ——, mean values; - - - -, 95% CI in each outcome group.

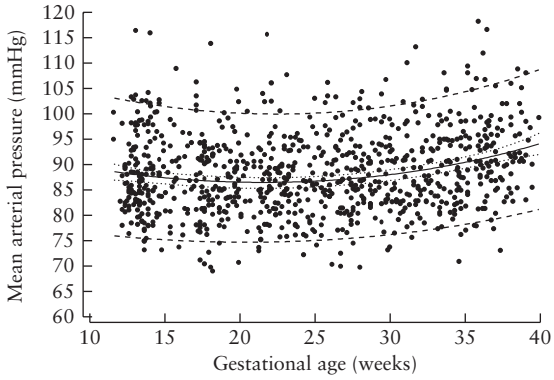

Figure 4 Mean arterial pressure in pregnancies with normal outcome. ——, mean values; -----, 5th and 95th centiles; ·····, 95% CI of mean values.

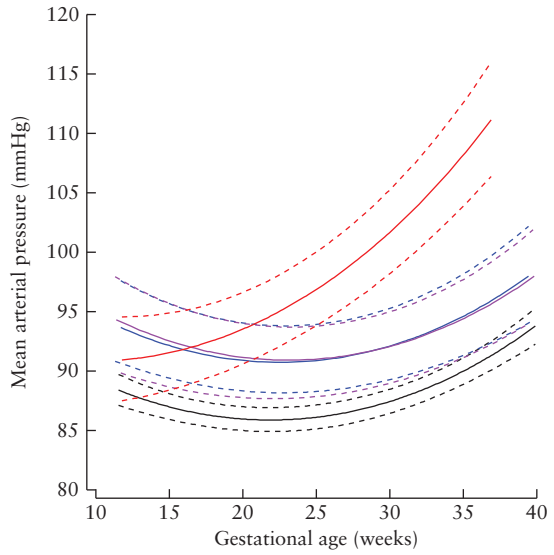

Figure 5 Mean arterial pressure in pregnancies with normal outcome (——) and those complicated with preterm pre-eclampsia (PE) (——), term PE (——) and gestational hypertension (——). ——, mean values; - - - -, 95% CI in each outcome group.

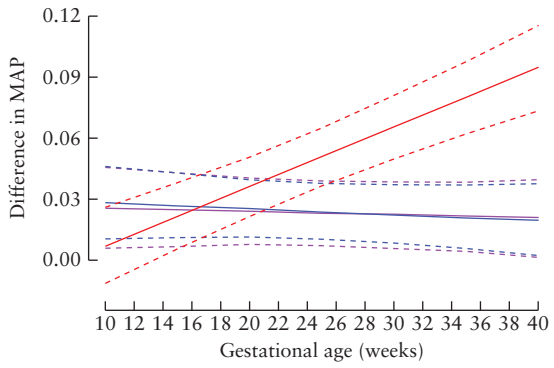

Figure 6 Difference in mean arterial pressure (MAP) between each outcome group and normotensive pregnancies. ——, Preterm pre-eclampsia (PE); ——, term PE; ——, gestational hypertension. ——, mean values; - - - -, 95% CI in each outcome group.

findings are in part similar to those of a retrospective study of serial blood pressure measurements recorded during routine antenatal care from 8 weeks' gestation to delivery in 13 016 pregnancies[27]. It was reported that patterns of BP change with gestational age could distinguish between women who develop PE or GH and those with normal pregnancies. At 8 weeks, BP in the PE and GH groups was similar and higher than that in the normal outcome group. The difference in BP between the hypertensive and normal groups increased with gestational age, but the increase between 18 and 30 weeks' gestation was sharper in the PE group than in the GH group.

Several studies have demonstrated that women who will later develop PE can be predicted based on MAP and UtA-PI measured as early as 11 weeks' gestation[7,8,12]. In a large screening study at 11–13 weeks' gestation, MAP was significantly higher in women who later developed PE or GH as compared to the unaffected group. However, UtA-PI was significantly higher in women who later developed PE but not GH[28,29]. For a 10% false-positive rate, detection rates using UtA-PI were 78% in early PE and 47% in late PE. Using MAP alone, the detection rates for PE and GH were 38% and 32%, respectively, for the same false-positive rate[28,29]. In a screening study including 3529 singleton pregnancies at 22–24 weeks' gestation, both UtA-PI and MAP were significantly higher in women who later developed PE or GH as compared to the unaffected group. For a 10% false-positive rate, the detection rate using UtA-PI and MAP were 96% and 65%, respectively, in the early-PE group, 41% and 40%, respectively, in the late-PE group and 20% and 39%, respectively, in the GH group[12]. Similarly, UtA-PI recorded at 30–33 weeks' gestation, was significantly higher in women who later developed PE, but not GH, as compared to the unaffected group. In this study the detection rate for the late-PE group using UtA-PI and MAP were 27% and 70%, respectively, for a false-positive rate of 10%[13,14].

In our cohort MAP was significantly higher in both the PE and GH groups. The difference increased significantly with GA in pregnancies complicated by preterm PE, but not term PE, which might be related to severity of the disease reflected in the GA at delivery[30]. Similarly, in the large screening study by Lai *et al.*, including 5099 women with singleton pregnancies, BP was significantly higher in both the PE and GH groups at 30–33 weeks' gestation and the rate of increase was also related to severity of the disease[14].

Early identification of women at risk for developing PE is likely to facilitate targeted antenatal surveillance and, possibly, intervention[31]. Recent evidence suggests that low-dose aspirin, when commenced prior to 16 weeks' gestation, can result in significant reduction in the prevalence of preterm PE and associated perinatal mortality[32–34]. In the UK, The National Institute for Health and Clinical Excellence (NICE) recommends that all women should be screened routinely in the first trimester to determine the risk of PE based on maternal characteristics and previous history, and those at high risk should be treated with aspirin[35]. The effect of aspirin on changes in biophysical and biochemical markers, previously described in women who subsequently develop PE, is unknown. We have previously demonstrated that the best approach in estimating a maternal factor-based risk is to incorporate the various characteristics into a combined algorithm derived by multivariate analysis[31]. The extent to which testing at a later stage in pregnancy in a contingent manner could improve accuracy in predicting PE, allowing for an improved risk stratification and a lower false-positive rate, merits further investigation.

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