Ultrasound Obstet Gynecol 2009; **34**: 142–148
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.6452

Hypertensive disorders in pregnancy: screening by uterine artery Doppler at 11–13 weeks

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

ABSTRACT

Objectives *To examine the performance of screening for hypertensive disorders in pregnancy by a combination of the maternal factor-derived* a-priori *risk with the uterine artery (UtA) pulsatility index (PI) and to determine whether it is best in such screening to use the mean PI of the two arteries, the highest PI or the lowest PI.*

Methods *This was a prospective screening study for pre-eclampsia (PE) requiring delivery before 34 weeks (early PE), late PE and gestational hypertension (GH) in women attending their routine first hospital visit in pregnancy at 11 + 0 to 13 + 6 weeks of gestation. Maternal history was recorded and color flow Doppler imaging was used to measure the left and right UtA-PI. The performance of screening for PE and GH by a combination of the maternal factor-derived* a-priori *risks determined in a previous study and the UtA-PI was assessed.*

Results *There were 8061 (96.4%) cases unaffected by PE or GH, 37 (0.4%) that developed early PE, 128 (1.5%) with late PE and 140 (1.7%) with GH. The lowest, mean and highest UtA-PI were significantly higher in early PE and late PE than in the controls (*$P < 0.0001$*) and in early PE than late PE (*$P < 0.0001$*). The lowest UtA-PI was higher in GH than in controls (*$P = 0.014$*). The best performance in screening was provided by the lowest PI. The detection rate of early PE at a 10% false-positive rate increased from 47% in screening by maternal factors alone to 81% in screening by maternal factors and the lowest UtA-PI. The respective detection rates for late PE increased from 41% to 45% and those for GH increased from 31% to 35%.*

Conclusions *The patient-specific risk for PE and GH can be derived by combining the disease-specific maternal factor-derived* a-priori *risk with the measurement of the lowest UtA-PI in a multivariate regression model.*

INTRODUCTION

Pre-eclampsia (PE), which affects about 2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality[1–3]. Hypertension developing in the second half of pregnancy is subdivided, according to the presence or absence of coexisting significant proteinuria, into PE and gestational hypertension (GH). Recent evidence suggests that PE can be further subdivided into early PE and late PE, the former being associated with a higher incidence of fetal growth restriction and both short-term and long-term maternal mortality and morbidity[4–6].

In normal pregnancy the spiral arteries in the placental bed are invaded by trophoblast, which becomes incorporated into the vessel wall and replaces the endothelium, muscular layer and neural tissue[7–10]. These physiological changes convert the spiral arteries from narrow muscular vessels to wide non-muscular channels independent of maternal vasomotor control. In PE there is impaired trophoblastic invasion of spiral arteries[10–12] and this impairment is most marked in early PE[13–15]. Indirect evidence for impaired placental perfusion in pregnancies destined to develop PE has been provided by Doppler studies of the uterine arteries (UtAs) which showed increased pulsatility index (PI) both during the second trimester and also in the first trimester of pregnancy[16–18]. Impedance to flow in the UtAs is lower on the side of implantation than in the non-placental site[19]. Traditionally the PI is measured in both the UtAs and the mean of the two measurements is used in the prediction of risk for PE. However, there are no prospective studies to document that the performance of screening is best by the use of the mean rather than the lowest or highest PI.

In the UK, the National Institute for Health and Clinical Excellence (NICE) has issued guidelines on routine antenatal care, recommending that a woman's level of risk for PE, based on factors in her history, should be determined at the booking visit and the subsequent intensity of antenatal care should be based on this risk[20]. We have demonstrated recently that the

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Accepted: 11 May 2009

NICE recommendation of screening for PE by maternal characteristics and previous history is potentially useful only when the various factors are incorporated into a combined algorithm derived by multivariate analysis[21]. Such an approach made it possible to derive the *a-priori* risk for early PE, late PE and GH based on maternal age, body mass index (BMI), racial origin, history of PE, chronic hypertension and method of conception. The estimated detection rates for early PE, late PE and GH are about 47%, 41% and 31%, respectively, at a 10% false-positive rate[21].

The aim of this study was to examine the performance of screening for hypertensive disorders in pregnancy by a combination of the maternal factor-derived *a-priori* risk and the UtA-PI, and to determine whether it is best in such screening to use the mean PI of the two arteries, the highest PI or the lowest PI.

METHODS

This was a prospective screening study for hypertensive disorders in women attending for their routine first hospital visit in pregnancy. At this visit, which is held at $11+0$ to $13+6$ weeks of gestation, all women have an ultrasound scan to confirm gestational age from the measurement of fetal crown–rump length (CRL), to diagnose any major fetal abnormalities and measure fetal nuchal translucency thickness as part of screening for chromosomal abnormalities[22,23]. We recorded maternal characteristics and medical history, and performed UtA Doppler imaging by transabdominal ultrasound examination[18]. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by King's College Hospital Ethics Committee.

We prospectively examined 9149 singleton pregnancies between March 2006 and November 2007. We excluded 783 (8.6%) because: they had missing outcome data ($n = 443$), there was a major fetal defect or aneuploidy ($n = 153$), the pregnancies resulted in fetal death or miscarriage before 24 weeks of gestation ($n = 139$), the pregnancies were terminated for social reasons ($n = 15$), or the patients had at least one episode of hypertension but it was not possible to determine if the diagnosis was PE on the basis of the available data ($n = 33$). Of the remaining 8366 cases, 165 (2.0%) developed PE, including 37 that required delivery before 34 weeks (early PE) and 128 with late PE, 140 with GH and 8061 (96.4%) cases that were unaffected by PE or GH.

For the measurement of UtA-PI by transabdominal ultrasound imaging, a sagittal section of the uterus was obtained, and the cervical canal and internal cervical os were identified. Subsequently, the transducer was gently tilted from side to side and color flow mapping was used to identify each UtA along the side of the cervix and uterus at the level of the internal os[18]. Pulsed wave Doppler imaging was used with the sampling gate set at 2 mm to cover the whole vessel and care was taken to ensure that the angle of insonation was $< 30°$. When three similar consecutive waveforms were obtained the UtA-PI was measured from the left and right arteries. All ultrasound and Doppler studies were carried out by sonographers who had received the appropriate Certificate of Competence in the 11–13-week scan and Doppler of The Fetal Medicine Foundation (http://www.fetalmedicine.com). The results of the Doppler studies were not given to the women or their doctors, and did not influence the subsequent management of the pregnancies.

This study is part of a research program on the early prediction of pregnancy complications and the data from 6015 of the patients were the subject of a previous study in which we reported the finding of the mean UtA-PI only[18]. In a previous paper we used the same population as in the present study to derive algorithms for calculation of the *a-priori* risk for early PE, late PE and GH based on maternal age, BMI, racial origin, history of PE, chronic hypertension and method of conception[21].

Maternal history

Women were asked to complete a questionnaire on maternal age, racial origin (white, black, Indian or Pakistani, Chinese or Japanese and mixed), cigarette smoking during pregnancy (yes or no), method of conception (spontaneous or assisted conception by either ovulation induction alone or *in-vitro* fertilization), medical history (including chronic hypertension, diabetes mellitus, antiphospholipid syndrome, thrombophilia and sickle cell disease), medication (including antihypertensive, antidepressant, antiepileptic, aspirin, steroids, betamimetic, insulin and thyroxine), parity (parous, nulliparous with no previous pregnancies, nulliparous with miscarriage or termination before 24 weeks), previous pregnancy with PE (yes or no) and family history of PE (mother, sister or both). The questionnaire was then reviewed by a doctor together with the patient. The maternal weight and height were measured and the BMI was calculated in kg/m^2.

Outcome measures

The definitions of PE and GH were those of the International Society for the Study of Hypertension in Pregnancy[24]. In GH the diastolic blood pressure should be ≥ 90 mmHg on at least two occasions 4 h apart, developing after 20 weeks of gestation in previously normotensive women in the absence of significant proteinuria. In PE there should be GH with proteinuria of 300 mg or more 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. In PE superimposed on chronic hypertension significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks of gestation in the absence of trophoblastic disease).

Statistical analysis

The distributions of the lowest, mean and highest UtA-PI were made Gaussian after logarithmic transformation. Multiple regression analysis in the unaffected group was used to determine which of the factors among the maternal characteristics and gestation were significant predictors of the log UtA-PI (lowest), log UtA-PI (mean) and log UtA-PI (highest). Then the distribution of log UtA-PI (lowest), log UtA-PI (mean) and log UtA-PI (highest), expressed as multiples of the median (MoM) of the unaffected group, were determined in the PE and GH groups. Comparison of the lowest, mean and highest UtA-PI MoM between each hypertensive disorder group and controls was by Mann–Whitney *U*-test, with *post-hoc* Bonferroni correction (critical statistical significance $P < 0.0167$). The *a-priori* risks for early PE, late PE and GH based on specific maternal risk factors were determined as described previously[21] and logarithmically transformed. Logistic regression analysis was used to determine if the log transformed maternal factor-derived *a-priori* risk, log UtA-PI (lowest) MoM, log UtA-PI (mean) MoM and log UtA-PI (highest) MoM had a significant contribution in predicting early PE, late PE and GH. The performance of screening was determined by receiver–operating characteristics (ROC) curves.

The statistical software package SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was used for all data analyses.

RESULTS

Unaffected group

Multiple regression analysis in the unaffected group demonstrated that for the lowest, mean and highest log UtA-PI significant independent contributions were provided by fetal CRL, maternal BMI, age and racial origin:

Log expected UtA-PI (lowest) =
0.348 − (0.002 × CRL in mm)
− (0.002 × BMI in kg/m^2)
− (0.001 × age in years)
+ (0.035 if black, 0.023 if mixed,
0 if other racial origins)
($R^2 = 0.030$, $P < 0.0001$)

Log expected UtA-PI (mean) =
0.404 − (0.002 × CRL in mm)
− (0.002 × BMI in kg/m^2)
− (0.001 × age in years)
+ (0.022 if black, 0.019 if mixed,
0 if other racial origins)
($R^2 = 0.028$, $P < 0.0001$)

Log expected UtA-PI (highest) =
0.451 − (0.002 × CRL in mm)
− (0.002 × BMI in kg/m^2)
− (0.001 × age in years)
+ (0.013 if black, 0.017 if mixed,
0 if other racial origins)
($R^2 = 0.022$, $P < 0.0001$).

In each patient we used these formulae to derive the expected log UtA-PI (lowest), log UtA-PI (mean) and log UtA-PI (highest) and then expressed the observed value as MoM of the expected value (Table 1). The lowest, mean and highest UtA-PI MoM were significantly higher in early PE and late PE than in the controls ($P < 0.0001$), in early PE than in late PE ($P < 0.0001$), and in early PE than in GH ($P < 0.0001$). The lowest UtA-PI MoM was higher in GH than in controls ($P = 0.014$).

Patient-specific risks for pre-eclampsia and gestational hypertension

The patient-specific risk for each hypertensive disorder is calculated from the formula: odds/(1 + odds), where odds = e^Y and Y is derived from multivariate logistic regression analysis of disease-specific maternal factor-derived *a-priori* risks and UtA-PI. Logistic regression analysis demonstrated, in the detection of early PE and late PE, that there were significant contributions from

Table 1 Lowest, mean and highest uterine artery pulsatility indices in the four outcome groups

	Uterine artery pulsatility index (median (IQR))					
	Lowest		*Mean*		*Highest*	
Group	*MoM*	*Unit*	*MoM*	*Unit*	*MoM*	*Unit*
Unaffected	1.01 (0.83–1.23)	1.40 (1.14–1.72)	1.01 (0.83–1.22)	1.63 (1.34–1.97)	1.01 (0.82–1.23)	1.84 (1.50–2.24)
Early pre-eclampsia	1.60 (1.31–1.77)	2.26 (1.82–2.41)	1.51 (1.19–1.65)	2.42 (1.97–2.64)	1.41 (1.14–1.58)	2.56 (2.13–2.81)
Late pre-eclampsia	1.23 (0.88–1.54)	1.68 (1.24–2.16)	1.19 (0.89–1.45)	1.91 (1.52–2.36)	1.15 (0.88–1.42)	2.09 (1.60–2.60)
Gestational hypertension	1.10 (0.85–1.38)	1.51 (1.18–1.86)	1.08 (0.88–1.30)	1.74 (1.40–2.06)	1.07 (0.87–1.29)	1.96 (1.55–2.33)

MoM, multiples of the median.

a combination of specific maternal risk factors with either the lowest, mean or highest UtA-PI MoM. In the detection of GH there was significant contribution from the combination of maternal factor-derived *a-priori* risks with the lowest UtA-PI MoM.

Early pre-eclampsia

$$Y = -0.903 + (2.354 \times \log \text{maternal factor-derived } \textit{a-priori} \text{ risk for early PE}) + (11.194 \times \log \text{UtA-PI (lowest) MoM}) \quad (R^2 = 0.264, P < 0.0001)$$

$$Y = -0.964 + (2.282 \times \log \text{maternal factor-derived } \textit{a-priori} \text{ risk for early PE}) + (11.622 \times \log \text{UtA-PI (mean) MoM}) \quad (R^2 = 0.247, P < 0.0001)$$

$$Y = -0.666 + (2.286 \times \log \text{maternal factor-derived } \textit{a-priori} \text{ risk for early PE}) + (9.006 \times \log \text{UtA-PI (highest) MoM}) \quad (R^2 = 0.210, P < 0.0001)$$

Late pre-eclampsia

$$Y = 0.155 + (2.429 \times \log \text{maternal factor-derived } \textit{a-priori} \text{ risk for late PE}) + (3.182 \times \log \text{UtA-PI (lowest) MoM}) \quad (R^2 = 0.145, P < 0.0001)$$

$$Y = 0.145 + (2.420 \times \log \text{maternal factor-derived } \textit{a-priori} \text{ risk for late PE}) + (3.338 \times \log \text{UtA-PI (mean) MoM}) \quad (R^2 = 0.143, P < 0.0001)$$

$$Y = 0.172 + (2.421 \times \log \text{maternal factor-derived } \textit{a-priori} \text{ risk for late PE}) + (2.642 \times \log \text{UtA-PI (highest) MoM}) \quad (R^2 = 0.138, P < 0.0001)$$

Gestational hypertension

$$Y = 0.160 + (2.392 \times \log \text{maternal factor-derived } \textit{a-priori} \text{ risk for GH}) + (1.483 \times \log \text{UtA-PI (lowest) MoM}) \quad (R^2 = 0.074, P < 0.0001)$$

Example

For a 28-year-old black woman in her first pregnancy who does not smoke, with a BMI of 20 kg/m^2, no family history of PE, and with a UtA-PI (lowest) of 1.6 at 12 weeks of gestation (CRL 65 mm), the risks of developing early PE, late PE and GH are 0.57%, 1.98% and 1.17%, respectively.

$$\begin{aligned}&\text{Log expected UtA-PI (lowest)} =\\ &0.348 - (0.002 \times 65 \text{ (CRL in mm)})\\ &+ 0.035 \text{ (black race)}\\ &- (0.002 \times 20 \text{ (BMI in kg/m}^2\text{)})\\ &- (0.001 \times 28 \text{ (age in years)})\\ &= 0.182 \text{Log UtA-PI (lowest) MoM} = 0.023\end{aligned}$$

Maternal factor-derived *a-priori* risk for early PE:

$$\begin{aligned}Y &= -5.674 + 1.267 \text{ (black race)}\\ &+ 0 \text{ (history of chronic hypertension)}\\ &+ 0 \text{ (spontaneous conception)}\\ &+ 0 \text{ (nulliparous)}\\ &= -4.406\end{aligned}$$

$$\text{Odds} = e^y = 0.012202$$

$$\textit{A-priori} = \text{odds}/(1 + \text{odds}) = 0.012055.$$

Table 2 Screening for pre-eclampsia and gestational hypertension by maternal risk factor and uterine artery pulsatility index (UtA-PI): comparison of receiver–operating characteristics (ROC) curves

	Area under ROC curve (95% CI)		
Screening test	*Early pre-eclampsia*	*Late pre-eclampsia*	*Gestational hypertension*
Maternal risk factor	0.794 (0.720–0.869)	0.796 (0.761–0.830)	0.721 (0.677–0.765)
Maternal risk factor plus UtA-PI			
Lowest	0.912 (0.863–0.962)	0.812 (0.777–0.847)	0.729 (0.686–0.771)
Mean	0.902 (0.853–0.952)	0.813 (0.778–0.847)	—
Highest	0.884 (0.834–0.935)	0.810 (0.777–0.844)	—

Table 3 Comparison of the performance of screening for pre-eclampsia and gestational hypertension by maternal risk factor and uterine artery pulsatility index (UtA-PI)

	Detection rate (% (95% CI)) for fixed false-positive rate (FPR)					
	Early pre-eclampsia		*Late pre-eclampsia*		*Gestational hypertension*	
Screening test	*FPR = 5%*	*FPR = 10%*	*FPR = 5%*	*FPR = 10%*	*FPR = 5%*	*FPR = 10%*
Maternal risk factor	37.0 (12.5–50.0)	47.0 (22.5–65.0)	28.9 (21.2–37.6)	41.4 (32.8–50.4)	20.7 (14.3–28.4)	30.7 (23.2–39.1)
Maternal risk factor plus UtA-PI						
Lowest	64.9 (47.5–79.8)	81.1 (64.8–92.0)	32.0 (24.1–40.9)	45.3 (36.5–54.3)	17.9 (11.9–25.2)	35.0 (27.1–43.5)
Mean	62.2 (44.8–77.5)	78.4 (61.8–90.1)	30.5 (22.6–39.2)	46.9 (38.0–55.9)	—	—
Highest	54.1 (36.9–70.5)	64.9 (47.5–79.8)	29.7 (21.9–38.4)	46.1 (37.3–55.1)	—	—

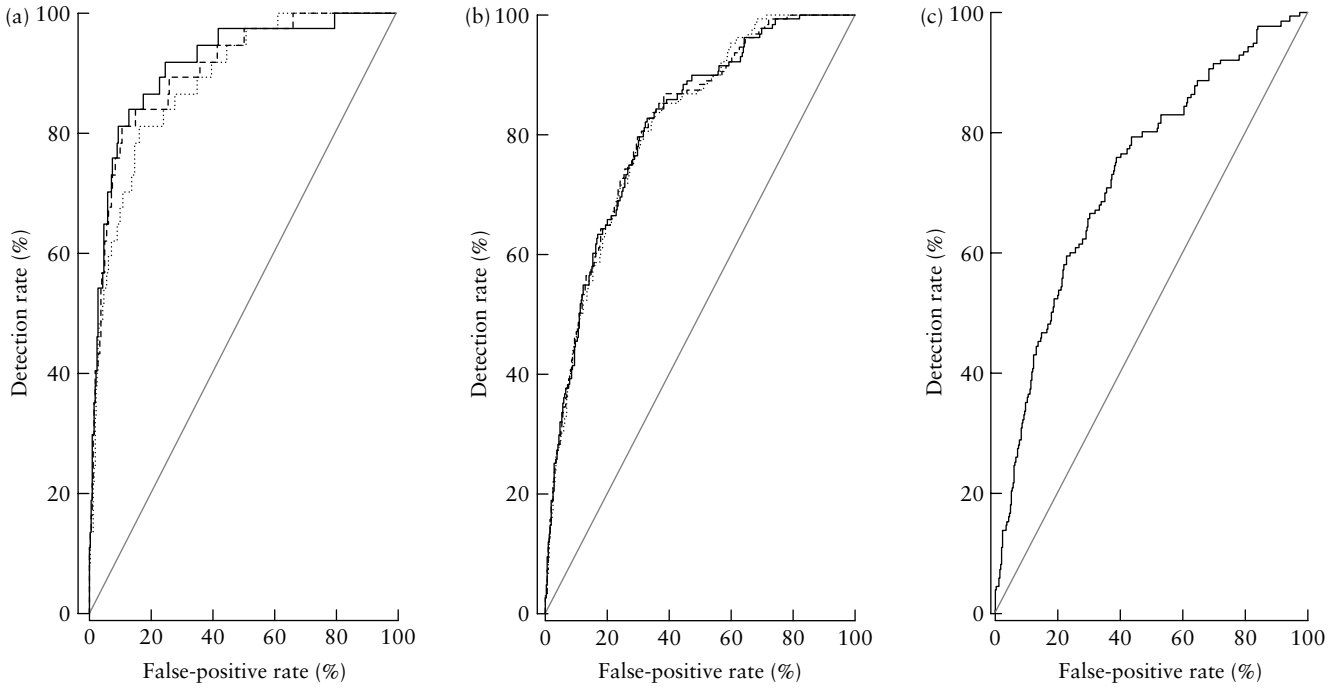

Figure 1 Receiver–operating characteristics curves of maternal risk factor with lowest uterine artery pulsatility index (UtA-PI) (——), maternal risk factor with mean UtA-PI (- - - -) and maternal risk factor with highest UtA-PI (·····) in the prediction of early pre-eclampsia (a), late pre-eclampsia (b) and gestational hypertension (c).

Maternal factor-derived *a-priori* risk for late PE:

$$Y = -7.860 + (0.034 \times 28 \text{ (age in years)}) + (0.096 \times 20 \text{ (BMI in kg/m}^2\text{)}) + 1.089 \text{ (black race)} + 0 \text{ (woman's mother had PE)} + 0 \text{ (nulliparous)} = -3.892$$

$$\text{Odds} = e^y = 0.020404$$

$$\textit{A-priori} = \text{odds}/(1 + \text{odds}) = 0.019996$$

Maternal factor-derived *a-priori* risk for GH:

$$Y = -7.532 + (0.040 \times 28 \text{ (age in years)}) + (0.098 \times 20 \text{ (BMI in kg/m}^2\text{)}) + 0 \text{ (woman's mother had PE)} + 0 \text{ (nulliparous)} = -4.446$$

$$\text{Odds} = e^y = 0.011727$$

$$\textit{A-priori} = \text{odds}/(1 + \text{odds}) = 0.011591$$

A-posteriori risk for early PE:

$$Y = -0.903 + (2.354 \times -1.919 \text{ (log maternal factor-derived } \textit{a-priori} \text{ risk for early PE)}) + (11.194 \times 0.023(\log \text{UtA-PI (lowest) MoM})) = -5.168$$

$$\text{Odds} = e^y = 0.005695$$

Risk for early PE = 0.005662 or 0.57%.

A-posteriori risk for late PE:

$$Y = 0.155 + (2.429 \times -1.699 \text{ (log maternal factor-derived } \textit{a-priori} \text{ risk for late-PE))} + (3.182 \times 0.023(\log \text{UtA-PI (lowest) MoM})) = -3.900$$

$$\text{Odds} = e^y = 0.02025$$

$$\text{Risk for late PE} = 0.019848 = 1.98\%$$

A-posteriori risk for GH:

$$Y = 0.160 + (2.392 \times -1.936 \text{ (log maternal factor-derived } \textit{a-priori} \text{ risk for GH)} + (1.483 \times 0.023(\log \text{UtA-PI (lowest) MoM})) = -4.436$$

$$\text{Odds} = e^y = 0.011844$$

$$\text{Risk for late PE} = 0.011705 = 1.17\%$$

If the same woman had had a previous pregnancy with PE, her BMI was 35 kg/m^2 and her UtA-PI (lowest) was 2.2, her risks for early PE, late PE and GH would have been 13.42%, 23.71% and 6.35%, respectively.

Performance of screening

The areas under the ROC curves, and detection rates of early PE, late PE and GH for different false-positive rates in screening by maternal risk factor and UtA-PI MoM are given in Tables 2 and 3, and Figure 1.

DISCUSSION

The findings of this study confirm that UtA-PI at 11–13 weeks is increased in pregnancies that subsequently develop PE and that the increase is particularly marked for early PE[17,18]. Although there was no significant difference between the mean, lowest or highest PI, the performance of screening appeared to be best with the lowest PI. The lowest UtA-PI, but not the mean or highest, was also significantly increased in pregnancies that subsequently developed GH.

In the unaffected group, which did not develop PE or GH, UtA-PI decreased with increasing gestational age and increasing maternal BMI, and was higher in Black women than in other racial groups. Consequently, the measured PI must be adjusted for these variables and expressed as a MoM in order to assess whether a given value is within the normal range or increased. This is analogous to biochemical testing with serum pregnancy-associated plasma protein-A (PAPP-A) where the measured concentration is expressed as a MoM after adjustment for maternal characteristics[25]. The relationship between UtA-PI and maternal BMI is unlikely to be the consequence of enhanced trophoblastic invasion in obese women but rather vasodilatation in the uterine circulation owing to the increased levels of circulating estrogens associated with increased BMI[26].

Impedance to flow in the UtAs is lower on the side of implantation than in the non-placental site but it decreases with increasing gestational age at both sites[19]. The decrease on the side of implantation is consistent with trophoblastic invasion and conversion of the spiral arteries from small vessels to large channels. Because the uterine circulation has many collateral vessels a fall in resistance in the placental bed would also be transmitted to the non-placental UtA. In our study we did not attempt to characterize the two UtAs as placental and non-placental because in about one-third of cases the placenta is located centrally[19]. Nevertheless, it can be assumed that the vessel with the lower PI is likely to be the placental one. In this respect, the finding that in screening for hypertensive disorders the best performance was provided by the vessel with the lowest PI is not surprising because this is likely to be a better reflection of the degree of trophoblastic invasion of the spiral arteries.

The approach to early screening for hypertensive disorders in pregnancy may be analogous to first-trimester screening for trisomy 21. In this condition the patient-specific risk is derived by multiplying the maternal age-related *a-priori* risk by the likelihood ratio associated with fetal nuchal translucency thickness and maternal serum free β-human chorionic gonadotropin (β-hCG) and PAPP-A[23]. In screening for early PE, late PE and GH the patient-specific risk is derived by combining the disease-specific maternal factor-derived *a-priori* risk[21] with the measurement of the lowest UtA-PI in a multivariate regression model. Significant predictors of the maternal factor-derived *a-priori* risk for early PE were black race, chronic hypertension, previous PE and use of ovulation drugs, whereas predictors of late PE and GH were increased maternal age and BMI, and family or previous history of PE[21]. Additionally, late PE was more common in black, Indian and Pakistani women than in white women. In screening for trisomy 21 the detection rate, for a 5% false-positive rate, is increased from about 30% in screening by maternal age alone to 90% with combined screening by maternal age, fetal nuchal translucency thickness, and maternal serum free β-hCG and PAPP-A[23]. Similarly, as shown in this study, in screening for early PE the detection rate, for a 10% false-positive rate, is increased from 47% in screening by maternal factors alone to 81% with combined screening by maternal factors and UtA-PI. The respective detection rates for late PE increased from 41% to 45% and those for GH increased from 31% to 35%. Further improvement in screening is likely to be achieved with the inclusion of maternal blood pressure and serum concentration of placental products, such as PAPP-A and placental growth factor[27–29].

ACKNOWLEDGMENT

This study was supported by a grant from The Fetal Medicine Foundation (charity number 1037116).

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