Ultrasound Obstet Gynecol 2008; **32**: 138–146
Published online 15 July 2008 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.5402

Uterine artery Doppler at 11 + 0 to 13 + 6 weeks and 21 + 0 to 24 + 6 weeks in the prediction of pre-eclampsia

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KEYWORDS: pre-eclampsia; uterine artery Doppler; uterine artery pulsatility index

ABSTRACT

Objective *To evaluate the performance of screening for pre-eclampsia by uterine artery pulsatility index (PI) at 11 + 0 to 13 + 6 weeks' gestation and the change in uterine artery PI between 11 + 0 to 13 + 6 and 21 + 0 to 24 + 6 weeks.*

Methods *In 3107 singleton pregnancies attending for routine care at 11 + 0 to 13 + 6 and 21 + 0 to 24 + 6 weeks' gestation we recorded maternal characteristics and medical and obstetric history, and measured uterine artery PI. The distributions of uterine artery PI were made Gaussian after logarithmic transformation and the log of the ratio of uterine artery PI at 21 + 0 to 24 + 6 weeks to that at 11 + 0 to 13 + 6 weeks was calculated. Multiple regression analysis was used to determine which of the maternal variables and Doppler findings were significant predictors of early and late pre-eclampsia. The performance of screening was described by receiver–operating characteristics curves.*

Results *Pre-eclampsia developed in 93 (3.0%) pregnancies, including 22 (0.7%) in which delivery was before 34 weeks (early pre-eclampsia) and 71 (2.3%) with delivery at 34 weeks or more (late pre-eclampsia). Seventy-three (2.3%) women developed gestational hypertension, 346 (11.1%) delivered small-for-gestational-age (SGA) babies with no hypertensive disorders and 2595 (83.5%) were unaffected by pre-eclampsia, gestational hypertension or SGA. Multiple regression analysis demonstrated that maternal variables, uterine artery PI at 11 + 0 to 13 + 6 weeks and the change in uterine artery PI between 11 + 0 to 13 + 6 and 21 + 0 to 24 + 6 weeks' gestation provided significant independent contributions to the prediction of pre-eclampsia. For a false positive rate of 5% the predicted detection rates of early and late pre-eclampsia were 90.9 and 31.0%, respectively. The same performance of screening was achieved by reserving second-trimester testing for only the 20% of women at the highest risk after first-trimester screening.*

Conclusion *The decrease in uterine artery PI between 11 + 0 to 13 + 6 and 21 + 0 to 24 + 6 weeks is steeper in pregnancies with a normal outcome than in those developing pre-eclampsia. Effective screening for pre-eclampsia can be achieved by the Doppler measurement of uterine artery PI at 11 + 0 to 13 + 6 weeks and the change in PI between 11 + 0 to 13 + 6 and 21 + 0 to 24 + 6 weeks.* *Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

The development of pre-eclampsia is thought to be a consequence of impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels into wide non-muscular channels[1–3]. The physiological process of trophoblastic invasion is reflected in the observation from Doppler ultrasound studies that impedance to flow in the uterine arteries decreases with gestation between 6 and 24 weeks and remains constant thereafter[4–7].

In pregnancies that subsequently develop pre-eclampsia the pulsatility index (PI) in the uterine arteries is increased in both the first and second trimesters of pregnancy. Doppler screening studies at 12 and 22 weeks' gestation have reported that for a 10% false positive rate the detection rates of pre-eclampsia were about 40% and 50%, respectively[8,9], while pathological studies have shown that the prevalence of placental lesions in women with pre-eclampsia is inversely related to the gestational age at delivery[10,11]. This is compatible with the results of the Doppler studies, which reported that for a 10% false-positive rate the detection rates of pre-eclampsia

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Accepted: 15 April 2008

requiring delivery before 34 weeks are about 80% and 85% for assessment of the uterine arteries at 12 and 22 weeks, respectively[8,9].

In a previous study of normal pregnancies we reported a significant association in impedance to flow in the uterine arteries between the first and second trimesters[4]. The aim of this screening study was to investigate whether the rate of decrease in PI between 12 and 22 weeks' gestation is steeper in pregnancies with a normal outcome than in those developing pre-eclampsia, and if so whether this measurement could improve the prediction of pre-eclampsia provided by a single early assessment of the uterine arteries.

PATIENTS AND METHODS

This was a prospective screening study for pre-eclampsia in singleton pregnancies by uterine artery Doppler ultrasonography at 11 + 0 to 13 + 6 weeks and at 21 + 0 to 24 + 6 weeks. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the hospital ethics committee. In our hospital women with singleton pregnancies attending for routine antenatal care are offered one ultrasound examination at 11 + 0 to 13 + 6 weeks' gestation and another at 21 + 0 to 24 + 6 weeks. Gestational age is determined from the menstrual history and confirmed by the measurement of fetal crown–rump length (CRL) at the first-trimester scan.

The women were asked to complete a questionnaire on maternal age, ethnic origin (Caucasian, Afro-Caribbean, Indian or Pakistani or Bangladeshi, Chinese or Japanese and mixed), cigarette smoking during pregnancy (yes or no), alcohol intake during pregnancy (yes or no), drug abuse during pregnancy (cannabis, cocaine, other or none), medical history (including chronic hypertension, diabetes mellitus, antiphospholipid syndrome, thrombophilia, human immunodeficiency virus infection, and sickle cell disease), medication (including antihypertensive, antidepressant, anti-epileptic, anti-inflammatory, antiretroviral, antithyroid, aspirin, beta-mimetic, insulin, lithium, steroids and thyroxine), parity (nulliparous if no delivery beyond 23 weeks, or parous), obstetric history (including previous pregnancy with pre-eclampsia) and family history of pre-eclampsia (mother). The maternal weight and height were measured and the body mass index (BMI) was calculated in kg/m^2.

At 11 + 0 to 13 + 6 weeks transabdominal ultrasound examination was carried out for measurement of fetal CRL and nuchal translucency thickness, diagnosis of any major fetal defects and measurement of uterine artery PI. For the Doppler studies 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 uterine artery along the side of the cervix and uterus at the level of the internal os[12]. Pulsed wave Doppler 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 less than 50°. When three similar consecutive waveforms were obtained the PI was measured and the mean PI of the left and right arteries was calculated. Similarly, pulsed Doppler was used to measure the mean PI at 21 + 0 to 24 + 6 weeks. However, at this scan transvaginal, rather than transabdominal, sonography was used because at the same time we measured cervical length for the assessment of the risk of premature delivery. All Doppler studies were carried out by sonographers who had received the Certificate of Competence in Doppler of the Fetal Medicine Foundation (www.fetalmedicine.com).

The ultrasound findings and patient characteristics, including demographic data and obstetric and medical history, were entered into a computer database. Data on pregnancy outcome were collected from the hospital maternity records or their general medical practitioners. The obstetric records of all patients with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was chronic hypertension, pre-eclampsia or gestational hypertension. Similarly, for quality control we examined the records of 500 randomly selected cases without pregnancy-associated hypertension.

Outcome measures

The outcome measures were pre-eclampsia, gestational hypertension and small-for-gestational-age (SGA) babies. In pre-eclampsia and gestational hypertension we included all cases with SGA, but in SGA we excluded cases with pre-eclampsia or gestational hypertension. The group of pre-eclampsia included those with pre-eclampsia superimposed on chronic hypertension.

The definitions of pre-eclampsia and gestational hypertension were those of the International Society for the Study of Hypertension in Pregnancy[13]. Gestational hypertension is defined as diastolic blood pressure $\geq$ 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. Pre-eclampsia is defined as gestational hypertension 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. Chronic hypertension is defined as a 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, and pre-eclampsia superimposed on chronic hypertension requires the development of significant proteinuria (as defined above) after 20 weeks of gestation in women with known chronic hypertension[13].

For all the babies the birth weight was converted into a percentile after correction for gestational age at delivery and sex of the newborn, maternal ethnic origin, weight, height and parity[14]. The newborn was considered to be SGA if the birth weight was less than the 10th percentile.

Statistical analysis

The following seven steps were taken:

1) The women were subdivided into five groups depending on pregnancy outcome: early pre-eclampsia; late pre-eclampsia; gestational hypertension; SGA; and unaffected by pre-eclampsia, gestational hypertension, or SGA. The ANOVA test (with the Bonferroni post-hoc test) and the chi-square test were used to compare the demographic characteristics of the unaffected group with each group with pregnancy complications.
2) The distributions of uterine artery PI were made Gaussian after logarithmic transformation and the normality of the distributions was confirmed by the Kolmogorov–Smirnov test.
3) Linear regression analysis was used to adjust the uterine artery PI to gestational age.
4) The distribution of log uterine artery PI, expressed as multiples of the median (MoM) were determined in each of the outcome groups and 'box-and-whisker' plots were constructed.
5) The log ratio of uterine artery PI MoMs at 21 + 0 to 24 + 6 weeks to PI MoMs at 11 + 0 to 13 + 6 weeks was calculated and box-and-whisker plots were constructed for each outcome group.
6) Backward stepwise multiple regression analysis was used to determine which of the factors among the maternal characteristics, medical and obstetric history (Table 1) and Doppler findings were significant predictors of early and late pre-eclampsia.
7) The performance of screening was described by a receiver–operating characteristics (ROC) curve.

The statistical software package SPSS 12.0 (SPSS Inc., Chicago, IL, USA) was used for all data analysis.

RESULTS

Study population

First- and second-trimester Doppler screening was carried out in 3330 consecutive singleton pregnancies at median gestations of 12 and 23 weeks. We excluded 187 (5.6%) because they had missing outcome data ($n = 155$), there was a major fetal defect ($n = 14$), or the pregnancies resulted in miscarriage or fetal death ($n = 18$). In addition, there were 36 (1.1%) pregnancies in which there was at least one episode of hypertension but on the basis of the available data it was not possible to determine whether the diagnosis was pre-eclampsia, gestational hypertension or neither, so these cases were also excluded from further analysis.

In the remaining 3107 cases there were 93 (3.0%) who developed pre-eclampsia, including 22 (0.7%) in which delivery was before 34 weeks (early pre-eclampsia) and 71 (2.3%) with delivery at 34 weeks or later (late pre-eclampsia), 73 (2.3%) who developed gestational hypertension, 346 (11.1%) who delivered SGA newborns but did not develop pre-eclampsia or gestational hypertension and 2595 (83.5%) who were unaffected by pre-eclampsia, gestational hypertension or SGA. The characteristics of the five outcome groups are summarized in Table 1. In the quality-control assessment of the 500 cases with reported normal outcome there was one case of gestational hypertension.

Log uterine artery PI

At 11 + 0 to 13 + 6 weeks the mean log uterine artery PI decreased significantly with gestation (log uterine artery PI = 0.438 − (0.003 × gestational age in days), $R^2 = 0.06$, $P < 0.0001$). Similarly, at 21 + 0 to 24 + 6 weeks the mean log uterine artery PI decreased significantly with gestation (log uterine artery PI = 0.268 − (0.002 × gestational age in days), $R^2 = 0.02$, $P = 0.007$).

In each patient the observed log uterine artery PI was expressed as a multiple of the expected median for gestation. The median (interquartile range) log uterine artery PI at 11 + 0 to 13 + 6 weeks was −0.004 (−0.082 to 0.081) MoM in the unaffected group, 0.175 (0.155 to 0.227) MoM in the early pre-eclampsia group, 0.051 (−0.040 to 0.153) MoM in the late pre-eclampsia group, 0.014 (−0.090 to 0.079) MoM in the gestational hypertension group and 0.029 (−0.058 to 0.124) MoM in the SGA group (Figure 1). Therefore, compared to the unaffected group, the mean log uterine artery PI was significantly higher in the early pre-eclampsia group ($P < 0.001$), in the late pre-eclampsia group ($P = 0.040$) and in the SGA group ($P < 0.001$), but not in the gestational hypertension group ($P = 0.779$).

The median (interquartile range) log uterine artery PI at 21 + 0 to 24 + 6 weeks was −0.008 (−0.079 to 0.059) MoM in the unaffected group, 0.253 (0.165 to 0.351) MoM in the early pre-eclampsia group, 0.068 (−0.052 to 0.172) MoM in the late pre-eclampsia group, 0.003 (−0.048 to 0.059) MoM in the gestational hypertension group and 0.036 (−0.041 to 0.110) MoM in the SGA group (Figure 1). Therefore, compared to the unaffected group the mean log uterine artery PI was significantly higher in the early pre-eclampsia group ($P < 0.001$), in the late pre-eclampsia group ($P < 0.001$), in the gestational hypertension group ($P = 0.037$) and in the SGA group ($P < 0.001$).

Log ratio of uterine artery PI at 21 + 0 to 24 + 6 weeks to PI at 11 + 0 to 13 + 6 weeks

In each patient the log ratio was calculated:

log ratio (uterine artery PI at 21 + 0 to 24 + 6 weeks in MoMs/uterine artery PI at 11 + 0 to 13 + 6 weeks in MoMs) = log uterine artery PI at 21 + 0 to 24 + 6 weeks in MoMs − log uterine artery PI at 11 + 0 to 13 + 6 weeks in MoMs.

The median (interquartile range) log ratio of uterine artery PI was −0.006 (−0.080 to 0.071) MoM in the

Table 1 Maternal characteristics and medical and obstetric history in the unaffected, early pre-eclampsia, late pre-eclampsia, gestational hypertension and small-for-gestational-age groups

Characteristic	*Unaffected* (n = *2595*)	*Early pre-eclampsia* (n = *22*)	*Late pre-eclampsia* (n = *71*)	*Gestational hypertension* (n = *73*)	*Small-for-gestational age* (n = *346*)
Maternal age (years)	31.1 (16.2–49.6)	29.1 (17.6–39.7)	31.1 (18.8–41.9)	32.8 (17.3–46.4)	30.8 (16.0–46.0)
Body mass index (kg/m^2)	25.6 (15.8–59.2)	27.1 (18.7–38.1)	28.8 (19.2–46.4)*	28.4 (20.4–53.9)*	26.1 (15.8–45.8)
Crown–rump length (mm)	63.8 (45.0–84.0)	67.3 (52.0–84.0)	63.5 (46.0–81.4)	63.3 (50.0–84.0)	62.5 (45.6–84.0)*
Ethnicity					
Caucasian	1441 (55.5)	6 (27.3)*	24 (33.8)*	48 (65.8)	174 (50.3)
Afro-Caribbean	856 (33.0)	15 (68.2)*	39 (54.9)*	21 (28.8)	143 (41.3)*
Indian or Pakistani	142 (5.5)	—	2 (2.8)	—	8 (2.3)*
Chinese or Japanese	41 (1.6)	—	2 (2.8)	1 (1.4)	3 (0.9)
Mixed	115 (4.4)	1 (4.5)	4 (5.6)	3 (4.1)	18 (5.2)
Parity					
Nulliparous	1266 (48.8)	12 (54.5)	44 (62.0)*	43 (58.9)	182 (52.6)
Parous/no previous pre-eclampsia	1263 (48.7)	5 (22.7)*	16 (22.5)*	23 (31.5)*	159 (46.0)
Parous/previous pre-eclampsia	66 (2.5)	5 (22.7)*	11 (15.5)*	7 (9.6)*	5 (1.4)
Cigarette smoker	183 (7.1)	—	5 (7.0)	5 (6.8)	50 (14.5)*
Alcohol drinker	26 (1.0)	—	1 (1.4)	1 (1.4)	3 (0.9)
Drug abuser	12 (0.5)	—	—	1 (1.4)	3 (0.9)
Family history of pre-eclampsia (mother)	87 (3.4)	3 (13.6)*	9 (12.7)*	8 (11.0)*	18 (5.2)
Conception					
Spontaneous	2487 (95.8)	18 (81.8)*	67 (94.4)	71 (97.3)	322 (93.1)*
Ovulation drugs	77 (3.0)	4 (18.2)*	3 (4.2)	—	17 (4.9)
In-vitro fertilization	31 (1.2)	—	1 (1.4)	2 (2.7)	7 (2.0)
Medical history					
None	2533 (97.6)	19 (86.4)*	68 (95.8)	72 (98.6)	329 (95.1)*
Chronic hypertension	23 (0.9)	3 (13.6)*	3 (4.2)*	—	8 (2.3)*
Diabetes mellitus	13 (0.5)	—	—	1 (1.4)	1 (0.3)
Antiphospholipid syndrome	2 (0.1)	—	—	—	1 (0.3)
Thrombophilia	14 (0.5)	—	—	—	3 (0.9)
Sickle cell disease	5 (0.2)	—	—	—	2 (0.6)
Human immunodeficiency viral infection	5 (0.2)	—	—	—	2 (0.6)
Medication during pregnancy					
None	2424 (93.4)	19 (86.4)	65 (91.5)	65 (89.0)	306 (88.4)*
Antihypertensive	18 (0.7)	2 (9.1)*	1 (1.4)	—	7 (2.0)*
Insulin	12 (0.5)	—	—	1 (1.4)	2 (0.6)
Steroid	3 (0.1)	1 (4.5)*	—	—	—
β-mimetic	32 (1.2)	—	3 (4.2)	1 (1.4)	7 (2.0)
Combined asthma medication	25 (1.0)	—	1 (1.4)	2 (2.7)	9 (2.6)*
Thyroxine	28 (1.1)	—	—	2 (2.7)	3 (0.9)
Aspirin	25 (1.0)	—	—	1 (1.4)	7 (2.0)
Antithyroid	2 (0.1)	—	—	—	—
Anti-epileptic	7 (0.3)	—	—	1 (1.4)	—
Lithium	3 (0.1)	—	—	—	—
Antidepressant	12 (0.5)	—	1 (1.4)	—	3 (0.9)
Antiretroviral	3 (0.1)	—	—	—	2 (0.6)
Anti-inflammatory	1 (0.0)	—	—	—	—

Values are mean (range) or *n* (%). *Statistically significant differences between uncomplicated pregnancies and the disease groups.

unaffected group, 0.082 (0.018 to 0.171) MoM in the early pre-eclampsia group, −0.005 (−0.059 to 0.104) MoM in the late pre-eclampsia group, 0.013 (−0.045 to 0.089) MoM in the gestational hypertension group and 0.011 (−0.053 to 0.090) MoM in the SGA group (Figure 2). Therefore, compared to the unaffected group, the mean log ratio of uterine artery PI was significantly higher in the early pre-eclampsia group ($P < 0.001$), in the late pre-eclampsia group ($P = 0.024$), in the gestational hypertension group ($P = 0.039$) and in the SGA group ($P = 0.001$).

Prediction of pre-eclampsia

The risk of developing pre-eclampsia is calculated from the formula: risk = odds/(1 + odds), where odds = e^Y and Y is derived from the multiple regression analysis of maternal characteristics, medical and obstetric history and uterine artery PI at 11 + 0 to 13 + 6 weeks:

Early pre-eclampsia: Y = −6.546 + (3.769 if the patient had chronic hypertension, 0 if she did not) + (15.692× uterine artery PI (log MoM)); $R^2 = 0.254$, $P < 0.001$.

Late pre-eclampsia: Y = −6.140 + (0.082 × BMI) + 0.813 if the patient is Afro-Caribbean + (0 if nulliparous,

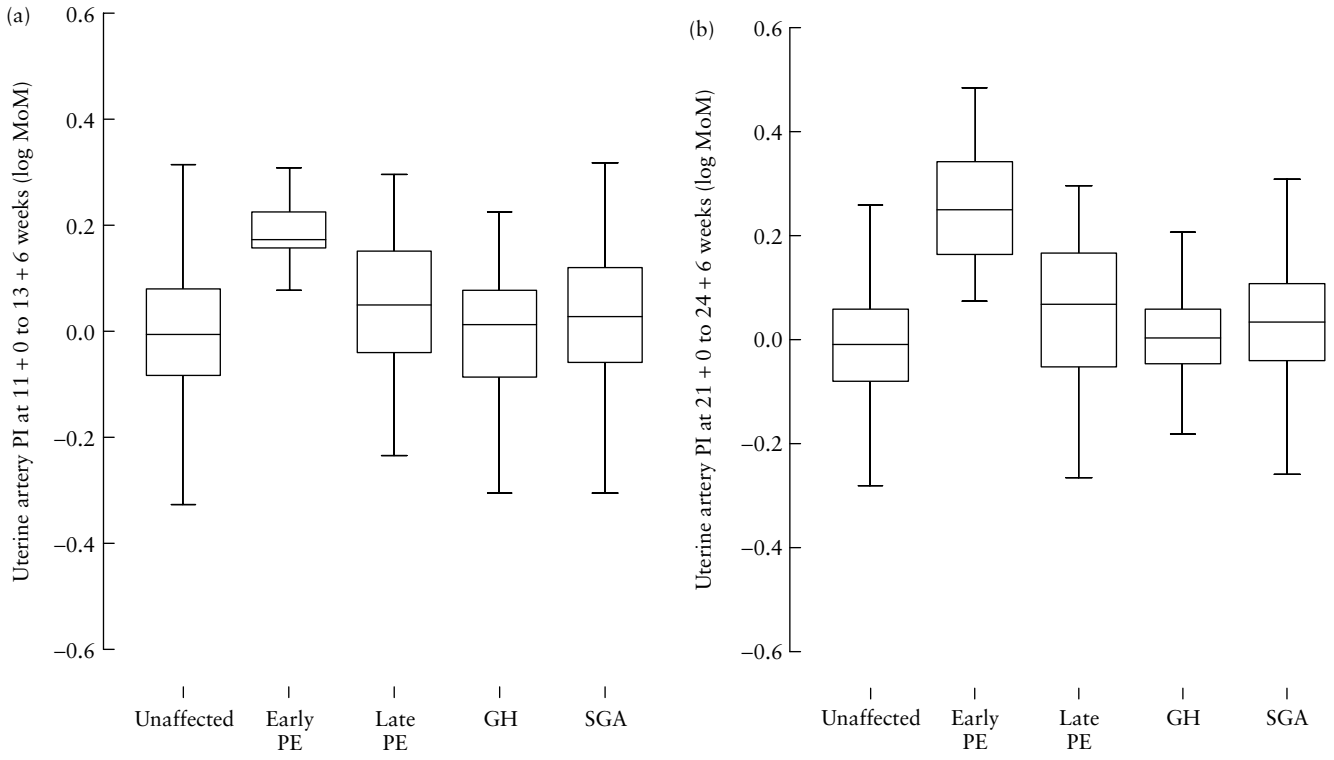

Figure 1 Box-and-whisker plots (median, 25th and 75th centiles and range) of log multiples of the median (MoM) uterine artery pulsatility index (PI) in the unaffected pregnancies and in those complicated by early and late pre-eclampsia (PE), gestational hypertension (GH) and delivery of small-for-gestational-age (SGA) newborns, at 11 + 0 to 13 + 6 weeks' gestation (a) and at 21 + 0 to 24 + 6 weeks (b).

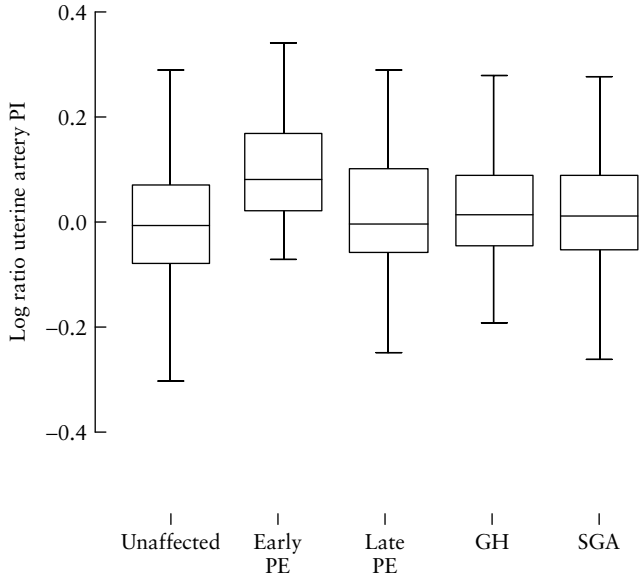

Figure 2 Box-and-whisker plots (median, 25th and 75th centiles and range) of log ratio of uterine artery pulsatility index (PI) at 21 + 0 to 24 + 6 weeks to PI at 11 + 0 to 13 + 6 weeks in the unaffected pregnancies and in those complicated by early and late pre-eclampsia (PE), gestational hypertension (GH) and delivery of small-for-gestational-age (SGA) newborns.

−1.234 if parous with no previous history of pre-eclampsia, + 0.922 if parous with a previous history of pre-eclampsia) + 1.049 if patient's mother had pre-eclampsia + (2.198 × uterine artery PI (log MoM)); $R^2 = 0.123$, $P < 0.001$.

Multiple regression analysis demonstrated that the ratio of uterine artery PI at 21 + 0 to 24 + 6 weeks to the PI at 11 + 0 to 13 + 6 weeks improved significantly the prediction of pre-eclampsia:

Early pre-eclampsia: Y = −7.753 − (1.328 if parous without a previous history of pre-eclampsia and 0 if nulliparous or parous with a previous history of pre-eclampsia) + (3.633 if the patient had chronic hypertension, 0 if she did not) + (24.644 × uterine artery PI at 11 + 0 to 13 + 6 weeks (log MoM)) + (21.068 × log ratio uterine artery PI); $R^2 = 0.540$, $P < 0.001$.

Late pre-eclampsia: Y = −5.952 + (0.07 × BMI) + 0.792 if the patient is Afro-Caribbean + (0 if nulliparous, −1.245 if parous with no previous history of pre-eclampsia, + 0.827 if parous with a previous history of pre-eclampsia) + 1.0 if patient's mother had pre-eclampsia + (4.504 × uterine artery PI (log MoM)) + (4.410 × log ratio uterine artery PI); $R^2 = 0.142$, $P < 0.001$.

Examples of the calculation of patient-specific risk

In a nulliparous Caucasian woman with a BMI of 20 kg/m^2, without chronic hypertension and no family history of pre-eclampsia, at 12 + 6 weeks the mean uterine artery PI is 2.4.

Uterine artery PI MoMs (12 + 6 weeks):

- log observed uterine artery PI = 0.380

- log expected uterine artery PI = 0.438 − (0.003 × 90[gestation in days]) = 0.168
- log MoM uterine artery PI = log(observed PI/expected PI) = log observed PI − log expected PI = 0.380 − 0.168 = 0.212

Risk for early pre-eclampsia:

- Y = −6.546 + 0[no chronic hypertension] + (15.692 × 0.212[uterine artery PI (log MoM)]) = −3.212
- Odds = e^Y = 0.04
- Risk for early pre-eclampsia = odds/(1 + odds) = 0.039 = 3.9%

Risk for late pre-eclampsia:

- Y = −6.140 + (0.082 × 20[BMI]) + 0[Caucasian] + 0 [nulliparous] + 0[no family history of pre-eclampsia] + (2.198 × 0.212[uterine artery PI (log MoM)]) = −4.03
- Odds = e^Y = 0.018
- Risk for late pre-eclampsia = odds/(1 + odds) = 0.018 = 1.8%

If at 22 + 0 weeks the mean uterine artery PI is 1.7, then uterine artery PI MoM (22 weeks) and ratio of uterine artery PI at 22 weeks and 12 + 6 weeks are given by:

- log observed uterine artery PI (22 weeks) = 0.231
- log expected uterine artery PI (22 weeks) = 0.268 − (0.002 × 154[gestation in days]) = −0.04
- log MoM uterine artery PI (22 weeks) = log(observed PI/expected PI) = log observed PI − log expected PI = 0.231 − (−0.04) = 0.271
- log ratio (uterine artery PI MoM at 22 weeks/uterine artery PI MoM at 12 + 6 weeks) = uterine artery PI (log MoM) at 22 weeks − uterine artery PI (log MoM) at 12 + 6 weeks = 0.271 − 0.212 = 0.059.

Risk for early pre-eclampsia:

- Y = −7.753 + 0[nulliparous] + 0[no chronic hypertension] + (24.644 × 0.212[uterine artery PI at 12 + 6 weeks(log MoM)]) + (21.068 × 0.059[log ratio uterine artery PI]) = −1.286
- Odds = e^Y = 0.276
- Risk for early pre-eclampsia = odds/(1 + odds) = 0.216 = 21.6%

Risk for late pre-eclampsia:

- Y = −5.952 + (0.073 × 20[BMI]) + 0[Caucasian] + 0 [nulliparous] + 0[no family history of pre-eclampsia] + (4.504 × 0.212[uterine artery PI at 12 + 6 weeks (log MoM)]) + (4.410 × 0.059[log ratio uterine artery PI]) = −3.277
- Odds = e^Y = 0.038
- Risk for late pre-eclampsia = odds/(1 + odds) = 0.037 = 3.7%

If the same patient at 22 + 0 weeks had a mean uterine artery PI of 1.1, the risk for early and late pre-eclampsia would have been 0.5 and 1.6%, respectively.

Performance of screening

The detection rates of early and late pre-eclampsia for different false positive rates in screening by maternal factors and uterine artery PI at 11 + 0 to 13 + 6 weeks only and by combination with the ratio of uterine artery PI at 21 + 0 to 24 + 6 weeks to the PI at 11 + 0 to 13 + 6 weeks are given in Table 2 and illustrated in Figure 3. At 21 + 0 to 24 + 6 weeks there was persistence of uterine artery PI above the 90th centile in 94.1% of the early pre-eclampsia cases, 73.7% of the late pre-eclampsia cases and 37.4% of those that did not develop pre-eclampsia. In combined screening by maternal factors and uterine artery PI at 11 + 0 to 13 + 6 weeks the detection rates of early pre-eclampsia were 45.5, 77.3, 90.9 and 95.5% at false positive rates of 5, 10, 15 and 20%, respectively. Inclusion of the PI ratio improved the detection rates to 90.9 and 100% at false positive rates of 5 and 10%, respectively.

Contingency screening

In this method the individual risk for pre-eclampsia is calculated from maternal factors and uterine artery PI at 11 + 0 to 13 + 6 weeks, and in those with a risk above a cut-off Doppler sonography is also performed at 21 + 0 to 24 + 6 weeks and a new risk is calculated from the combined findings (Table 3). If second-trimester testing is carried out in all cases the detection of early pre-eclampsia is 90.9% for a false positive rate of 5%. The same detection rate can be achieved by reserving second-trimester testing for only the 20% of women with the highest risk after first-trimester screening.

DISCUSSION

This study has demonstrated that the decrease in impedance to flow in the uterine arteries between 12 and 23 weeks is steeper in pregnancies with a normal outcome than in those developing pre-eclampsia. Consequently, assessment of the rate of change in PI improves the performance of screening and can be used in the follow-up of cases presenting with a high PI at the 11 + 0 to 13 + 6 weeks' scan. In the majority of normal pregnancies presenting with high uterine artery PI in the first trimester there is normalization in impedance to flow with advancing gestation, presumably owing to progressive physiological trophoblastic invasion. In contrast, in those pregnancies destined to develop pre-eclampsia owing to impaired trophoblastic invasion the PI remains high.

We examined 3107 pregnancies including 22 that subsequently developed early pre-eclampsia and 71 that developed late pre-eclampsia. At 11 + 0 to 13 + 6 weeks the uterine artery PI was above the 90th centile in 77% of the early pre-eclampsia cases and in 27% of the late pre-eclampsia cases. At 21 + 0 to 24 + 6 weeks

Table 2 Performance of screening for early and late pre-eclampsia, by uterine artery pulsatility index (PI) at 11 + 0 to 13 + 6 weeks alone, combined with maternal factors, and with the ratio of uterine artery PI between 11 + 0 and 13 + 6 weeks and between 21 + 0 and 24 + 6 weeks

Performance of screening test	*Early pre-eclampsia*	*Late pre-eclampsia*
Area under receiver–operating characteristics curve (mean (95% CI))		
Uterine artery PI at 11 + 0 to 13 + 6 weeks	0.872 (0.781–0.962)	0.590 (0.513–0.668)
Uterine artery PI at 11 + 0 to 13 + 6 weeks and history	0.931 (0.904–0.958)	0.779 (0.726–0.832)
Combined screening including ratio	0.983 (0.972–0.993)	0.783 (0.729–0.837)
Detection rate for 5% false-positive rate (% (95% CI))		
Uterine artery PI at 11 + 0 to 13 + 6 weeks	45.5 (24.4–67.8)	15.5 (8.0–26.0)
Uterine artery PI at 11 + 0 to 13 + 6 weeks and history	45.5 (24.4–67.8)	31.0 (20.5–43.1)
Combined screening including ratio	90.9 (70.8–98.6)	31.0 (20.5–43.1)
Detection rate for 10% false-positive rate (% (95% CI))		
Uterine artery PI at 11 + 0 to 13 + 6 weeks	77.3 (54.6–92.1)	26.8 (16.9–38.6)
Uterine artery PI at 11 + 0 to 13 + 6 weeks and history	77.3 (54.6–92.1)	42.3 (30.6–54.6)
Combined screening including ratio	100 (84.4–100)	46.5 (34.5–58.7)

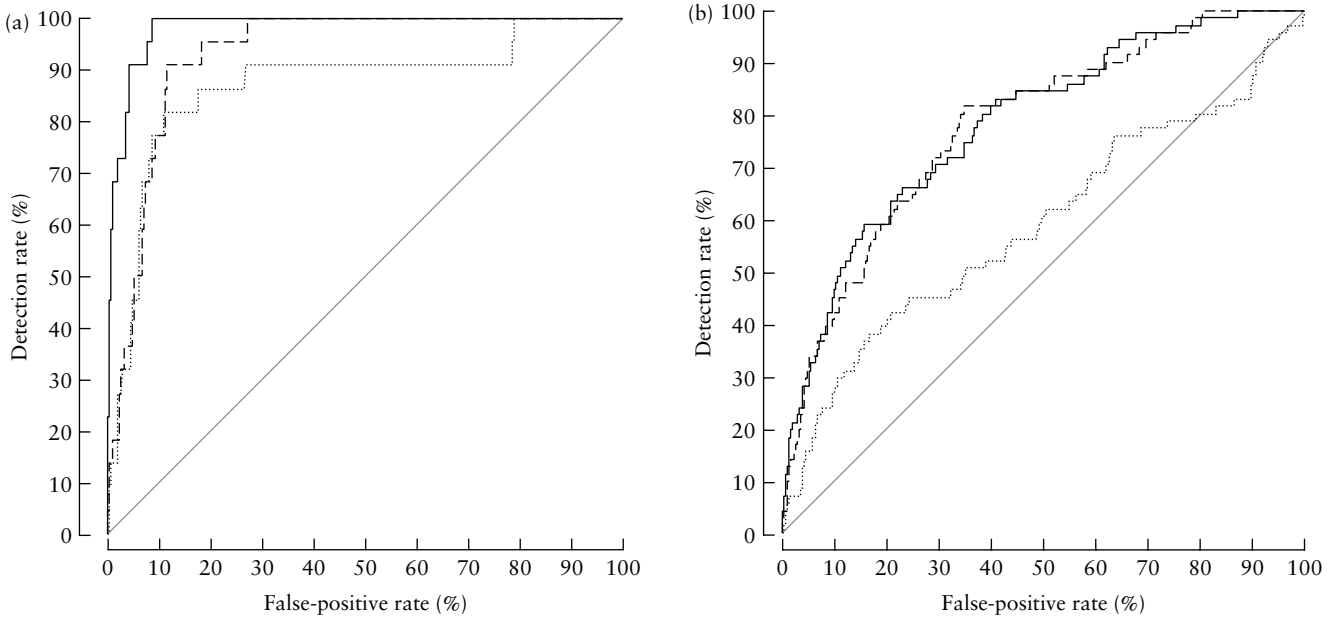

Figure 3 Detection and false-positive rates in screening for early (a) and late (b) pre-eclampsia by uterine artery pulsatility index (PI) at 11 + 0 to 13 + 6 weeks (·····), maternal factors and uterine artery PI at 11 + 0 to 13 + 6 weeks (- - - -), and maternal factors, uterine artery PI at 11 + 0 to 13 + 6 weeks and the ratio of uterine artery PI at 21 + 0 to 24 + 6 weeks to the PI at 11 + 0 to 13 + 6 weeks (———).

Table 3 Detection rate of second-trimester Doppler ultrasound in those cases with risk above the cut-off after first-trimester assessment with history and uterine artery Doppler

	Detection rate (95% CI)			
	Early pre-eclampsia		*Late pre-eclampsia*	
Cut-off	*False-positive rate 5%*	*False-positive rate 10%*	*False-positive rate 5%*	*False-positive rate 10%*
95th centile	68.2 (45.1–86.1)	90.9 (70.8–98.6)	26.8 (16.9–38.6)	40.8 (29.3–53.2)
90th centile	86.4 (65.1–96.9)	86.4 (65.1–96.9)	29.6 (19.3–41.6)	40.8 (29.3–53.2)
85th centile	86.4 (65.1–96.9)	90.9 (70.8–98.6)	29.6 (19.3–41.6)	42.3 (30.6–54.6)
80th centile	90.9 (70.8–98.6)	95.5 (77.1–99.2)	29.6 (19.3–41.6)	43.7 (31.9–56.0)
50th centile	90.9 (70.8–98.6)	100 (84.4–100)	31.0 (20.5–43.1)	46.5 (34.5–58.7)
All	90.9 (70.8–98.6)	100 (84.4–100)	31.0 (20.5–43.1)	46.5 (34.5–58.7)

there was persistence of uterine artery PI above the 90th centile in 94% of the early pre-eclampsia cases, 74% of the late pre-eclampsia cases and 37% of those who did not develop pre-eclampsia. These findings are generally compatible with the results of two previous studies[15,16]. Gomez *et al.* assessed the uterine arteries by Doppler sonography for the presence of bilateral notches in the waveforms at 11–14 weeks and 19–22 weeks in 870 pregnancies including 27 (3.1%) that subsequently developed pre-eclampsia or gestational hypertension[15]. At 11–14 weeks bilateral notches were observed in 368 (42.3%) cases including 18 (66.7%) of the 27 that developed hypertensive disorders. At 19–22 weeks there was persistence of bilateral notches in 11 (61.1%) of the 18 who developed hypertensive disorders and in 72 (20.6%) of the 350 with no such disorders. Similarly, Carbillon *et al.* assessed the uterine arteries by Doppler sonography for the presence of either unilateral or bilateral notches in the waveforms at 12–14 weeks and 22–24 weeks in 243 pregnancies including 12 (4.9%) that subsequently developed pre-eclampsia[16]. Notches at 12–14 weeks were observed in 139 (57.2%) cases including 10 (83.3%) of the 12 that developed pre-eclampsia. At 22–24 weeks there was persistence of notches in eight (80.0%) of the 10 that developed pre-eclampsia and in only 27 (20.9%) of the 129 that did not develop pre-eclampsia.

The findings of our study confirm that firstly, the risk of developing pre-eclampsia increases with BMI and is higher in women of Afro-Caribbean origin than in other ethnic groups and in those with chronic hypertension and a personal or family history of pre-eclampsia[8]; secondly, effective screening for pre-eclampsia can be achieved by a combination of maternal variables and uterine artery Doppler[9]; and thirdly, combined screening is more effective in predicting early than late pre-eclampsia[8,9]. This is particularly important because it is early rather than late pre-eclampsia that is associated with increased risk of perinatal mortality and morbidity and both short-term and long-term maternal complications[17–19].

In combined screening by maternal factors and uterine artery PI at 11 + 0 to 13 + 6 weeks a 90.9% detection rate of early pre-eclampsia was achieved at a false positive rate of 15%, and after inclusion of the ratio of uterine artery PI at 21 + 0 to 24 + 6 weeks to the PI at 11 + 0 to 13 + 6 weeks the same 90.9% detection rate was achieved with a substantial reduction in false positive rate to 5%. In addition, the data from contingency screening have demonstrated that second-trimester testing need not be carried out in all cases but only in the 20% of women with the highest risk after first-trimester screening.

In the UK, the National Institute for Clinical Excellence (NICE) has issued guidelines on routine antenatal care recommending that a woman's level of risk for pre-eclampsia should be evaluated at her first medical visit so that a plan for her schedule of antenatal appointments can be formulated[20]. At present there are no prophylactic interventions that can substantially reduce the risk of developing pre-eclampsia[21–24]. However, the rationale of the recommended policy, that the frequency of antenatal visits should be based on the patient-specific risk for pre-eclampsia, is that in women at high risk increased surveillance and timely intervention could potentially improve both maternal and fetal outcome[20]. In addition, the identification of women at high risk for pre-eclampsia during the first trimester could form the basis of therapeutic interventions in early pregnancy that may prove to be more effective than those instituted during the second trimester.

The findings of our study could provide the scientific basis for the rationalization of antenatal care. Combined screening for pre-eclampsia by maternal factors and uterine artery Doppler could be undertaken in all women at their 11 + 0 to 13 + 6-week hospital visit, which is routinely performed for early determination of gestational age, diagnosis of multiple pregnancies and chorionicity and screening for chromosomal abnormalities and major defects. In the 20% of women with the highest risk for pre-eclampsia Doppler assessment of the uterine arteries could be repeated in the second trimester. On the basis of findings in the first trimester and the change in uterine artery PI between the first and second trimesters 75% of the 20% of cases with the highest risk at 11 + 0 to 13 + 6 weeks could be assigned to the low-risk group and 25% (or 5% of the total) remain in the high-risk group in need for increased surveillance.

ACKNOWLEDGMENT

This study was supported by a grant from The Fetal Medicine Foundation (Charity No: 1037116).

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