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

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KEYWORDS: Doppler; first trimester; high-risk pregnancy prediction; pre-eclampsia; uterine artery

ABSTRACT

Objective *To determine the performance of screening for pre-eclampsia (PET) by maternal characteristics and uterine artery pulsatility index (PI) at 11 + 0 to 13 + 6 weeks' gestation.*

Methods *In women with singleton pregnancies attending for routine care at 11 + 0 to 13 + 6 weeks' gestation we recorded maternal variables and measured the uterine artery PI. We identified 107 cases that subsequently developed PET and 5041 that were unaffected by PET, gestational hypertension or delivery of newborns with birth weight below the 10th centile. A multivariate Gaussian model was fitted to the distribution of log multiples of the median (MoM) PI in the PET and unaffected groups. Likelihood ratios for log MoM PI were computed and used together with maternal variables to produce patient-specific risks for each case. Predicted detection rates (DR) and false-positive rates (FPR) were calculated by taking the proportions with risks above a given risk threshold.*

Results *In the unaffected group log MoM PI was influenced by maternal ethnic origin, body mass index, previous history of PET and fetal crown–rump length. In the prediction of PET significant contributions were provided by log MoM PI, ethnic origin, body mass index and previous and family history of PET. For an FPR of 10% the DRs of all PET and PET leading to delivery before 34 weeks' gestation by log MoM PI and maternal variables were 61.7% and 81.8%, respectively.*

Conclusion *Maternal variables together with uterine artery PI at 11 + 0 to 13 + 6 weeks' gestation provide sensitive prediction of the development of PET, especially of severe early-onset PET. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Pre-eclampsia (PET), which affects about 2% of pregnancies, is a major cause of perinatal and maternal morbidity and mortality[1–3]. Routine antenatal care has evolved with the aim of identifying women at high risk for subsequent development of PET. The likelihood of developing PET is increased by a number of factors in the maternal history, including Afro-Caribbean race, nulliparity, high body mass index (BMI) and personal or family history of PET[4,5]. However, screening by maternal history may detect only about 30% of those that will develop PET for a false-positive rate of 10%[5].

A more effective method of screening for PET is provided by uterine artery Doppler velocimetry at 22 weeks' gestation either alone or in combination with maternal history, with detection rates of 52% and 57%, respectively[5,6]. Indeed, Doppler is particularly effective in screening for severe PET that necessitates iatrogenic delivery before 34 weeks, with a detection rate of 85% for a false-positive rate of 10%[5].

Identification of women at high risk for PET during the second trimester could potentially improve pregnancy outcome because intensive maternal and fetal monitoring in such patients would lead to an earlier diagnosis of the clinical signs of the disease and the associated fetal growth restriction and avoid the development of serious complications through such interventions as the administration of antihypertensive medication and early delivery. Another important reason for the early identification of these high-risk women would be to determine whether the administration of prophylactic therapy would prevent or significantly ameliorate these conditions. However, attempts at the prevention of PET by the prophylactic use of drugs from mid-gestation have been largely unsuccessful in the case of calcium and antioxidant vitamins, or they have had a small effect (10%) in the case of low-dose aspirin[7–10]. It is uncertain whether pharmacological interventions starting from the

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first rather than the second trimester would prove to be more effective in the prevention of PET, but before this can be investigated it is essential to develop a method of effective and early identification of the high-risk group.

The aim of this prospective study was to determine the performance of screening for PET by maternal characteristics and uterine artery Doppler velocimetry at 11 + 0 to 13 + 6 weeks' gestation.

METHODS

This was a prospective screening study for PET in singleton pregnancies. All patients were attending our center for routine assessment of risk for chromosomal abnormalities by measurement of fetal nuchal translucency (NT) thickness and maternal serum free beta-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 11 + 0 to 13 + 6 weeks' gestation[11,12]. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the Institution Review Board.

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, antiepileptic, anti-inflammatory, antiretroviral, antithyroid, aspirin, betamimetic, insulin, lithium, steroids, thyroxine), parity (parous or nulliparous if no previous conception or pregnancy progressing beyond 23 weeks), obstetric history (including previous pregnancy with PET) and family history of PET (sister, mother or both). The maternal weight and height were measured and the BMI (kg/m^2) was calculated.

Transabdominal ultrasound examination was carried out for the measurement of fetal crown–rump length (CRL) and NT thickness, diagnosis of any major fetal defects and measurement of uterine artery pulsatility index (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[13]. 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. All ultrasound and Doppler studies were carried out by sonographers who had received the appropriate Certificate of Competence in the 11 + 0 to 13 + 6 weeks' scan and Doppler of The Fetal Medicine Foundation (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.

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 whether the condition was chronic hypertension, PET or gestational hypertension (GH).

Outcome measures

The outcome measures were PET, GH and small-for-gestational age (SGA). In PET and GH we included all cases with SGA but in the SGA group we excluded cases with PET and GH.

The definitions of PET and GH used were those of the guidelines of the International Society for the Study of Hypertension in Pregnancy[14]. In PET the diastolic blood pressure should be more than 90 mmHg on at least two occasions 4 h apart in previously normotensive women, and proteinuria should be 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 GH the diastolic blood pressure should be more than 90 mmHg on at least two occasions 4 h apart in previously normotensive women in the absence of significant proteinuria.

In all patients the birth weight was converted into a percentile after correction for gestation at delivery and sex of the newborn, maternal ethnic origin, weight, height and parity[11]. Newborns were considered to be SGA if the birth weight was less than the 10th percentile.

Statistical analysis

The following seven steps were taken:

1. The patients were subdivided into four groups depending on pregnancy outcome: PET, GH, SGA and unaffected by PET, GH or SGA.
2. The distribution of uterine artery PI was made Gaussian after logarithmic transformation.
3. Multiple regression analysis was used to determine which of the factors among the maternal characteristics, medical and obstetric histories and gestation were significant predictors of log uterine artery PI in the unaffected group.
4. The distribution of log uterine artery PI, expressed as multiples of the median (MoM) of the unaffected group, were determined in the PET, GH and SGA groups.
5. Multiple regression analysis was used to determine which of the factors amongst the maternal characteristics, medical and obstetric histories and gestation had

a significant contribution in explaining the *a priori* risk for PET, GH and SGA.
6. Likelihood ratios were computed from the fitted distributions of log MoM values in the unaffected pregnancies and in each of the three groups with pregnancy complications.
7. Patient-specific risks for each complication were derived by multiplying the appropriate *a priori* risk with the likelihood ratio.

RESULTS

Study population

First-trimester screening was carried out in 6592 consecutive singleton pregnancies with a live fetus at 11 + 0 to 13 + 6 weeks' gestation and the uterine artery PI was successfully measured in 6519 (98.9%) cases. We excluded 504 (7.6%) because they had missing outcome data ($n = 341$), there was a major fetal defect ($n = 12$), the pregnancies resulted in fetal death or miscarriage before 24 weeks' gestation ($n = 64$), or the pregnancies were terminated for fetal abnormalities ($n = 77$) or social reasons ($n = 10$). In the remaining 6015 cases there were 107 (1.8%) that developed PET, 107 (1.8%) that developed GH, 760 (12.6%) that did not develop PET or GH but delivered SGA newborns and 5041 (83.8%) cases that were unaffected by PET, GH or SGA. The characteristics of the four outcome groups are summarized in Table 1.

Log uterine artery PI in the unaffected group

In the multiple regression model for log uterine artery PI in the unaffected group significant independent contributions were provided by maternal ethnic origin, BMI, previous history of PET and fetal CRL (Table 2), but not medical condition, medication, age, smoking, alcohol intake, drug abuse, method of conception or family history of PET. The multiple regression equation for log uterine artery PI is:

$$\log \text{uterine artery PI} = 0.393 - 0.002 \times \text{CRL (mm)} + (0.028 \text{ if Afro-Caribbean, 0 if any other ethnic origin}) - 0.002 \times \text{BMI (kg/m}^2) - (0.009 \text{ if parous without previous PET, 0 if parous with previous PET or nulliparous}); R^2 = 0.031, P < 0.0001.$$

Distributions of log MoM uterine artery PI

In each patient we log-transformed the measured PI (log observed uterine artery PI), used the formula above for log uterine artery PI in the unaffected group to calculate the log expected uterine artery PI and then calculated the ratio of the observed to expected values:

$$\log (\text{observed/expected}) = \log \text{MoM uterine artery PI} = \log \text{observed} - \log \text{expected}$$

The mean log uterine artery PI, expressed as MoMs of the unaffected group, was 0.0 (95% CI, – 0.0033 to 0.0033) MoM in the unaffected group, 0.0768 (95% CI, 0.0472–0.1063) MoM in the PET group, 0.0279 (95% CI, 0.0074–0.0484) MoM in the GH group and 0.0299 (95% CI, 0.0209–0.0389) MoM in the SGA group. Therefore, the mean log MoM uterine artery PI in all three pregnancy complications was significantly higher than that in the unaffected group. In the PET group the mean log MoM uterine artery PI decreased significantly with gestation at delivery ($r = 0.415$, $P < 0.001$). In subsequent analyses the results for PET are presented as total, early (delivery before 34 weeks) and late (delivery at or after 34 weeks).

The mean log MoM uterine artery PI in the pregnancies that were excluded from this study (mean 0.0089, 95% CI, −0.0017 to 0.0196) was not significantly different from the mean in unaffected pregnancies ($P = 0.118$). The Kolmogorov–Smirnov test demonstrated that the distribution of log MoM uterine artery PI in the unaffected, PET, GH and SGA groups was not significantly different from the Gaussian form ($P = 0.054$, 0.077, 0.655 and 0.129, respectively).

Figure 1 illustrates the median, interquartile range and range of log uterine artery PI in the four groups.

Likelihood ratios for PET, GH and SGA

The overlapping Gaussian distributions of log MoM uterine artery PI in the unaffected group and each of the PET, GH and SGA groups were used to calculate the likelihood ratios for each pregnancy complication (Table 3).

The *a priori* risk for PET, GH and SGA

The *a priori* risk for each pregnancy complication is calculated from the formula: odds/(1 + odds), where odds = e^Y and Y is derived from multiple regression analysis of maternal characteristics, medical and obstetric history:

All PET: $Y = -6.253 + (1.432$ if Afro-Caribbean, 1.465 if mixed, 0 if other ethnic origin) + 0.084 × BMI + (0.81 if patient's mother had PET, 0 if she did not) + (0 if nulliparous, − 1.539 if parous without previous PET, 1.049 if parous with previous PET); $R^2 = 0.157$, $P < 0.0001$.

Early PET: $Y = -6.431 + (1.680$ if Afro-Caribbean, 1.889 if mixed, 0 if other ethnic origin) + (2.822 if parous with previous PET, 0 if nulliparous or parous without previous PET); $R^2 = 0.143$, $P < 0.0001$.

Late PET: $Y = -6.585 + (1.368$ if Afro-Caribbean, 1.311 if mixed, 0 if other ethnic origin) + 0.091 × BMI + (0.960 if patient's mother had PET, 0 if she did not) − (1.663 if parous without previous PET, 0 if nulliparous or parous with previous PET); $R^2 = 0.143$, $P < 0.0001$.

Table 1 Maternal characteristics, medical and obstetric history and gestation in the four groups of pregnancy outcome: pre-eclampsia (PET), gestational hypertension, small-for-gestational age and unaffected by any of the previous three

Maternal characteristic	*Unaffected (n = 5041)*	*Pre-eclampsia (n = 107)*	*Gestational hypertension (n = 107)*	*Small-for-gestational age (n = 760)*
Maternal age (years)	32.0 (15–47)	31.6 (17–49)	32.6 (17–46)	32.0 (16–46)
BMI (kg/m^2)	25.5 (14.3–59.2)	28.6 (18.9–46.4)	28.2 (19.6–53.9)	25.7 (16.4–50.9)
CRL (mm)	64.7 (45–84)	64.3 (47–84)	64.3 (47.4–84)	62.9 (45.6–84)
Ethnicity				
Caucasian	3730 (74)	46 (43)	81 (75.7)	520 (68.4)
Afro-Caribbean	831 (16.5)	47 (43.9)	21 (19.6)	150 (19.7)
Indian or Pakistani	240 (4.8)	5 (4.7)	—	42 (5.5)
Chinese or Japanese	79 (1.6)	2 (1.9)	1 (0.9)	9 (1.2)
Mixed	161 (3.2)	7 (6.5)	4 (3.7)	39 (5.1)
Parity				
Nulliparous	2322 (46.1)	68 (63.6)	62 (57.9)	369 (48.6)
Parous: no previous PET	2592 (51.4)	21 (19.6)	34 (31.8)	366 (48.2)
Parous: previous PET	127 (2.5)	18 (16.8)	11 (10.3)	25 (3.3)
Cigarette smoker	360 (7.1)	5 (4.7)	9 (8.4)	135 (17.8)
Alcohol drinker	51 (1.0)	1 (0.9)	—	8 (1.1)
Drug abuser	19 (0.4)	—	1 (0.9)	5 (0.7)
Family history of PET				
Mother	197 (3.9)	12 (11.2)	9 (8.4)	25 (3.3)
Sister	93 (1.8)	3 (2.8)	—	17 (2.2)
Conception				
Spontaneous	4916 (97.5)	104 (97.2)	102 (95.3)	732 (96.3)
Ovulation drugs	47 (0.9)	1 (0.9)	—	13 (1.7)
In-vitro fertilization	78 (1.5)	2 (1.9)	5 (4.7)	15 (2.0)
Medical history				
None	4917 (97.5)	98 (91.6)	104 (97.2)	728 (95.8)
Chronic hypertension	34 (0.7)	6 (5.6)	—	14 (1.8)
Diabetes mellitus	45 (0.9)	1 (0.9)	2 (1.9)	7 (0.9)
Antiphospholipid syndrome	12 (0.2)	1 (0.9)	—	1 (0.1)
Thrombophilia	23 (0.5)	1 (0.9)	1 (0.9)	5 (0.7)
Sickle cell disease	7 (0.1)	—	—	2 (0.3)
HIV infection	3 (0.1)	—	—	3 (0.4)
Medication during pregnancy				
None	4689 (93.0)	93 (86.9)	94 (87.9)	674 (88.7)
Antihypertensives	21 (0.4)	4 (3.7)		10 (1.3)
Insulin	42 (0.8)	1 (0.9)	2 (1.9)	7 (0.9)
Steroids	8 (0.2)	—	—	2 (0.3)
β-mimetics	67 (1.3)	2 (1.9)	1 (0.9)	19 (2.5)
Combined asthma medications	46 (0.9)	2 (1.9)	3 (2.8)	14 (1.8)
Thyroxine	59 (1.2)	3 (2.8)	2 (1.9)	12 (1.6)
Aspirin	51 (1.0)	1 (0.9)	2 (1.9)	8 (1.1)
Antithyroid medication	4 (0.1)	—	—	—
Antiepileptic	22 (0.4)	—	2 (1.9)	5 (0.7)
Lithium	2 (0.05)	—	—	—
Antidepressants	25 (0.5)	1 (0.9)	1 (0.9)	6 (0.8)
Antiretroviral	—	—	—	3 (0.4)
Anti-inflammatory	5 (0.1)	—	—	—

Data are given as mean (range) or *n* (%). BMI, body mass index; CRL, crown–rump length; HIV, human immunodeficiency virus.

GH: $Y = -5.949 + 0.088 \times BMI + (-0.816$ if parous without previous PET, 0.887 if parous with previous PET, 0 if nulliparous) + (1.035 if conception by *in-vitro* fertilization (IVF), 0 if conception was spontaneous or after use of ovulation drugs); $R^2 = 0.059$, $P < 0.0001$.

SGA: $Y = -0.659 +$ (0.428 if Afro-Caribbean, 0.411 if Indian, Pakistani or Bangladeshi, 0.563 if mixed, 0 if other ethnic origin) + 0.024 × age in years + 1.145 × (1 if smoker, 0 if not smoker) + (0.728 if on treatment for asthma, 0 if on other medications or none) − (0.227 if parous without previous PET, 0 if parous with previous PET or nulliparous) − 0.034 × CRL (mm) + (0.686 if conception after use of ovulation drugs, 0 if conception is spontaneous or by IVF); $R^2 = 0.051$, $P < 0.0001$.

Patient-specific risk for PET, GH and SGA

To derive the patient-specific risk the likelihood ratios for each pregnancy complication (Table 3) are multiplied by the corresponding *a priori* risk. For example, in

Table 2 Multiple regression for mean uterine artery pulsatility index with maternal characteristics and gestation in the unaffected group

	log MoM mean uterine artery pulsatility index		
Variable	*b*	*95% CI*	P
BMI (kg/m^2)	−0.002	−0.003 to −0.001	< 0.0001
CRL (mm)	−0.002	−0.003 to −0.002	< 0.0001
Parity			
Nulliparous			
Parous: no previous PET	−0.009	−0.016 to −0.002	0.008
Parous: previous PET	0.025	−0.001 to 0.05	0.062
Ethnicity			
Caucasian			
Afro-Caribbean	0.028	0.019 to 0.038	< 0.0001
Indian, Pakistani or Bangladeshi	0.007	−0.009 to 0.022	0.405
Chinese or Japanese	−0.006	−0.032 to 0.021	0.679
Mixed	0.006	−0.013 to 0.024	0.567

BMI, body mass index; CRL, crown–rump length; MoM, multiples of the median; PET, pre-eclampsia.

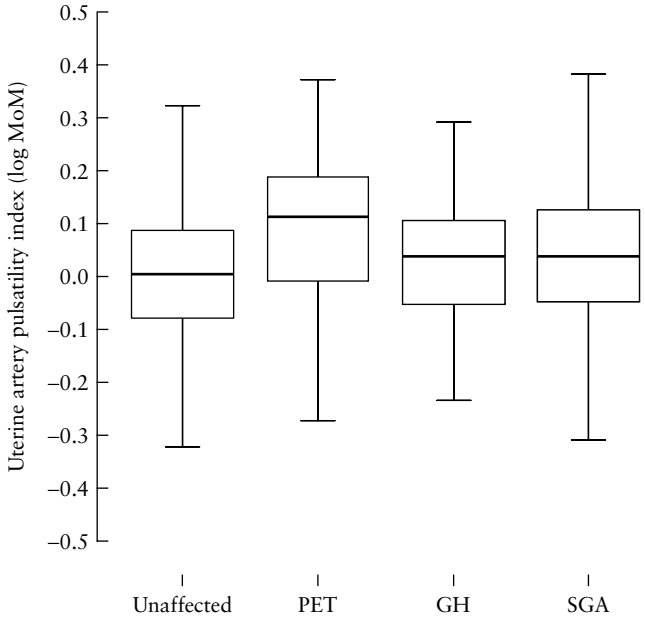

Figure 1 Box-and-whisker plot showing distribution of log uterine artery pulsatility index expressed as multiples of the median (MoM) according to pregnancy outcome. Median, interquartile range and range are shown. GH, gestational hypertension; PET, pre-eclampsia; SGA, small-for-gestational age.

an Afro-Caribbean woman in her first pregnancy, with no family history of PET, who is 28 years old, has a BMI of 20 kg/m^2, does not smoke and at 12 weeks of gestation the CRL is 65 mm and her uterine artery PI is 1.6, the risk of developing PET is 2.5%.

A priori risk for PET:

- $Y = -6.253 + 1.432$ (Afro-Caribbean) $+ 0.084 \times 20$ (BMI) $+ 0$ (no family history of PET) $+ 0$ (nulliparous) $= -3.141$
- Odds $= e^y = 0.04323954$
- A priori risk = odds/(1 + odds) = 0.04144737

Likelihood ratio for PET:

- Measured uterine artery PI = 1.6, log observed uterine artery PI = 0.204
- log expected uterine artery PI $= 0.393 - 0.002 \times 65$ (CRL) $+ 0.028$ (Afro-Caribbean) $- 0.002 \times 20$ (BMI) $+ 0$ (nulliparous) $= 0.251$
- log MoM uterine artery PI $= 0.204 - 0.251 = -0.047$
- Likelihood ratio for log MoM uterine artery PI of −0.047 (see Table 3) = 0.6

A posteriori risk = *A priori* risk × likelihood ratio:

- Risk for PET $= 0.04144737 \times 0.6 = 0.025$ or 2.5%.

If the same woman had had a previous pregnancy with PET and her BMI was 35 kg/m^2 her risk for PET would have been 19.7%.

Performance of screening

The detection rates of PET for different false-positive rates in screening by maternal factors alone, uterine artery PI alone and by the combination of the two are given in Figure 2. The performance of the three methods of

Table 3 Likelihood ratio for all, early and late pre-eclampsia (PET), gestational hypertension (GH) and small-for-gestational age (SGA) groups based on uterine artery pulsatility index (PI) in log multiples of the median (MoM)

	Likelihood ratio				
	PET				
log MoM uterine artery PI	*All*	*Early*	*Late*	*GH*	*SGA*
−0.06	0.59	0.04	0.68	0.90	0.83
−0.05	0.60	0.05	0.69	0.94	0.85
−0.04	0.62	0.07	0.69	0.97	0.86
−0.03	0.63	0.08	0.70	1.00	0.87
−0.02	0.65	0.11	0.71	1.03	0.89
−0.01	0.66	0.13	0.72	1.05	0.90
0.00	0.68	0.17	0.73	1.08	0.92
0.01	0.71	0.21	0.75	1.11	0.94
0.02	0.73	0.26	0.77	1.13	0.96
0.03	0.76	0.32	0.79	1.15	0.98
0.04	0.80	0.39	0.81	1.18	1.00
0.05	0.83	0.48	0.84	1.20	1.02
0.06	0.87	0.58	0.87	1.21	1.04
0.07	0.92	0.70	0.91	1.23	1.07
0.08	0.97	0.84	0.95	1.24	1.10
0.09	1.03	1.01	0.99	1.26	1.12
0.10	1.09	1.20	1.04	1.26	1.15
0.11	1.16	1.42	1.09	1.27	1.18
0.12	1.23	1.68	1.15	1.28	1.22
0.15	1.52	2.68	1.37	1.28	1.32
0.20	2.29	5.27	1.95	1.24	1.55
0.25	3.68	9.09	2.96	1.15	1.84
0.30	6.36	13.90	4.85	1.02	2.24
0.35	13.60	19.62	9.72	0.83	2.90
0.40	27.51	22.64	18.67	0.66	3.67

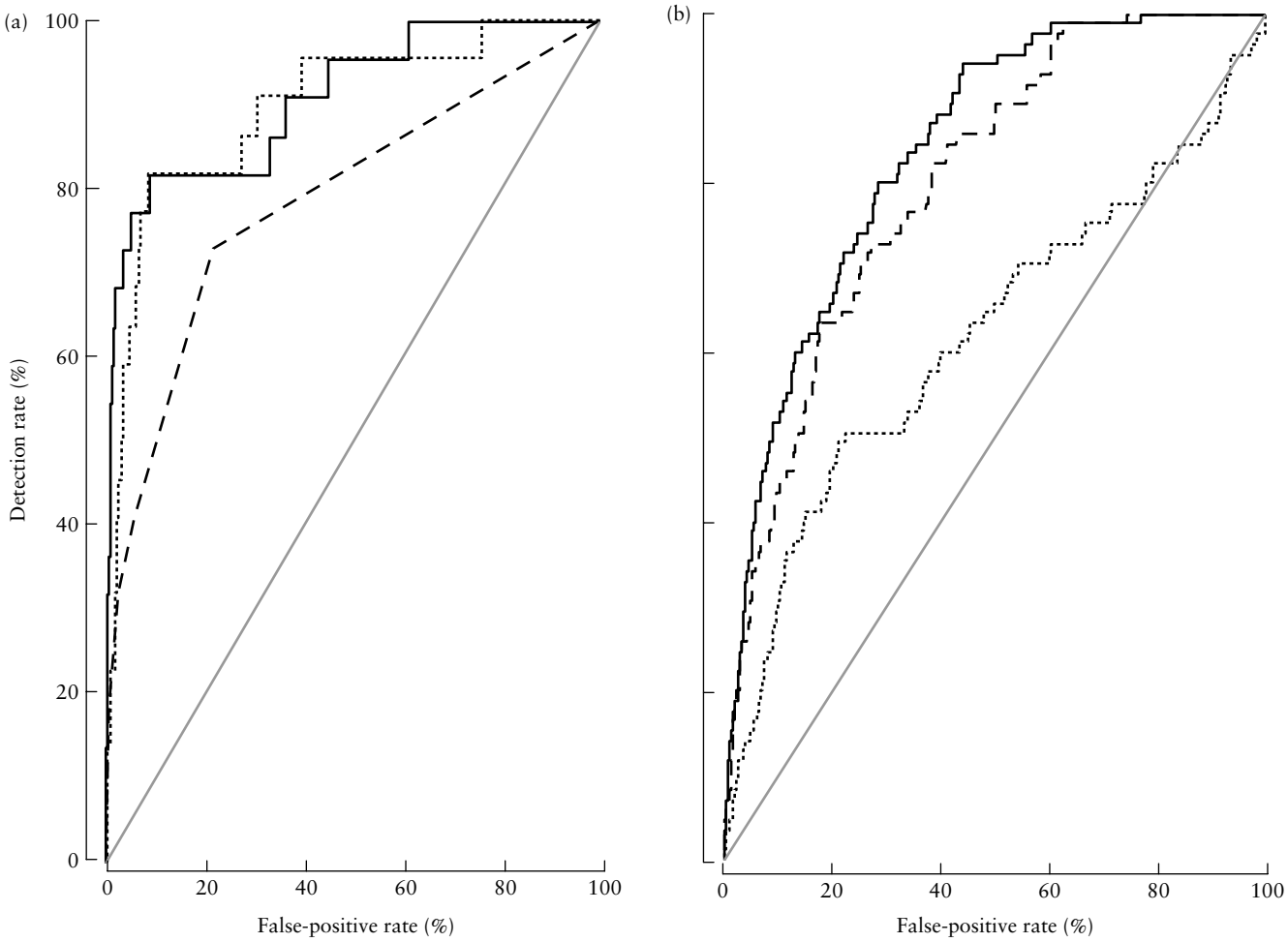

Figure 2 Receiver–operating characteristics curves for detection rates of pre-eclampsia before (a) and after (b) 34 weeks' gestation (– – –, history; ·····, uterine artery pulsatility index; ———, combined).

Table 4 Comparison of the performance of screening for pre-eclampsia, gestational hypertension and small-for-gestational age by maternal factors only, uterine artery pulsatility index (PI) alone and by the combination of the two

Performance of screening test	*Pre-eclampsia*			*Gestational hypertension*	*Small-for-gestation*
	Total	*Early*	*Late*		
Area under receiver–operating characteristics curve					
Screening by history alone (mean (95% CI))	0.806 (0.795–0.816)	0.784 (0.773–0.796)	0.801 (0.790–0.812)	0.690 (0.677–0.702)	0.641 (0.628–0.653)
Screening by uterine artery PI (mean (95% CI))	0.677 (0.664–0.689)	0.895 (0.886–0.903)	0.620 (0.607–0.633)	0.570 (0.556–0.583)	0.576 (0.563–0.589)
Combined screening (mean (95% CI))	0.852 (0.842–0.861)	0.908 (0.899–0.915)	0.838 (0.828–0.848)	0.708 (0.695–0.720)	0.661 (0.648–0.673)
Detection rate for 10% false-positive rate					
Screening by history alone (%)	46.7	50.0	43.5	31.8	22.9
Screening by uterine artery PI (%)	41.1	81.8	30.6	12.1	18.4
Combined screening (%)	61.7	81.8	51.8	28.0	24.6

screening for PET, GH and SGA is compared by the areas under the receiver–operating characteristics curves and detection rates for a fixed false-positive rate of 10% in Table 4.

DISCUSSION

In this screening study for hypertensive disorders of pregnancy and SGA newborns we examined prospectively a large population of pregnant women attending

for routine care in a well-defined gestational age range, which is now widely used in screening for chromosomal defects[12]; used a well defined methodology and appropriately trained doctors to measure uterine artery PI[13]; employed widely accepted criteria to define PET, GH and SGA[14,15]; and applied a statistical approach that is widely accepted in screening for trisomy 21[16] to examine the performance of screening and calculate patient-specific risks.

In the unaffected group that did not develop PET, GH or SGA, uterine artery PI decreased with gestation and maternal BMI and was higher in women of Afro-Caribbean origin than in other ethnic groups, and in nulliparous women and in those with previous pregnancies affected by PET than in parous women who did not have PET. The risk of developing PET increased with BMI and was higher in those of Afro-Caribbean origin than in other ethnic groups and in those with a personal or family history of PET. The decrease in impedance to flow with gestation is compatible with the results of previous Doppler studies and is presumably the consequence of the physiological trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide non-muscular channels[17]. The relationship between uterine artery PI and maternal BMI is unlikely to be the consequence of enhanced trophoblastic invasion in obese women but rather vasodilation in the uterine circulation due to the increased levels of circulating estrogens associated with increased BMI[18]. The association between Afro-Caribbean race and obesity with increased risk of PET is well documented[19,20]. Similarly, the finding that a history of PET increases the risk of developing this disorder is in agreement with previous studies reporting 7-fold and 3-fold increases, respectively, in the risk for PET in women with a personal and family history of the disease[20]. The additional finding in our study, that in women not developing PET the uterine artery PI was higher in those of Afro-Caribbean origin and those with a previous history of PET, implies that such women demonstrate evidence of impaired placentation, but presumably this is not sufficiently severe to cause PET.

Screening by uterine artery Doppler is particularly effective in identifying women who develop severe early-onset PET rather than late-onset disease, GH or SGA. For a false-positive rate of 10% the predicted detection rate of PET requiring delivery before 34 weeks was 82%, compared to 31% for late PET, 12% for GH and 18% for SGA. This is particularly important because it is early rather than late PET which is associated with an increased risk of perinatal mortality and morbidity and both short-term and long-term maternal complications[21,22]. Our findings are in agreement with those of previous Doppler studies in the second trimester[5] and the results of pathological studies that demonstrated that the prevalence of placental lesions in women with PET is inversely related to the gestation at delivery[23,24].

We chose 11 + 0 to 13 + 6 weeks as the gestational age for screening because this is being established as the first hospital visit of pregnant women at which combined sonographic and biochemical testing for chromosomal and other major defects is carried out[12]. At this visit a record is made of maternal characteristics, such as age, ethnic origin, BMI, smoking status and medical and obstetric history; an ultrasound scan is carried out to determine the number of fetuses, confirm the gestation from the fetal CRL, exclude major defects, measure the NT thickness and other first-trimester markers of chromosomal defects; and maternal blood is taken for measurement of free β-hCG and PAPP-A. It would be easy to train competent sonographers to successfully measure the uterine artery PI of women at this same visit and utilize the same methodology to calculate the patient-specific risk for both chromosomal defects and PET. Essentially, factors from the maternal characteristics and history can be used to calculate the *a priori* risk, which is multiplied by the likelihood ratio associated with biophysical and biochemical measurements to derive patient-specific risks. This methodology could be applied to improve screening in the future with the use of additional biophysical and biochemical markers, such as maternal mean arterial pressure, cardiac output and serum placental protein 13 and placental growth factor[25–27].

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