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Uterine artery pulsatility index at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia

N. O'GORMAN*, G. TAMPAKOUDIS*, A. WRIGHT†, D. WRIGHT† and K. H. NICOLAIDES*

**Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK; †Institute of Health Research, University of Exeter, Exeter, UK*

KEYWORDS: Bayes' theorem; impaired placentation; pre-eclampsia; pyramid of pregnancy care; screening; uterine artery Doppler

ABSTRACT

Objective *To examine the distribution of uterine artery pulsatility index (UtA-PI) at 12, 22, 32 and 36 weeks' gestation in singleton pregnancies which develop pre-eclampsia (PE) and examine the performance of this biomarker in screening for PE.*

Methods *UtA-PI was measured in 92 712 singleton pregnancies at 11–13 weeks, in 67 605 cases at 19–24 weeks, in 31 741 at 30–34 weeks and in 5523 at 35–37 weeks. Bayes' theorem was used to combine the* a-priori *risk from maternal characteristics and medical history with UtA-PI. The performance of screening for PE requiring delivery < 32, at 32 + 0 to 36 + 6, < 37 and ≥ 37 weeks' gestation was estimated. The results of combined screening were compared to those of screening by UtA-PI and by maternal factors alone.*

Results *In pregnancies that developed PE, UtA-PI was increased and the separation in multiples of the median (MoM) values from normal was greater with earlier, compared to later, gestational age at which delivery for PE became necessary. Additionally, the slope of regression lines of UtA-PI MoM with gestational age at delivery in pregnancies that developed PE increased with increasing gestational age at screening. The detection rate (DR), at a 10% false-positive rate (FPR), for PE delivering < 32 weeks was 71% and 88% with combined screening at 11–13 and 19–24 weeks, respectively, and the DR for PE delivering at 32 + 0 to 36 + 6 weeks was 52%, 63% and 71% with screening at 11–13, 19–24 and 30–34 weeks, respectively. However, the DR of PE delivering ≥ 37 weeks was only about 40%, irrespective of the gestational age at screening. The performance of screening by the approach utilizing Bayes' theorem was superior to that of using a percentile cut-off of UtA-PI for gestational age.*

Conclusions *The performance of combined screening with maternal factors and UtA-PI is superior for detection of early, compared to late, PE and, to a certain extent, improves with advancing gestational age at screening.*

INTRODUCTION

Pre-eclampsia is thought to be the consequence of impaired placentation manifested in increased impedance to flow in the uterine arteries (UtAs)[1–12]. Several UtA Doppler studies have reported that, in pregnancies that develop PE, especially in those requiring early delivery, the pulsatility index (PI) is increased in the first, second and third trimesters of pregnancy[4–12].

There are two approaches for assessing the value of increased impedance to flow in the UtAs in the prediction of PE. The traditional approach is to examine the proportion of affected and unaffected pregnancies with abnormal Doppler results, defined either qualitatively by the presence of unilateral or bilateral notching of the waveform, or quantitatively by a cut-off in the measurement of various indices of impedance to flow, either corrected or uncorrected for gestational age[12]. We have proposed that a better approach to screening for PE is to use Bayes' theorem to combine the *a-priori* risk from maternal characteristics and medical history with the measurement of biomarkers[13–15]. However, UtA-PI is dependent on variables from maternal characteristics and medical history and, for its effective use in risk assessment and screening, these covariates need to be taken into account. This can be achieved by standardizing UtA-PI levels into multiples of the normal median (MoM)[16]. Our approach assumes that if the pregnancy was to continue indefinitely all women would develop PE and whether they do so or not before a

Correspondence to: Prof. K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK (e-mail: kypros@fetalmedicine.com)

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specified gestational age depends on competition between delivery before or after development of PE. The effect of maternal factors and biomarkers is to modify the mean of the distribution of gestational age at delivery with PE so that, in pregnancies at low risk for PE, the gestational-age distribution is shifted to the right with the implication that, in most pregnancies, delivery will actually occur before development of PE. In high-risk pregnancies the distribution is shifted to the left and the smaller the mean gestational age the higher is the risk for PE.

The objectives of this study were to present the distribution of UtA-PI values at 11–13, 19–24, 30–34 and 35–37 weeks' gestation in pregnancies that develop PE and examine the performance of screening for PE by UtA-PI at these stages in pregnancy.

METHODS

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending three routine hospital visits at King's College Hospital, University College London Hospital and Medway Maritime Hospital, UK, between January 2006 and March 2014. In the first visit, at 11 + 0 to 13 + 6 weeks' gestation, we recorded maternal characteristics and medical history and performed combined screening for aneuploidy[17]. The second visit, at 19 + 0 to 24 + 6 weeks' gestation, and third visit, initially at 30 + 0 to 34 + 6 weeks and subsequently at 35 + 0 to 37 + 6 weeks, included ultrasound examination of the fetal anatomy and estimation of fetal size from measurement of fetal head circumference, abdominal circumference and femur length. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or the fetal head circumference at 19–24 weeks[18,19].

Written informed consent was obtained from women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital. The inclusion criteria for this study were singleton pregnancy delivering phenotypically normal live birth or stillbirth at or after 24 weeks' gestation. Pregnancies with aneuploidy or major fetal abnormality and those ending in termination, miscarriage or fetal death before 24 weeks were excluded.

Patient characteristics

Patient characteristics included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous/assisted conception requiring the use of ovulation drugs/*in-vitro* fertilization), cigarette smoking during pregnancy, medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, family history of PE in the mother of the patient and obstetric history including parity (parous/nulliparous if no previous pregnancy at or after 24 weeks), previous pregnancy with PE, gestational age at delivery and birth weight of the neonate in the last pregnancy and interval in years between birth of the last child and estimated date of conception of the current pregnancy. Maternal height was measured at the first visit and maternal weight at each visit.

Uterine artery pulsatility index

First- and third-trimester Doppler ultrasound examinations were carried out transabdominally, however in the second trimester a transvaginal approach was used because the cervical length was also measured. At 11 + 0 to 13 + 6 weeks' gestation, 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[4,5]. At 19 + 0 to 24 + 6 weeks, women were asked to empty their bladder and were placed in the dorsal lithotomy position. The ultrasound probe was inserted into the vagina and advanced into the left and right lateral fornices. The UtAs were identified using color Doppler at the level of the internal cervical os[20]. At 30 + 0 to 37 + 6 weeks, color Doppler was used to identify each UtA at the apparent crossover with the external iliac arteries[6].

After identification of each UtA, pulsed-wave Doppler was used with the sampling gate set at 2 mm to cover the whole vessel. Care was taken to ensure that the angle of insonation was $< 30^\circ$ and the peak systolic velocity was > 60 cm/s so that the UtA, rather than the arcuate artery, was examined. When three similar waveforms were obtained consecutively, the PI was measured and the mean PI of the left and right arteries was calculated.

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).

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was PE, as defined by the International Society for the Study of Hypertension in Pregnancy[21]. The outcome measures for this study were PE delivering < 32, at 32 + 0 to 36 + 6, < 37 and ≥ 37 weeks' gestation.

Statistical analysis

Competing-risks model

The distribution of gestational age at delivery with PE was defined by two components: first, the prior distribution based on maternal characteristics[13] and second, the distribution of UtA-PI MoM values with gestational age at delivery in pregnancies affected by PE. The values of

UtA-PI were $\log_{10}$-transformed to achieve homogeneity of variance and approximate Gaussian distributional form. Each measured value in the unaffected and PE pregnancies was expressed as a MoM, adjusting for characteristics found to provide a substantive contribution to the $\log_{10}$-transformed value[16]. In the PE group, regression analysis demonstrated that the $\log_{10}$ MoM UtA-PI changed linearly with gestational age at delivery and this linear relationship was assumed to continue until the mean $\log_{10}$ MoM reached zero, beyond which the mean was taken as zero. The point at which the mean $\log_{10}$ MoM reached zero was determined using the method of least squares. Standard errors were obtained using bootstrapping. Risks of PE were obtained by applying Bayes' theorem to derive the posterior distribution of gestational age at delivery with PE from the maternal-factors specific prior distribution[13] and the likelihood function of UtA-PI. The likelihood function comprised the regression of $\log_{10}$ MoM UtA-PI on gestational age at delivery with PE.

Model-based estimates of screening performance using Bayes' theorem

To provide model-based estimates of screening performance, the following procedure was adopted. First, we obtained the dataset of 120 492 singleton pregnancies, including 2704 (2.2%) with PE, that was previously used to develop a model for PE based on maternal demographic characteristics and medical history[13,22]. Second, for each of the records, UtA MoM values were simulated from the fitted multivariate Gaussian distribution for log-transformed MoM values. Third, risks were obtained using the competing-risks model from the simulated MoM values and the pregnancy characteristics. These three steps were applied to the pregnancies within the normal group with no restriction on the time of delivery. Fourth, for a given false-positive rate, risks from the normal group were used to define a risk cut-off. The proportion of PE risks was then used to obtain an estimate of the associated detection rate (DR). The area under the receiver–operating characteristics curve (AUC) was also calculated. The simulations were repeated 10 times to reduce variability due to the simulation process and provide suitably precise model-based estimates of performance.

Empirical performance of screening

Five-fold cross validation was used to assess the performance of screening for subgroups of PE according to gestational age at delivery, by models combining maternal factors with UtA-PI. The data were divided into five equal subgroups, the model was then fitted five times to different combinations of four of the five subgroups and used to predict risk of PE in the remaining one-fifth of the data. In each case, the maternal-factor model and the regression models were fitted to the training dataset comprising four-fifths of the data and used to produce risks for the hold-out sample comprising the remaining one-fifth of the data.

Performance of UtA-PI adjusted for gestational age

Regression analysis of $\log_{10}$ UtA-PI on gestational age at the time of measurement was used to determine the 90th and 95th percentiles for unaffected pregnancies specific to gestational age at the time of measurement. Five-fold cross validation was used to assess the performance of screening for PE using the 90th and 95th percentiles of UtA-PI.

The statistical software package R was used for data analyses[23] and the survival package[24] was used for fitting the maternal-factors model.

RESULTS

Characteristics of the study population

The characteristics of the study population of singleton pregnancies with measurements of UtA-PI are summarized in Table 1. In the first phase of the study UtA-PI was measured only in the first-trimester visit but this was subsequently extended to the second- and then the third-trimester visits.

Distribution of $\log_{10}$ MoM values of UtA-PI in pre-eclampsia

In pregnancies that developed PE, UtA-PI MoM was inversely related to gestational age at delivery for each stage of screening (Figure 1). The regression equations are given in Table S1. The SD for $\log_{10}$ UtA-PI MoM in unaffected pregnancies and in those that developed PE are given in Table S2.

Performance of screening for pre-eclampsia by maternal factors and UtA-PI

Empirical and model-based performance of screening for PE by maternal factors and UtA-PI at 11–13, 19–24, 30–34 and 35–37 weeks' gestation are shown in Tables 2 and S3 and Figure 2. In general there was good agreement between empirical and model-based results and all except two model-based results were within the 95% CI of the empirical data.

On the basis of the results from combined screening, the following conclusions can be drawn: first, the DR was higher for early compared to late PE; second, the DR of PE delivering < 32, $32+0$ to $36+6$ and < 37 weeks' gestation was higher with screening at 19–24 weeks than at 11–13 weeks; third, the DR of PE delivering at $32+0$ to $36+6$ weeks was higher with screening at 30–34 weeks than at 19–24 weeks, and fourth, the performance of screening for PE delivering ≥ 37 weeks was poor, irrespective of the gestational age at screening.

Performance of screening for pre-eclampsia by UtA-PI above the 90th and 95th percentiles for gestational age

Log_{10} UtA-PI decreased linearly with gestational age at 11–14, 19–24 and 30–34 weeks' gestation, but did not

Table 1 Maternal and pregnancy characteristics in women with singleton pregnancy screened at different weeks for prediction of pre-eclampsia (PE)

	11–13 weeks		*19–24 weeks*		*30–34 weeks*		*35–37 weeks*	
Characteristic	*Normal (n = 90 514)*	*PE (n = 2198)*	*Normal (n = 65 762)*	*PE (n = 1843)*	*Normal (n = 31 035)*	*PE (n = 706)*	*Normal (n = 5431)*	*PE (n = 92)*
Maternal age (years)	31.3 (26.8–35.1)	31.4 (26.6–35.8)	30.8 (26.2–34.7)	31.3 (26.4–35.8)*	31.3 (26.8–35.0)	31.6 (26.9–35.7)	31.2 (26.5–35.0)	33.0 (27.8–35.7)
Maternal weight (kg)	66.0 (58.9–76.0)	72.0 (62.2–86.0)*	70.0 (63.0–80.2)	76.8 (67.0–90.6)	75.4 (67.7–85.6)	82.9 (72.0–97.2)	79.0 (70.6–90.0)	85.0 (77.3–98.4)
Maternal height (cm)	164 (160–169)	163 (159–168)	164 (160–169)	163 (159–168)	165 (160–169)	164 (160–168)	164 (160–168)	164 (160–170)
Body mass index (kg/m^2)	24.3 (21.8–28.0)	27.0 (23.4–31.9)*	25.9 (23.4–29.6)	28.8 (25.2–33.5)	27.8 (25.2–31.5)	30.7 (27.3–35.4)	29.3 (26.3–33.2)	31.2 (28.6–35.2)
Gestational age (weeks)	12.7 (12.3–13.1)	12.7 (12.3–13.1)	22.2 (21.6–22.7)	22.3 (21.6–22.7)	32.3 (32.0–32.9)	32.2 (32.0–32.7)	36.1 (36.0–36.4)	36.1 (35.9–36.4)
Racial origin		*		*		*		
Caucasian	66 436 (73.4)	1247 (56.7)	46 275 (70.4)	1002 (54.4)	21 749 (70.1)	383 (54.3)	3819 (70.3)	62 (67.4)
Afro-Caribbean	14 751 (16.3)	736 (33.5)	13 067 (19.9)	694 (37.7)	5767 (18.6)	265 (37.5)	1089 (20.1)	22 (23.9)
South Asian	4697 (5.2)	123 (5.6)	3177 (4.8)	81 (4.4)	1809 (5.8)	33 (4.7)	221 (4.1)	4 (4.4)
East Asian	2372 (2.6)	40 (1.8)	1616 (2.5)	27 (1.5)	969 (3.1)	12 (1.7)	112 (2.1)	1 (1.1)
Mixed	2258 (2.5)	52 (2.4)	1627 (2.5)	39 (2.1)	741 (2.4)	13 (1.8)	190 (3.5)	3 (3.3)
Medical history								
Chronic hypertension	955 (1.1)	242 (11.0)*	752 (1.1)	222 (12.1)*	353 (1.1)	104 (14.7)*	72 (1.3)	10 (10.9)*
Diabetes mellitus	720 (0.8)	53 (2.4)*	530 (0.8)	44 (2.4)*	296 (1.0)	17 (2.4)*	55 (1.0)	92 (100)
SLE/APS	160 (0.2)	14 (0.6)*	116 (0.2)	12 (0.7)*	61 (0.2)	1 (0.1)	13 (0.2)	92 (100)
Cigarette smoker	8650 (9.6)	164 (7.5)*	6624 (10.1)	136 (7.4)*	2823 (9.1)	48 (6.8)*	541 (10.0)	6 (6.5)
Family history of PE	3519 (3.9)	178 (8.1)*	2401 (3.7)	136 (7.4)*	893 (2.9)	35 (5.0)*	183 (3.4)	9 (9.8)*
Obstetric history								
Parous								
No previous PE	43 657 (48.2)	527 (24.0)*	30 533 (46.4)	451 (24.5)*	14 777 (47.6)	192 (27.2)*	2798 (51.5)	15 (16.3)*
Previous PE	2690 (3.0)	306 (13.9)*	2030 (3.1)	256 (13.9)*	902 (2.9)	89 (12.6)*	127 (2.3)	12 (13.0)*
Nulliparous	44 167 (48.8)	1365 (62.1)*	33 199 (50.5)	1136 (61.6)*	15 356 (49.5)	425 (60.2)*	2506 (46.1)	65 (70.7)*
Interpregnancy interval (years)	2.9 (1.9–4.8)	4.0 (2.3–6.8)*	3.0 (1.9–5.0)	4.0 (2.3–7.0)*	3.0 (2.0–4.9)	3.7 (2.3–6.8)*	3.1 (2.1–5.1)	4.2 (2.3–9.6)*

Data are given as median (interquartile range) or *n* (%). Comparison with normal group by chi-square or Fisher's exact tests for categorical variables and Mann–Whitney *U*-test for continuous variables: *$P < 0.05$. APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

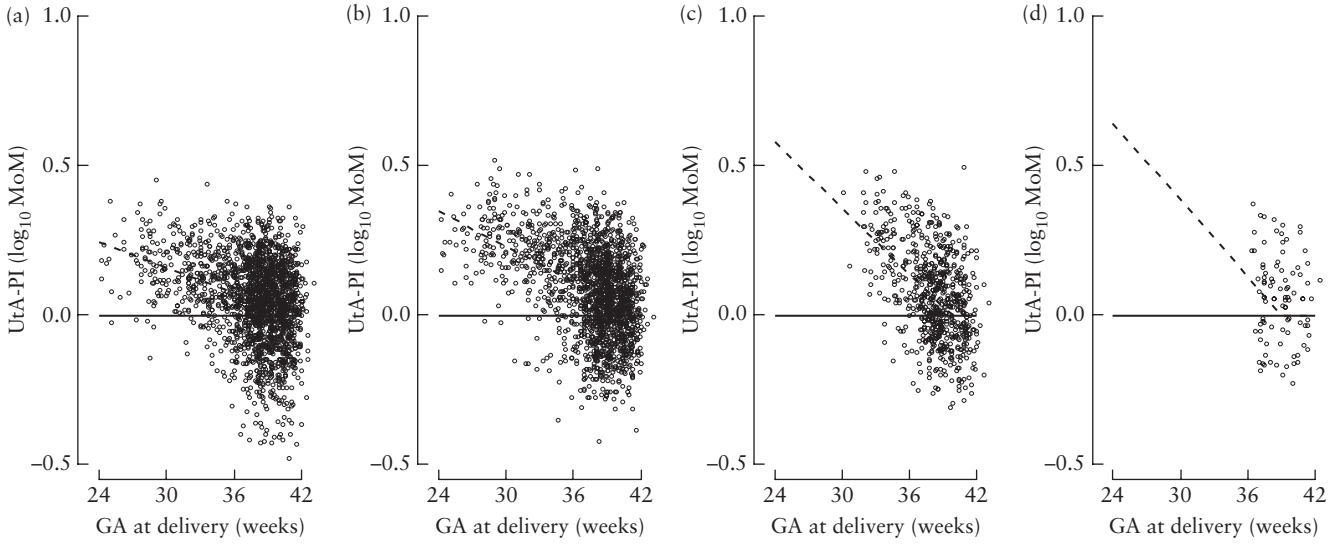

Figure 1 Relationship between uterine artery pulsatility index (UtA-PI) multiples of the median (MoM) and gestational age (GA) at delivery in pregnancies with pre-eclampsia, with screening at: (a) 11–13, (b) 19–24, (c) 30–34 and (d) 35–37 weeks' gestation. Regression lines (- - - -) are shown.

Table 2 Empirical and model-based detection rates of screening for pre-eclampsia (PE) by maternal factors and a combination of maternal factors and uterine artery pulsatility index at 11–13, 19–24, 30–34 and 35–37 weeks' gestation

	Detection rate of PE delivering:							
	< 32 weeks		*32 + 0 to 36 + 6 weeks*		*< 37 weeks*		*≥ 37 weeks*	
Screening	*Empirical (95% CI) (%) (n/N)*	*Model (%)*	*Empirical (95% CI) (%) (n/N)*	*Model (%)*	*Empirical (95% CI) (%) (n/N)*	*Model (%)*	*Empirical (95% CI) (%) (n/N)*	*Model (%)*
Maternal factors								
FPR = 5%								
11–13 weeks	44 (36–52) 68/155	41	31 (26–35) 136/445	31	34 (30–38) 204/600	34	26 (24–28) 418/1598	26
19–24 weeks	44 (36–52) 65/148	41	32 (28–37) 120/372	31	36 (31–40) 185/520	34	26 (24–29) 350/1323	26
30–34 weeks			30 (23–38) 48/161	31	31 (24–39) 52/166	31	29 (26–33) 159/540	26
35–37 weeks							24 (16–35) 21/86	26
FPR = 10%								
11–13 weeks	56 (48–64) 87/155	52	44 (40–50) 200/455	45	48 (44–52) 287/600	47	37 (35–40) 596/1598	37
19–24 weeks	55 (47–64) 82/148	52	44 (38–49) 162/372	45	47 (43–51) 244/520	47	37 (34–39) 485/1323	37
30–34 weeks			42 (34–50) 67/161	45	43 (35–51) 71/166	45	41 (37–46) 224/540	37
35–37 weeks							31 (22–42) 27/86	37
Combined								
FPR = 5%								
11–13 weeks	57 (49–65) 88/155	59	40 (35–44) 176/445	39	44 (40–48) 264/600	44	28 (26–30) 447/1598	27
19–24 weeks	79 (72–85) 117/148	79	56 (51–61) 208/372	50	63 (58–67) 325/520	57	30 (28–33) 397/1323	28
30–34 weeks			62 (54–70) 100/161	59	63 (55–71) 105/166	59	32 (28–36) 173/540	28
35–37 weeks							26 (17–36) 22/86	29
FPR = 10%								
11–13 weeks	71 (63–78) 110/155	71	53 (48–58) 236/445	52	58 (54–62) 346/600	57	39 (36–41) 621/1598	38
19–24 weeks	88 (81–93) 130/148	88	68 (63–72) 252/372	63	73 (69–77) 382/520	70	42 (40–45) 560/1323	40
30–34 weeks			75 (68–82) 121/161	71	76 (69–82) 126/166	71	42 (37–46) 225/540	39
35–37 weeks							36 (26–47) 31/86	41

change significantly with gestational age at 35–37 weeks. The regression equations are given in Table S4. The normal ranges and values of UtA-PI in pregnancies that developed PE are shown in Figure 3. The DRs of PE by UtA-PI above the 90th and 95th percentiles for gestational age at 11–13, 19–24, 30–34 and 35–37 weeks' gestation are shown in Table S5. In general, the performance of screening by this approach was inferior to that achieved by combined screening, especially for late PE (Table 2 and Figure 4).

DISCUSSION

Principal findings of the study

This study highlights four findings with clinical implications. First, in pregnancies that develop preterm PE, UtA-PI is increased and the separation in MoM values from normal is greater with earlier, compared to later, gestational age at which delivery for PE becomes necessary. Consequently, the performance of screening is superior for PE delivering < 32 than at 32 + 0 to

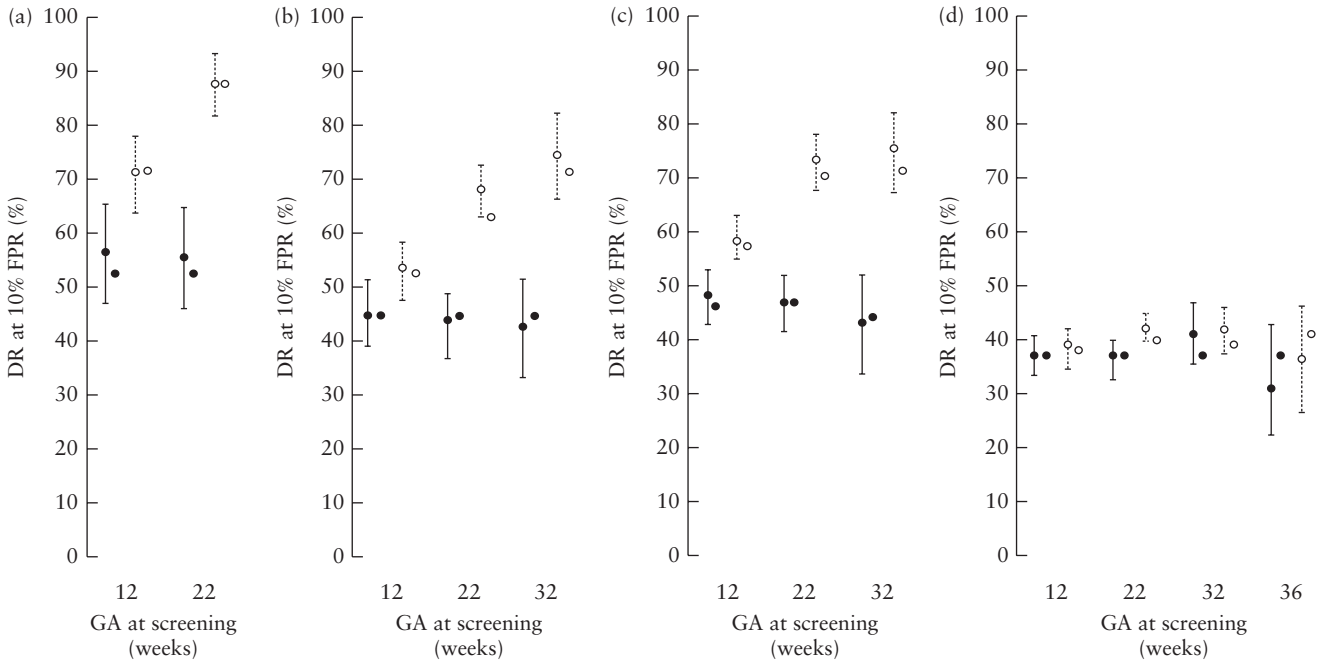

Figure 2 Empirical detection rate (DR) of pre-eclampsia delivering: (a) < 32 weeks; (b) at 32 + 0 to 36 + 6; (c) < 37; and (d) ≥ 37 weeks' gestation, when screening by maternal factors (•) and a combination of maternal factors with uterine artery pulsatility index (∘) at 11–13, 19–24, 30–34 and 35–37 weeks' gestation. Vertical lines represent 95% CIs. Adjacent circles without 95% CI represent model-based DR. FPR, false-positive rate; GA, gestational age.

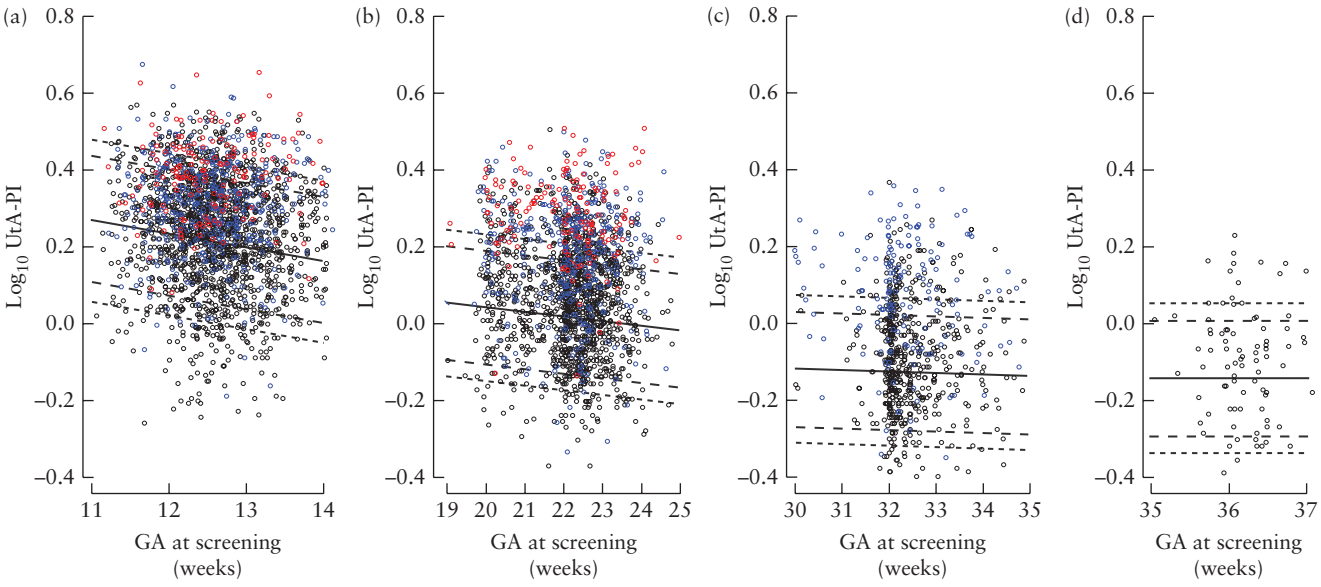

Figure 3 Uterine artery pulsatility index (UtA-PI) in pregnancies that developed pre-eclampsia and delivered < 32 weeks (∘), at 32 + 0 to 36 + 6 weeks (∘) or ≥ 37 (∘) weeks' gestation, with screening at: (a) 11–13; (b) 19–24; (c) 30–34; and (d) 35–37 weeks' gestation. Values are plotted on normal reference ranges for gestational age (——, median; – – –, 10th and 90th percentiles; - - - - -, 5th and 95th percentiles).

36 + 6 weeks. Second, the slope of the regression lines of UtA-PI MoM with gestational age at delivery in pregnancies that develop PE increases with increasing gestational age at screening. Consequently, the performance of screening for PE delivering < 32 weeks is superior with screening at 19–24 than at 11–13 weeks and the performance of screening for PE delivering at 32 + 0 to 36 + 6 weeks is superior with screening at 30–34 than at 19–24 or 11–13 weeks. Third, the regression lines of UtA-PI MoM with gestational age at delivery in pregnancies that develop PE intersect 1 MoM at about 40 weeks and this marker shows little or no discriminatory power for term PE; consequently, the performance of screening for PE ≥ 37 weeks is poor irrespective of the gestational age at screening. Fourth, the performance of screening for PE by a model combining UtA-PI with maternal characteristics and medical history is superior to that by UtA-PI alone; this is particularly so for PE delivering ≥ 37 weeks for which the performance of screening by UtA-PI alone is poor. A major advantage of the approach utilizing Bayes' theorem

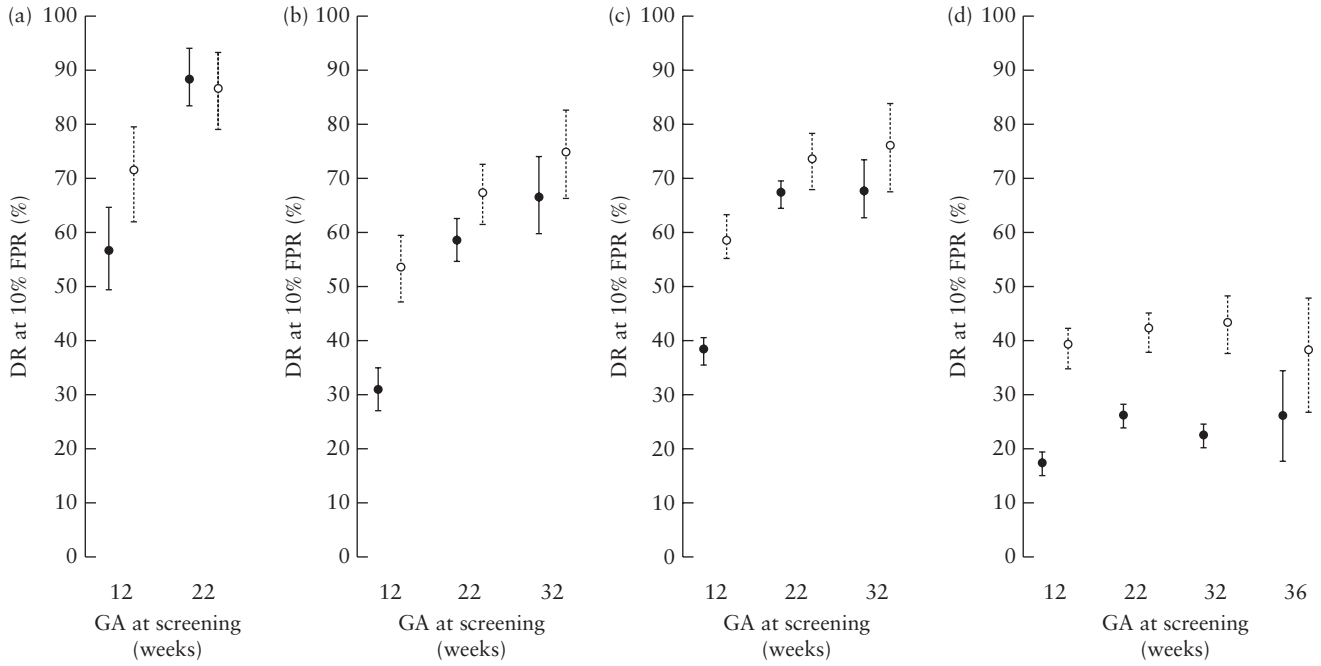

Figure 4 Empirical detection rate (DR) of pre-eclampsia delivering: (a) < 32 weeks; (b) at 32 + 0 to 36 + 6; (c) < 37; and (d) ≥ 37 weeks' gestation, when screening by uterine artery pulsatility index (UtA-PI) above the 90th percentile for gestational age (GA) (•) and by a combination of maternal factors with UtA-PI (○) at 11–13, 19–24, 30–34 and 35–37 weeks' gestation. Vertical lines represent 95% CIs. FPR, false-positive rate.

is that, in addition to UtA-PI, several other biomarkers can be combined with maternal factors to improve the overall performance of screening.

Strengths and limitations

The strengths of this screening study for PE in the three trimesters of pregnancy are first, examination of a large population of pregnant women attending for routine care, second, recording of data on maternal characteristics and medical history to identify known risk factors associated with PE, third, use of a specific methodology and appropriately trained doctors to measure UtA-PI, fourth, expression of the values of UtA-PI as MoMs after adjusting for factors that affect the measurements, and fifth, use of Bayes' theorem to combine the prior risk from maternal factors with UtA-PI to estimate patient-specific risks and the performance of screening for PE delivering at different stages of pregnancy.

A potential limitation of the study is that the performance of screening by a model derived and tested using the same dataset is overestimated. We used cross validation to reduce this effect and demonstrated that the modeled and empirical performance were similar, presumably because the study population was large and the number of variables small.

Comparison with previous studies

Several studies have documented that development of PE, especially preterm PE, is associated with an increase in UtA-PI during the first, second and third trimesters of pregnancy[4–12]. In this study we examined the performance of UtA-PI on its own and in combination with maternal factors in the prediction of early, intermediate and late PE and documented the relationship between gestational age at screening and performance of the test.

Clinical implications of the study

In a proposed new pyramid of pregnancy care[25], assessment at 11–13 weeks aims to identify the group at high risk of developing preterm PE and, through pharmacological intervention, with such medications as low-dose aspirin, reduce the prevalence of the disease[26,27]. Measurement of UtA-PI is an essential component of such assessment, which also includes measurement of mean arterial pressure and serum placental growth factor[28].

Assessment in the second and third trimesters aims to estimate the patient-specific risk of developing PE and, on the basis of such risk, define the subsequent management of pregnancy, including the timing and content of subsequent visits and decide on appropriate time, method and place for delivery. We found that the performance of UtA-PI for PE delivering ≥ 37 weeks is poor irrespective of the gestational age at screening. However, prediction of PE delivering < 32 and at 32 + 0 to 36 + 6 weeks is better if screening is carried out at 22 weeks, rather than 12 weeks. In this context, the main value of the assessment at 22 weeks is to identify first, the high-risk group for development of early PE who would then require close monitoring of fetal growth and wellbeing as well as blood pressure and proteinuria at 24–32 weeks and second, the high-risk group for

preterm PE who would require reassessment at around 32 weeks and, on the basis of such assessment, identify a high-risk group in need of close monitoring at 32 + 0 to 36 + 6 weeks. Future research should aim to identify better biomarkers for PE delivering ≥ 37 weeks.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Regression equations of uterine artery pulsatility index multiples of the median in pregnancies that developed pre-eclampsia

Table S2 Standard deviation (SD) for $\log_{10}$ uterine artery pulsatility index multiples of the median in unaffected pregnancies and those that developed pre-eclampsia

Table S3 Modelled and empirical areas under the receiver–operating characteristics curve (AUC) in screening for pre-eclampsia (PE) delivering < 32, < 37 and ≥ 37 weeks' gestation by maternal factors and a combination of maternal factors and uterine artery pulsatility index at 11–13, 19–24, 30–34 and 35–37 weeks' gestation

Table S4 Regression equations for the relationship between uterine artery pulsatility index and gestational age at assessment

Table S5 Detection rates of screening for pre-eclampsia (PE) by cut-off values of uterine artery pulsatility index above the 90th and 95th percentiles, adjusted for gestational age, at 11–13, 19–24, 30–34 and 35–37 weeks' gestation

