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First-trimester maternal serum pregnancy-associated plasma protein-A and pre-eclampsia

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KEYWORDS: first-trimester screening; PAPP-A; pre-eclampsia; uterine artery Doppler

ABSTRACT

Objectives *To examine the relationship between low maternal serum pregnancy-associated plasma protein-A (PAPP-A) and uterine artery pulsatility index (UtA-PI) at 11 + 0 to 13 + 6 weeks with subsequent development of pre-eclampsia (PE).*

Methods *UtA-PI and serum PAPP-A were measured in women attending for routine care at 11 + 0 to 13 + 6 weeks of gestation. In the population, 156 (1.9%) women developed PE, including 32 (0.4%) in whom delivery was before 34 weeks (early PE) and 124 (1.5%) with delivery at 34 weeks or more (late PE); 7895 (98.1%) women had no PE. Regression analysis was used to examine which of the factors amongst maternal characteristics, log PAPP-A multiples of the median (MoM) and log UtA-PI MoM contributed to the prediction of PE.*

Results *The median PAPP-A MoM was 1.002 (interquartile range (IQR), 0.685–1.411) in the unaffected group, 0.555 (IQR, 0.463–0.922) in early PE and 0.911 (IQR, 0.580–1.247) in late PE. Serum PAPP-A was below the 5th centile in 21.9% of early PE and 6.5% of late PE cases. The PAPP-A-related patient-specific risk for PE was strongly influenced by maternal characteristics. There was a significant association between log UtA-PI MoM and log PAPP-A MoM (P = 0.001), and the detection rate of screening for PE by maternal variables and UtA-PI was not improved by inclusion of PAPP-A. Regression analysis was used to establish tables that allow modification of the maternal history and PAPP-A-related patient-specific risk for PE by the measurement of UtA-PI.*

Conclusions *Low PAPP-A is a marker for subsequent development of PE. The PAPP-A-related patient-specific risk for PE can be modified by the measurement of UtA-PI. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Effective screening for trisomies 21, 18 and 13 is provided by a combination of maternal age, fetal nuchal translucency (NT) thickness, and maternal serum free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 11 + 0 to 13 + 6 weeks of gestation. All three trisomies are associated with increased maternal age, increased fetal NT and decreased maternal serum PAPP-A. In trisomy 21 serum free β-hCG is increased whereas it is decreased in trisomies 18 and 13[1]. In biochemical testing it is necessary to make adjustments in the measured maternal serum metabolite concentration to correct for certain maternal and pregnancy characteristics. Essentially, each measured level is first converted to a multiple of the expected normal median (MoM) specific to a pregnancy of the same gestational age, maternal weight, racial origin, smoking status, method of conception and parity, as well as the machine and reagents used for the assays[2]. In unaffected pregnancies the median free β-hCG and PAPP-A is 1.0 MoM, whereas in trisomy 21 pregnancies the median free β-hCG is 2.0 MoM and the median PAPP-A is 0.5 MoM; the respective values are 0.2 MoM and 0.2 MoM in trisomy 18, and 0.5 MoM and 0.3 MoM in trisomy 13[1].

In chromosomally normal pregnancies there is evidence that low maternal serum PAPP-A is associated with increased risk for subsequent development of pre-eclampsia (PE)[3–9]. However, measurement of PAPP-A is not an effective method of screening for PE because only 8–23% of affected cases have serum levels below the 5th centile, which is about 0.4 MoM. Nevertheless, the obstetrician should be aware of the increased risk for PE when managing individual patients found coincidentally to have a low PAPP-A level during first-trimester screening for trisomies. At the 5th centile of normal for PAPP-A the reported odds ratios for PE varies between 1.5 and 4.6[3–9].

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Effective first-trimester screening for PE is provided by a combination of the measurement of uterine artery pulsatility index (UtA-PI) by Doppler ultrasound imaging and maternal variables, such as racial origin, body mass index (BMI), and previous and family history of PE[10]. This method is particularly effective in identifying severe early-onset PE requiring delivery before 34 weeks (detection rate of about 80% for a false-positive rate of 10%) rather than late-onset disease, which is important because it is early- rather than late-onset disease that is associated with an increased risk of perinatal mortality and morbidity, and both short- and long-term maternal complications[11–13].

The aims of this study were to examine further the possible association between low maternal serum PAPP-A at 11 + 0 to 13 + 6 weeks and subsequent development of PE. We first investigated whether PAPP-A levels are related to the severity of PE, second, estimated the patient-specific risk for PE in relation to PAPP-A levels, third, examined the possible association between serum PAPP-A and UtA-PI, and, finally, determined the performance of screening for PE by combined testing based on maternal history, serum PAPP-A and UtA-PI.

METHODS

This was a prospective screening study for PE in singleton pregnancies. All women attended our center between March 2006 and June 2007 for routine assessment of trisomy 21 risk at 11 + 0 to 13 + 6 weeks of gestation by measurement of fetal NT thickness, and maternal serum free β-hCG and PAPP-A[14–16]. Written informed consent was obtained from women who agreed to participate in the study, which was approved by King's College Hospital Ethics Committee.

Patients were asked to complete a questionnaire on maternal age, racial origin (white, black, Indian or Pakistani, Chinese or Japanese, or mixed), cigarette smoking during pregnancy (yes or no), 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, β-mimetic, insulin, lithium, steroids, thyroxine), parity (parous or nulliparous if no delivery beyond 23 weeks), methods of conception (spontaneous, use of ovulation drugs or *in-vitro* fertilization), obstetric history (previous pregnancy with or without PE) and family history of PE (mother). The maternal weight and height were measured, and the BMI was calculated.

Maternal serum PAPP-A was measured using a DELFIA EXPRESS analyzer (PerkinElmer, Waltham, MA, USA). The measured concentration of PAPP-A was converted to a MoM corrected for fetal crown–rump length (CRL), maternal weight, smoking status, racial origin, parity and method of conception[2].

Transabdominal ultrasound examination was carried out for measurement of fetal CRL and NT thickness, diagnosis of any major fetal defects and measurement of UtA-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 UtA along the side of the cervix and uterus at the level of the internal os[10,17]. Pulsed wave Doppler imaging was used with the sampling gate set at 2 mm to cover the whole vessel and care was taken to ensure that the angle of insonation was less than 50°. When three similar consecutive waveforms had been obtained the UtA-PI was measured, and the mean UtA-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-week scan and Doppler of The Fetal Medicine Foundation (http://www.fetalmedicine.com/). The results of the Doppler studies were not given to the women or their doctors and did not influence the subsequent management of the pregnancies.

PAPP-A MoM values, ultrasound findings and women's 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 general medical practitioners. The obstetric records of all women with reported pre-existing or pregnancy-associated hypertension were examined to determine whether the condition was PE. Similarly, for quality control we examined the records of 500 randomly selected cases without reported pregnancy-associated hypertension.

Outcome measures

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy[18]. The diastolic blood pressure should be $\geq$ 90 mmHg on at least two occasions 4 h apart, developing after 20 weeks of gestation in previously normotensive women in the presence of significant proteinuria of $\geq$ 300 mg in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection is available. In PE superimposed on chronic hypertension significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks of gestation in the absence of trophoblastic disease)[18].

Statistical analysis

The following nine steps were taken. First, the women were divided into two groups depending on pregnancy outcome into those who developed PE and those unaffected by PE. Second, the distributions of UtA-PI and PAPP-A MoM were made Gaussian by logarithmic transformation. Third, multiple regression analysis was

used to determine which of the factors among the maternal characteristics were significant predictors of log UtA-PI in the unaffected group. Fourth, the distribution of log UtA-PI, expressed as MoM of the unaffected group, was determined in the PE group. Fifth, Mann–Whitney *U*-test was used to compare the median MoM of PAPP-A and UtA-PI between the outcome groups. Sixth, regression analysis was used to determine the significance of the association between gestational age at delivery with log UtA-PI MoM and log PAPP-A MoM in the two outcome groups. Seventh, regression analysis was used to determine the significance of the association between log UtA-PI MoM and log PAPP-A MoM in the two outcome groups. Eighth, regression analysis was used to determine which of the factors among the maternal characteristics, log UtA-PI MoM and log PAPP-A MoM had significantly contributed to predicting PE. Ninth, the detection and false-positive rates were calculated as the respective proportions of PE (detection rate) and unaffected pregnancies (false-positive rate) with MoM values above given cut-offs. The statistical software packages SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for the data analyses.

RESULTS

Study population

First-trimester screening was carried out in 8679 consecutive singleton pregnancies with a live fetus at 11 + 0 to 13 + 6 weeks. We excluded 628 (7.2%) because they had missing outcome data ($n = 391$), there were fetal abnormalities ($n = 90$), the pregnancies resulted in fetal death or miscarriage before 24 weeks of gestation ($n = 101$), or the pregnancies were terminated for social reasons ($n = 17$). In addition, a further 29 (0.3%) 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 if the diagnosis was PE, were also excluded from further analysis. The patients included in the study did not differ significantly in demographic characteristics from those excluded.

Among the remaining 8051 cases, 156 (1.9%) developed PE, including 32 (0.4%) in which delivery was before 34 weeks (early PE) and 124 (1.5%) with delivery at 34 weeks or later (late PE); 7895 (98.1%) cases were unaffected by PE. In the quality control assessment of 500 cases with reported normal outcome, examination of their records demonstrated that there were indeed no cases of PE. The characteristics of the outcome groups are summarized in Table 1.

Serum pregnancy-associated plasma protein-A and pre-eclampsia

The median PAPP-A was 1.002 (interquartile range (IQR), 0.685–1.411) MoM in the unaffected group, 0.555 (IQR, 0.463–0.922) MoM in the early PE group and 0.911 (IQR, 0.580–1.247) MoM in the late PE group (Figure 1a). Log PAPP-A MoM was significantly lower in both the early PE ($P < 0.001$) and late PE ($P = 0.03$) groups than in the unaffected group. In the PE group regression analysis demonstrated that log PAPP-A MoM increased with gestational age at delivery (Figure 2a):

$$\text{Log PAPP-A MoM} = -0.981 + 0.024 \times \text{gestational age in weeks} \ (P < 0.001).$$

The patient-specific risk for early PE (%) was calculated from the formula:

$$\text{Risk} = \text{Odds}/(1 + \text{odds})$$

where odds = e^Y. Y was derived from multiple regression analysis which demonstrated that in the prediction of early PE there were significant contributions from serum PAPP-A, maternal racial origin, previous history of PE and chronic hypertension, but not maternal age, BMI, smoking, family history of PE, medical history other than hypertension, medication or method of conception (Table 2 and Figure 3):

$$\begin{aligned} Y = {} & -6.413 - 3.612 \times \log \text{ PAPP-A MoM} \\ & + (1.803 \text{ if history of chronic hypertension}) \\ & + (1.564 \text{ if black, } 0 \text{ if other racial origin}) \\ & + (0 \text{ if nulliparous, } -1.005 \text{ if parous without previous PE, } 1.491 \text{ if parous with previous PE}) \\ & (R^2 = 0.176, P < 0.001). \end{aligned}$$

Multiple regression analysis demonstrated that in the prediction of late PE there were significant contributions from serum PAPP-A, maternal racial origin, BMI, previous and family history of PE, but not maternal age, smoking, medical history, medication or method of conception (Table 2):

$$\begin{aligned} Y = {} & -6.652 - 0.884 \times \log \text{ PAPP-A MoM} \\ & + (1.127 \text{ if family history of PE}) \\ & + (1.222 \text{ if black, } 0.936 \text{ if Indian or Pakistani, } 1.335 \text{ if mixed race, } 0 \text{ if other racial origin}) \\ & + 0.084 \times \text{BMI in kg/m}^2 + (0 \text{ if nulliparous, } -1.255 \text{ if parous without previous PE, } 0.818 \text{ if parous with previous PE}) \\ & (R^2 = 0.123, P < 0.001). \end{aligned}$$

Uterine artery pulsatility index and pre-eclampsia

Multiple regression analysis in the unaffected group demonstrated that for log UtA-PI significant independent

Table 1 Maternal characteristics and medical and obstetric history in the three groups of pregnancy outcome: unaffected by pre-eclampsia, early pre-eclampsia and late pre-eclampsia

Maternal characteristic	*Unaffected* (n = *7895*)	*Early pre-eclampsia* (n = *32*)	*Late Pre-eclampsia* (n = *124*)
Maternal age (years)	32.3 (16–49)	31.6 (17–49)	32.0 (17–44)
Body mass index (kg/m^2)	24.5 (15.3–59.2)	27.6 (18.7–38.1)*	27.4 (18.9–46.4)‡
Crown–rump length (mm)	63.6 (45–84)	65.7 (52–84)	62.0 (46–84)
Racial origin			
White	5588 (70.8)	13 (40.6)‡	54 (43.5)‡
Black	1529 (19.4)	15 (46.9)‡	52 (41.9)‡
Indian or Pakistani	389 (4.9)	2 (6.3)	8 (6.5)
Chinese or Japanese	113 (1.4)	0 (0)	2 (1.6)
Mixed	276 (3.5)	2 (6.3)	8 (6.5)
Parity			
Nulliparous	3768 (47.7)	17 (53.1)	76 (61.3)*
Parous; no previous pre-eclampsia	3919 (49.6)	8 (25.0)†	30 (24.2)‡
Parous; previous pre-eclampsia	208 (2.6)	7 (21.9)‡	18 (14.5)‡
Cigarette smoker	679 (8.6)	0 (0)	7 (5.6)
Family history of pre-eclampsia (mother)	317 (4.0)	3 (9.4)	16 (12.9)‡
Conception			
Spontaneous	7610 (96.4)	27 (84.4)†	118 (95.2)
Ovulation drugs	163 (2.1)	4 (12.5)†	4 (3.2)
In-vitro fertilization	122 (1.5)	1 (3.1)	2 (1.6)
Medical history			
None	7699 (97.5)	27 (84.4)†	116 (93.5)*
Chronic hypertension	84 (1.1)	4 (12.5)‡	6 (4.8)†
Diabetes mellitus	51 (0.6)	0 (0)	1 (0.8)
Antiphospholipid syndrome	13 (0.2)	1 (3.1)	0 (0)
Thrombophilia	31 (0.4)	0 (0)	1 (0.8)
Sickle cell disease	9 (0.1)	0 (0)	0 (0)
Human immunodeficiency viral infection	8 (0.1)	0 (0)	0 (0)
Medication during pregnancy			
None	7273 (92.1)	27 (84.4)	112 (90.3)
Antihypertensives	46 (0.6)	2 (6.3)*	4 (3.2)*
Insulin	49 (0.6)	0 (0)	1 (0.8)
Steroids	16 (0.2)	1 (3.1)	0 (0)
β-mimetics	134 (1.7)	0 (0)	4 (3.2)
Combined asthma medications	88 (1.1)	0 (0)	1 (0.8)
Thyroxine	97 (1.2)	1 (3.1)	1 (0.8)
Aspirin	86 (1.1)	1 (3.1)	0 (0)
Antithyroid medication	7 (0.1)	0 (0)	0 (0)
Antiepileptic	36 (0.5)	0 (0)	0 (0)
Lithium	4 (0.1)	0 (0)	0 (0)
Antidepressants	46 (0.6)	0 (0)	1 (0.8)
Antiretroviral	5 (0.1)	0 (0)	0 (0)
Anti-inflammatory	8 (0.1)	0 (0)	0 (0)

Values are median (range) or *n* (%). *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$ vs. unaffected group (chi-square test for categorical variables; ANOVA for continuous variables).

contributions were provided by maternal age, racial origin, BMI, previous history of PE and fetal CRL:

$$\text{Log UtA-PI} = 0.405 - 0.002 \times \text{CRL in mm} - 0.001 \times \text{age in years} - 0.002 \times \text{BMI in kg/m}^2 + (0.027 \text{ if black, } 0.020 \text{ if mixed race, } 0 \text{ if other racial origin}) + (0.022 \text{ if parous with previous PE, } 0 \text{ if nulliparous or parous without previous PE})$$

$$(R^2 = 0.029, P < 0.001).$$

In each patient in both the unaffected and PE groups we used the formula above to derive the expected log UtA-PI and then expressed the observed value as a MoM of the expected value. The median UtA-PI was 1.007 (IQR, 0.835–1.221) MoM in the unaffected group, 1.498 (IQR, 1.318–1.636) MoM in the early PE group and 1.189 (IQR, 0.931–1.442) MoM in the late PE group (Figure 1b). Log UtA-PI MoM was significantly higher in both the early PE ($P < 0.001$) and late PE groups ($P < 0.001$) than in the unaffected group. In the PE group regression analysis demonstrated that log UtA-PI MoM decreased with gestational age at delivery (Figure 2b):

$$\text{Log UtA-PI MoM} = 0.590 - 0.014 \times \text{gestational age in weeks} \; (P < 0.001).$$

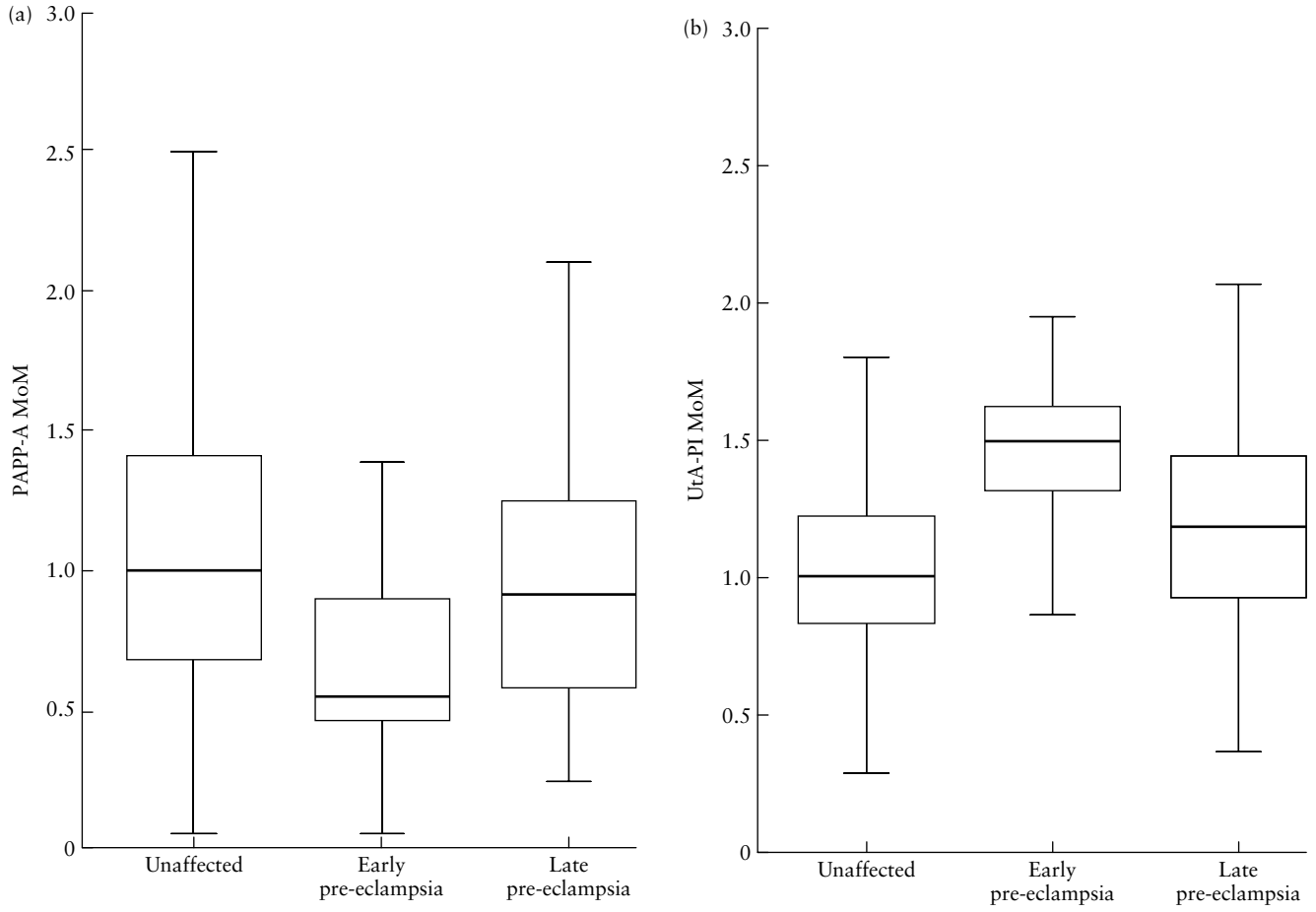

Figure 1 Pregnancy-associated plasma protein-A (PAPP-A) multiples of the median (MoM) (a) and uterine artery pulsatility index (UtA-PI) MoM (b) in unaffected pregnancies and those developing early and late pre-eclampsia. Median, interquartile range and range are shown.

Relationship between pregnancy-associated plasma protein-A and uterine artery pulsatility index

There was a significant association between log UtA-PI MoM and log PAPP-A MoM in the unaffected group (Figure 4a):

$$\text{Log UtA-PI MoM} = -0.001 - 0.095 \times \log \text{PAPP-A MoM} \; (P < 0.001).$$

There was also a significant association between log UtA-PI MoM and log PAPP-A MoM in the PE group (Figure 4b):

$$\text{Log UtA-PI MoM} = 0.057 - 0.141 \times \log \text{PAPP-A MoM} \; (P = 0.001).$$

Performance of screening for pre-eclampsia

The estimated detection rates of PE for different false-positive rates in screening based on maternal factors only, UtA-PI only, serum PAPP-A only and their combinations are shown in Table 3 and Figure 5.

The performance of different methods of screening was compared by examining areas under the receiver–operating characteristics (ROC) curves (Table 3). In the prediction of total PE, the area under the ROC curve was significantly higher for screening by history with UtA-PI than by history alone ($P = 0.048$), but there was no further improvement in screening if serum PAPP-A was included ($P = 0.501$). Similarly, in the prediction of early PE, the area under the curve was significantly higher in screening by history with UtA-PI than by history alone ($P = 0.008$), but there was no further improvement in screening if serum PAPP-A was included ($P = 0.728$). In the prediction of late PE the area under the ROC curve was not significantly higher for screening by history with UtA-PI than by history alone ($P = 0.135$), or by history with serum PAPP-A than by history alone ($P = 0.229$).

Modification of patient-specific risk for pre-eclampsia

The ROC curve analysis demonstrated that the detection rate of PE from screening based on history and UtA-PI was not improved by including serum PAPP-A. However, multiple regression analysis demonstrated that there were

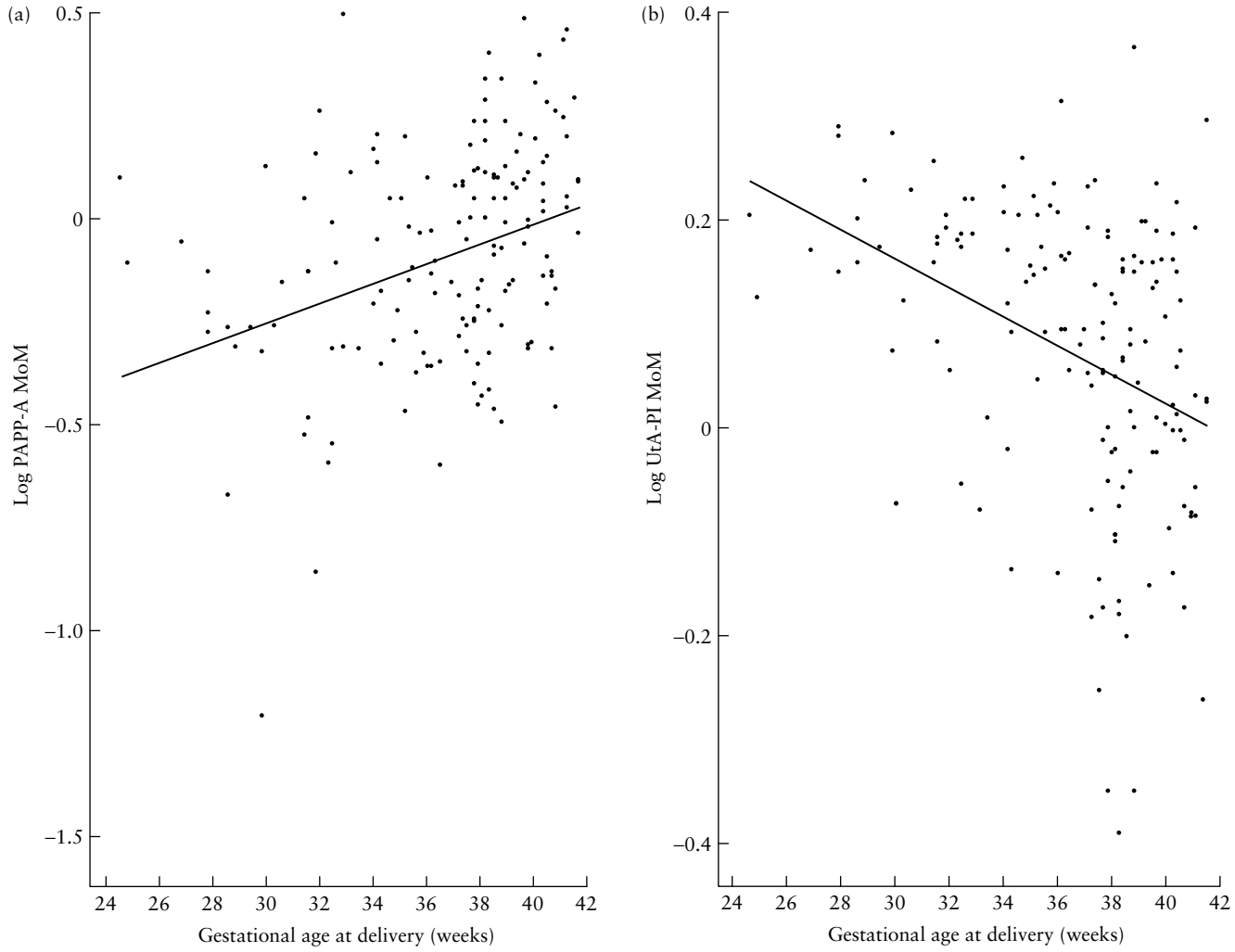

Figure 2 Relationship between log pregnancy-associated plasma protein-A (PAPP-A) multiples of the median (MoM) (a) and log uterine artery pulsatility index (UtA-PI) MoM (b) with gestational age at delivery in pregnancies developing pre-eclampsia. Regression lines are shown.

Table 2 Patient-specific risk for pre-eclampsia according to maternal characteristics and pregnancy-associated plasma protein-A (PAPP-A) multiples of the median (MoM)

	Patient-specific risk (%)					
	White			*Black*		
PAPP-A MoM	*Nulliparous*	*Parous with no previous pre-eclampsia*	*Parous with previous pre-eclampsia*	*Nulliparous*	*Parous with no previous pre-eclampsia*	*Parous with previous pre-eclampsia*
Early pre-eclampsia						
0.05	15.28	6.20	44.47	46.28	23.99	79.28
0.10	5.73	2.18	21.26	22.51	9.61	56.32
0.15	3.12	1.16	12.50	13.33	5.33	40.57
0.20	2.01	0.74	8.34	8.92	3.46	30.30
0.30	1.07	0.40	4.60	4.93	1.86	18.71
0.40	0.69	0.25	2.98	3.19	1.19	12.78
0.50	0.48	0.18	2.12	2.27	0.84	9.36
Late pre-eclampsia						
0.05	0.41	0.12	0.92	1.36	0.39	3.04
0.10	0.31	0.09	0.70	1.05	0.30	2.35
0.15	0.27	0.08	0.60	0.90	0.26	2.02
0.20	0.24	0.07	0.54	0.81	0.23	1.81
0.30	0.20	0.06	0.46	0.69	0.20	1.55
0.40	0.18	0.05	0.41	0.62	0.18	1.39
0.50	0.17	0.05	0.38	0.57	0.16	1.28

Table 3 Comparison of the performance of screening for pre-eclampsia by maternal factors, uterine artery pulsatility index (UtA-PI) and pregnancy-associated plasma protein-A (PAPP-A)

Screening test	Area under ROC curve (95% CI)			Detection rate (%) for fixed false-positive rate					
				All pre-eclampsia		Early pre-eclampsia		Late pre-eclampsia	
	All pre-eclampsia	Early pre-eclampsia	Late pre-eclampsia	5%	10%	5%	10%	5%	10%
History	0.780 (0.771–0.789)	0.781 (0.772–0.790)	0.787 (0.778–0.796)	28.8	44.2	32.0	45.0	28.2	40.3
UtA-PI	0.669 (0.658–0.679)	0.844 (0.836–0.852)	0.624 (0.613–0.634)	21.8	38.5	37.5	68.8	17.7	30.6
PAPP-A	0.591 (0.581–0.602)	0.721 (0.710–0.730)	0.558 (0.547–0.569)	9.6	20.5	21.9	37.5	6.5	16.1
UtA-PI with PAPP-A	0.675 (0.665–0.685)	0.852 (0.844–0.860)	—	20.5	35.9	46.9	59.4	—	—
History with:									
UtA-PI	0.809 (0.801–0.818)	0.897 (0.890–0.903)	0.806 (0.797–0.814)	35.3	47.4	65.6	78.1	29.8	43.5
PAPP-A	0.793 (0.784–0.802)	0.849 (0.841–0.857)	0.790 (0.781–0.799)	29.5	48.7	40.6	65.6	31.5	41.1
UtA-PI and PAPP-A	0.813 (0.805–0.822)	0.905 (0.898–0.911)	—	32.1	51.4	62.5	71.9	—	—

ROC, receiver–operating characteristics.

significant contributions from serum PAPP-A, UtA-PI and history in the prediction of early PE:

$$\begin{aligned} Y = {} & -7.318 - 2.864 \times \log \text{ PAPP-A MoM} \\ & + 11.456 \times \log \text{ UtA-PI MoM} + (1.939 \text{ if} \\ & \text{history of chronic hypertension}) \\ & + (1.569 \text{ if black, 0 if other racial origin}) \\ & (0 \text{ if nulliparous}, -0.869 \text{ if parous without} \\ & \text{previous PE, 1.297 if parous} \\ & \text{with previous PE})(R^2 = 0.278, P < 0.001). \end{aligned}$$

The risk for early PE was inversely related to serum PAPP-A (Figure 4). We used the above formula to determine the necessary UtA-PI that would result in a risk for early PE of 0.5% at various levels of reduced serum PAPP-A (Tables 4 and 5). For example, in a black woman with a previous history of PE and serum PAPP-A of 0.1 MoM the estimated risk for early PE is 56% (Table 2). If she is aged > 30 years, with a BMI > 25 kg/m^2 and the fetal CRL is > 65 mm, her risk for early PE would be reduced to 0.5% or less if the UtA-PI is ≤ 0.81 (Table 5).

DISCUSSION

The findings of this study confirm the results of previous reports that in pregnancies developing PE the maternal serum PAPP-A concentration at 11 + 0 to 13 + 6 weeks of gestation is reduced (Table 6)[3–9]. The additional findings of the study are that, first, the levels of PAPP-A are substantially lower in those developing early than late PE, second, the PAPP-A-related patient-specific risk for PE is strongly influenced by maternal variables and, third, there is a significant association between serum PAPP-A and UtA-PI.

At 11 + 0 to 13 + 6 weeks of gestation serum PAPP-A was below the 5th centile in about 10% of pregnancies that subsequently developed PE. There was a significant association between serum PAPP-A and the gestational age at delivery of pregnancies with PE, with low levels observed in about 20% and 7% of those with early- and late-onset disease, respectively.

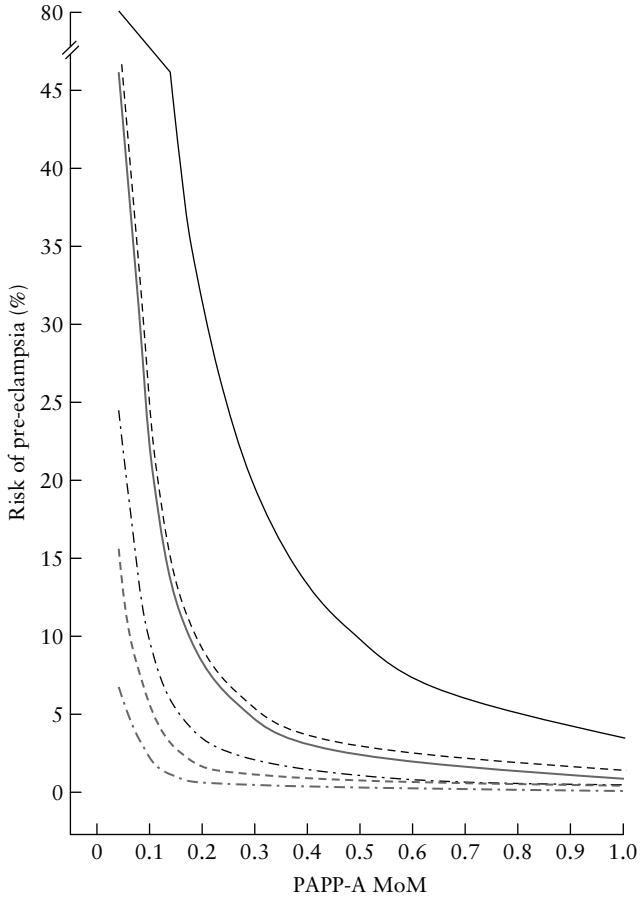

Figure 3 Relationship between maternal serum pregnancy-associated plasma protein-A (PAPP-A) multiples of the median (MoM) and risk for subsequent development of early-onset pre-eclampsia in women with previous pre-eclampsia (———), those with no previous pre-eclampsia (– · – · – ·) and nulliparous women (- - - -). The black lines are for black women and the thicker gray lines are for white women.

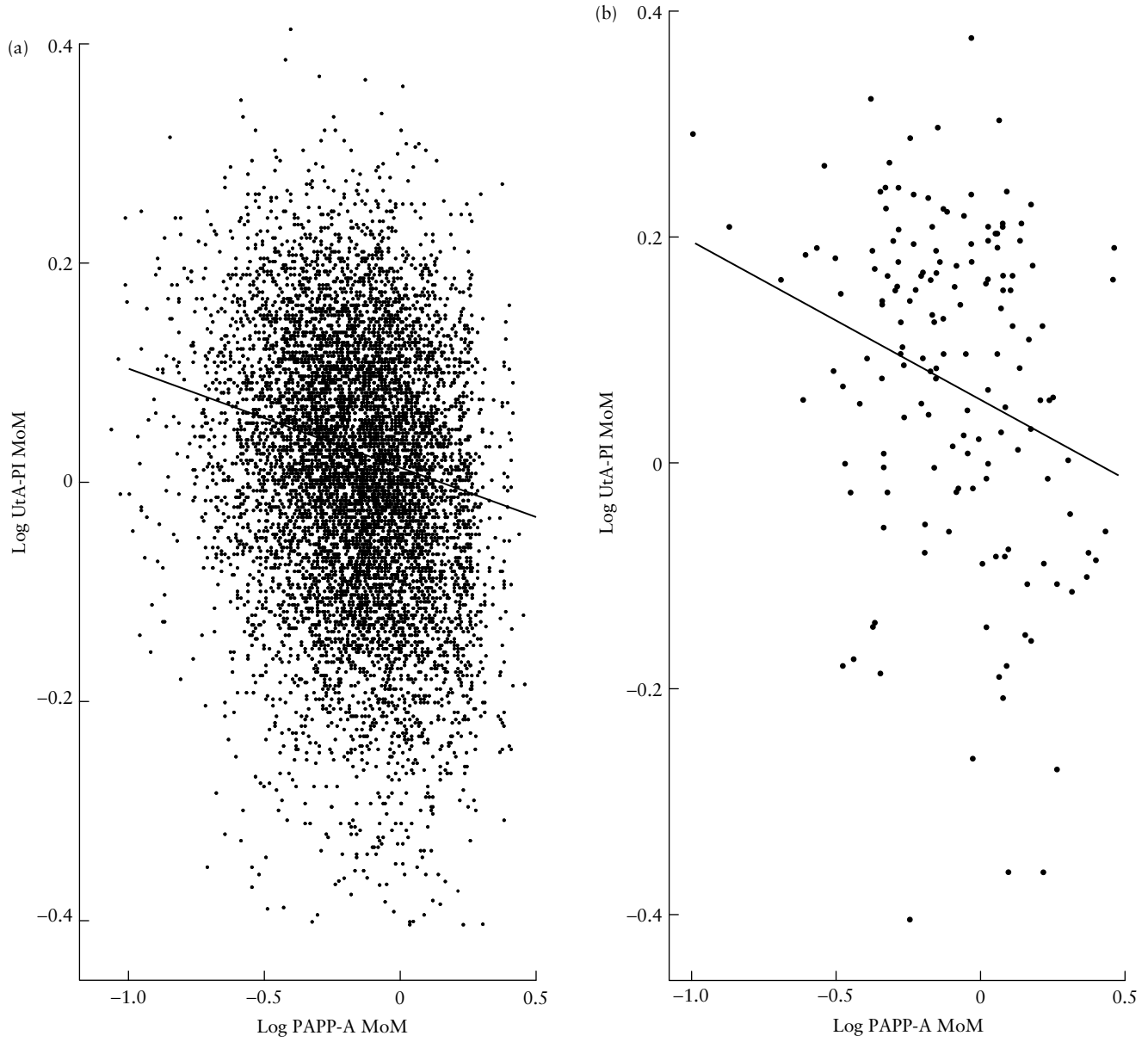

Figure 4 Relationship between log uterine artery pulsatility index (UtA-PI) multiples of the median (MoM) and log pregnancy-associated plasma protein-A (PAPP-A) MoM in unaffected pregnancies (a) and in pregnancies developing pre-eclampsia (b). Regression lines are shown.

The increase in patient-specific risk for PE, at a given low serum PAPP-A level, is substantially higher for early- than late-onset disease. Thus, for a PAPP-A level of 0.05 MoM in a black woman with a previous history of PE the risk of early PE is increased from the population average of about 0.5% to 80%, whereas the risk for late-onset disease is only doubled from about 1.5% to 3%. In deriving the PAPP-A-related patient-specific risk for PE it is also important to take maternal variables into account. Thus, for a PAPP-A level of 0.1 MoM the risk for early PE is about 5% for a white nulliparous woman and this is increased to 21% if she had a previous pregnancy with PE. The respective risks for a black woman are about 23% and 56%. In these calculations we applied the formulae derived from the regression analysis without applying any truncation limits that may become necessary after application into clinical practice.

Screening for PE based on a combination of maternal history and UtA-PI identified, for a 10% false-positive rate, about 80% and 40% of early- and late-onset disease, respectively. The finding that impaired placental perfusion, reflected in increased UtA-PI, is associated with the development of PE is compatible with the hypothesis that PE is the consequence of impaired placentation, and the results of previous first- and second-trimester Doppler studies as well as histological studies of the maternal spiral arteries[10,17,19–22]. Pathological studies have demonstrated that the prevalence of placental lesions in women with PE is inversely related to the gestational age at delivery[23,24].

A previous study of 401 uncomplicated pregnancies and 14 that developed gestational hypertension, including six with PE, found no significant association between UtA-PI and PAPP-A in either group[25]. In our study of more than 8000 pregnancies, including 156 that

developed PE, there was a significant association between serum PAPP-A and UtA-PI in both pregnancies that developed PE and in those that did not. There are two consequences from this finding. First, the detection rate of PE in screening based on history and UtA-PI is not improved by including serum PAPP-A. Second, the PAPP-A-related patient-specific risk for PE can be modified by the measurement of UtA-PI and the use of the appropriate multiple regression equation that combines the information from maternal variables, serum PAPP-A and UtA-PI. Ideally, the algorithm should be incorporated into the fetal medicine software used for the calculation of patient-specific risks for chromosomal defects. In the absence of such a computer-based algorithm, when the PAPP-A level is low, Table 2 can be used to estimate the patient-specific risk for early PE. If the risk is considered to be high the UtA-PI can be measured, and Tables 4 and 5 can then be used to determine whether the risk has been reduced to the overall average of 0.5%.

Low maternal serum PAPP-A at 11 + 0 to 13 + 6 weeks of gestation is associated with increased risk for trisomies 21, 18 and 13[1]. In chromosomally normal fetuses low PAPP-A is a marker for subsequent development of PE and in particular early-onset disease. However, the sensitivity of screening for PE is poor. The PAPP-A-related patient-specific risk for PE is strongly influenced by maternal characteristics and previous history of PE. Additionally, there is a significant association between serum PAPP-A and UtA-PI, and the PAPP-A-related patient-specific risk for PE can be modified by the measurement of UtA-PI.

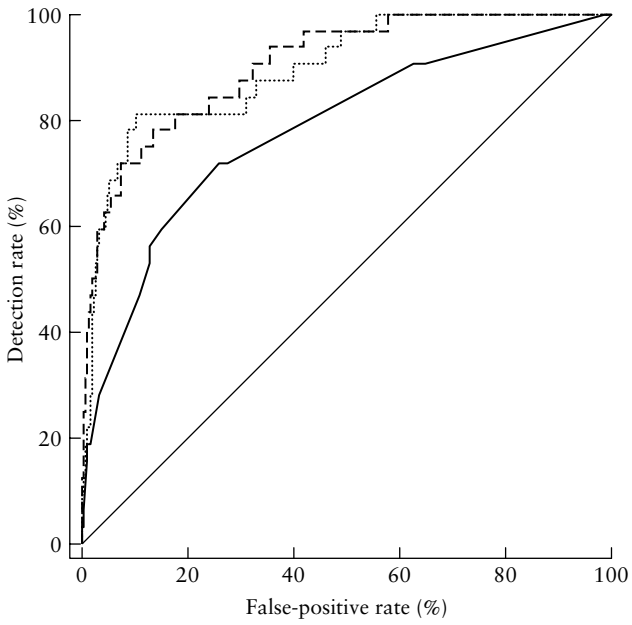

Figure 5 Receiver–operating characteristics curves for detection rates of early pre-eclampsia by screening based on maternal history (——), history and uterine artery pulsatility index (UtA-PI) (· · · · · ·), and history, UtA-PI and pregnancy-associated plasma protein-A (– – –).

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Table 4 Values of uterine artery pulsatility index that would result in a risk of early pre-eclampsia of 0.5% at various levels of reduced pregnancy-associated plasma protein-A (PAPP-A) multiples of the median (MoM) in white pregnant women aged ≤ 30 years or > 30 years

	Nulliparous				*Parous with no previous pre-eclampsia*				*Parous with previous pre-eclampsia*			
CRL (mm):	*≤ 65*		*> 65*		*≤ 65*		*> 65*		*≤ 65*		*> 65*	
BMI (kg/m²):	*≤ 25*	*> 25*	*≤ 25*	*> 25*	*≤ 25*	*> 25*	*≤ 25*	*> 25*	*≤ 25*	*> 25*	*≤ 25*	*> 25*
0.05 MoM												
≤ 30 years	1.18	1.16	1.13	1.10	1.41	1.38	1.34	1.31	0.96	0.94	0.91	0.89
> 30 years	1.16	1.14	1.11	1.08	1.39	1.35	1.32	1.29	0.94	0.92	0.90	0.88
0.10 MoM												
≤ 30 years	1.41	1.37	1.34	1.31	1.67	1.64	1.60	1.56	1.14	1.11	1.08	1.06
> 30 years	1.38	1.35	1.32	1.29	1.65	1.61	1.57	1.53	1.12	1.09	1.07	1.04
0.15 MoM												
≤ 30 years	1.56	1.52	1.48	1.45	1.85	1.81	1.77	1.72	1.26	1.23	1.20	1.17
> 30 years	1.53	1.50	1.46	1.43	1.82	1.78	1.74	1.70	1.24	1.21	1.18	1.15
0.20 MoM												
≤ 30 years	1.67	1.63	1.59	1.56	1.99	1.95	1.90	1.85	1.35	1.32	1.29	1.26
> 30 years	1.65	1.61	1.57	1.53	1.96	1.91	1.87	1.82	1.33	1.30	1.27	1.24
0.30 MoM												
≤ 30 years	1.85	1.81	1.76	1.72	2.20	2.15	2.10	2.05	1.50	1.46	1.43	1.39
> 30 years	1.82	1.78	1.74	1.70	2.17	2.12	2.07	2.02	1.48	1.44	1.41	1.37
0.40 MoM												
≤ 30 years	1.99	1.94	1.89	1.85	2.37	2.31	2.26	2.20	1.61	1.57	1.53	1.50
> 30 years	1.96	1.91	1.86	1.82	2.33	2.28	2.22	2.17	1.59	1.55	1.51	1.48
0.50 MoM												
≤ 30 years	2.10	2.05	2.00	1.96	2.50	2.45	2.39	2.33	1.70	1.66	1.62	1.58
> 30 years	2.07	2.02	1.97	1.93	2.46	2.41	2.35	2.29	1.68	1.64	1.60	1.56

BMI, body mass index; CRL crown–rump length.

Table 5 Values of uterine artery pulsatility index that would result in a risk of early pre-eclampsia of 0.5% at various levels of reduced pregnancy-associated plasma protein-A (PAPP-A) multiples of the median (MoM) in black pregnant women aged ≤ 30 years or > 30 years

	Nulliparous				*Parous with no previous pre-eclampsia*				*Parous with previous pre-eclampsia*			
CRL (mm):	*≤ 65*		*> 65*		*≤ 65*		*> 65*		*≤ 65*		*> 65*	
BMI (kg/m²):	*≤ 25*	*> 25*	*≤ 25*	*> 25*	*≤ 25*	*> 25*	*≤ 25*	*> 25*	*≤ 25*	*> 25*	*≤ 25*	*> 25*
0.05 MoM												
≤ 30 years	0.92	0.90	0.87	0.85	1.09	1.07	1.04	1.02	0.74	0.73	0.71	0.69
> 30 years	0.90	0.88	0.86	0.84	1.07	1.05	1.02	1.00	0.73	0.71	0.70	0.68
0.10 MoM												
≤ 30 years	1.09	1.07	1.04	1.02	1.30	1.27	1.24	1.21	0.88	0.86	0.84	0.82
> 30 years	1.07	1.05	1.02	1.00	1.28	1.25	1.22	1.19	0.87	0.85	0.83	0.81
0.15 MoM												
≤ 30 years	1.21	1.18	1.15	1.12	1.44	1.40	1.37	1.34	0.98	0.95	0.93	0.91
> 30 years	1.19	1.16	1.13	1.11	1.41	1.38	1.35	1.32	0.96	0.94	0.92	0.90
0.20 MoM												
≤ 30 years	1.30	1.27	1.24	1.21	1.54	1.51	1.47	1.44	1.05	1.03	1.00	0.98
> 30 years	1.28	1.25	1.22	1.19	1.52	1.49	1.45	1.41	1.03	1.01	0.98	0.96
0.30 MoM												
≤ 30 years	1.44	1.40	1.37	1.34	1.71	1.67	1.63	1.59	1.16	1.14	1.11	1.08
> 30 years	1.41	1.38	1.35	1.31	1.68	1.64	1.60	1.57	1.14	1.12	1.09	1.06
0.40 MoM												
≤ 30 years	1.54	1.51	1.47	1.44	1.84	1.79	1.75	1.71	1.25	1.22	1.19	1.16
> 30 years	1.52	1.48	1.45	1.41	1.81	1.77	1.72	1.68	1.23	1.20	1.17	1.14
0.50 MoM												
≤ 30 years	1.63	1.59	1.55	1.52	1.94	1.90	1.85	1.81	1.32	1.29	1.26	1.23
> 30 years	1.61	1.57	1.53	1.49	1.91	1.87	1.82	1.78	1.30	1.27	1.24	1.21

BMI, body mass index; CRL crown–rump length.

Table 6 Summary of studies of pregnancy-associated plasma protein-A (PAPP-A) in pre-eclampsia

		Screening for pre-eclampsia			
Reference	*Total number*	n *(%)*	*PAPP-A cut-off centile (MoM)*	*Detection rate (%)*	*Odds ratio or relative risk*
Ong *et al.* 2000[3]	5297	135 (2.6)	5th (–)	11.1	2.1
Yaron *et al.* 2002[4]	1622	27 (1.7)	15th (0.50)	22.2	1.7
Smith *et al.* 2002[5]	8839	331 (3.7)	5th (–)	10.6	2.3
Dugoff *et al.* 2004[6]	33 395	764 (2.3)	5th (0.42)	7.9	1.5
Spencer *et al.* 2005[7]	4390	64 (1.5)	5th (0.42)	14.1	2.8
Pilalis *et al.* 2007[8]	878	13 (1.5)	5th (0.41)	23.1	4.6
Spencer *et al.* 2007[9]	47 770	224 (0.5)	5th (0.42)	14.6	3.7
Present study	8051	156 (1.9)	5th (0.38)	9.6	2.0

MoM, multiples of the median.

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