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Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11–13 weeks

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Objective To develop models for prediction of pre-eclampsia (PE) based on maternal factors and biophysical and biochemical markers at 11–13 weeks' gestation.

Methods Screening study of singleton pregnancies at 11–13 weeks including 752 (2.2%) that subsequently developed PE and 32 850 that were unaffected by PE. Models were developed for the prediction of early PE, requiring delivery before 34 weeks, intermediate PE with delivery at 34–37 weeks and late PE delivering after 37 weeks. The data used for the models were firstly, maternal characteristics and history, uterine artery pulsatility index, mean arterial pressure and serum pregnancy-associated plasma protein-A obtained from the screening study and secondly, maternal serum or plasma concentration of placental growth factor, placental protein-13, inhibin-A, activin-A, soluble endoglin, pentraxin-3 and P-selectin obtained from case-control studies.

Results In screening for PE by maternal factors only at a fixed false positive rate of 5%, the estimated detection rates were 33.0% for early PE, 27.8% for intermediate PE and 24.5% for late PE. The respective detection rates in screening by a combination of maternal factors, biophysical and biochemical markers were 91.0, 79.4 and 60.9%.

Conclusions Effective prediction of PE can be achieved at 11–13 weeks' gestation. Copyright © 2011 John Wiley & Sons, Ltd.

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KEY WORDS: first-trimester screening; pre-eclampsia; uterine artery Doppler; mean arterial pressure; serum biochemistry

INTRODUCTION

Pre-eclampsia (PE), which affects 2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality World Health Organization (WHO), 2005; Lewis, 2007; Centre for Maternal and Child Enquiries (CMACE), 2010. In the UK, the National Collaborating Centre for Women's and Children's Health (NCCWCH) has issued guidelines on routine prenatal care recommending that at the first visit a woman's level of risk for PE should be evaluated, by a series of maternal characteristics, such as maternal age, body mass index and previous and family history of PE, so that a plan for her schedule of prenatal visits can be formulated (NCCWCH, 2008). The aim of such early identification of women at high-risk is to allow intensive maternal and fetal monitoring, leading to an earlier diagnosis of PE with the potential for mitigating an adverse outcome. Additionally, there is evidence from randomised studies on the prophylactic use of aspirin that this may reduce the incidence of PE by about 50%, provided treatment is initiated before 16 weeks (Bujold *et al*., 2010).

The approach to screening recommended by NCCWCH (2008), which essentially treats each of the risk factors as a separate screening test, would falsely classify two thirds of the obstetric population as being at high risk and in need of intensive monitoring (Poon *et al*., 2010a). An alternative approach is to combine the maternal characteristics and previous history into an algorithm derived by multivariate analysis to estimate the individual patient-specific risk for PE and with such an approach about one third of pregnancies developing PE would be detected at a false positive rate (FPR) of 10% (Poon *et al*., 2010a). The performance of screening can be improved by combining history with a series of biophysical and biochemical markers which are altered from as early as the first trimester of pregnancy in cases that subsequently develop PE. In the PE group, compared with unaffected controls, at 11–13 weeks' gestation uterine artery pulsatility index (PI) and mean arterial pressure (MAP) and maternal serum or plasma levels of soluble endoglin (sEng), inhibin-A, activin-A, pentraxin-3 (PTX3) and P-selectin are increased, whereas serum pregnancy-associated plasma protein-A

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(PAPP-A), placental growth factor (PLGF) and placental protein-13 (PP13) are decreased (Plasencia *et al*., 2007; Akolekar *et al*., 2008, 2009a, 2009b, 2009c, 2009d, 2010; Levine and Lindheimer, 2009; Foidart *et al*., 2010; Giguere *et al*., 2010; Poon *et al*., 2009, 2010b; Silasi *et al*., 2010; Zhong *et al*., 2010). These biophysical and biochemical markers are thought to be involved in placentation or in the cascade of events leading from impaired placentation to development of clinical symptoms of the PE.

There is evolving evidence that both the degree of impaired placentation and the incidence of adverse fetal and maternal short-term and long-term consequences of PE are inversely related to the gestational age at onset of the disease (Witlin *et al*., 2000; Irgens *et al*., 2001; von Dadelszen *et al*., 2003; Moldenhauer *et al*., 2003; Egbor *et al*., 2006; Yu *et al*., 2008). Consequently, the endpoint in screening for PE by first-trimester biophysical and biochemical markers should not be total PE but the condition should be subdivided according to gestational age at delivery. This subdivision has so far been limited to early PE, requiring delivery before 34 weeks and late PE. In our ongoing studies there are now sufficient data to allow further subdivision of the cases delivering at or after 34 weeks into intermediate PE and late PE groups, delivering at 34–37 weeks and after 37 weeks, respectively.

The aims of this study are to develop algorithms based on a combination of maternal factors, uterine artery PI, MAP and serum biomarkers to estimate patient-specific risks for early, intermediate and late PE and to evaluate the screening performance of such algorithms.

METHODS

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending their routine first hospital visit in pregnancy. In this visit, which is held at 11^{+0}–13^{+6} weeks of gestation, we record maternal characteristics and medical history and perform combined screening for aneuploidies by measurement of the fetal crown-rump length (CRL) and nuchal translucency (NT) thickness and maternal serum PAPP-A and free β-human chorionic gonadotrophin (β-hCG) (Robinson and Fleming, 1975; Snijders *et al*., 1998; Kagan *et al*., 2008a). The women were screened between March 2006 and September 2009. In the second part of the study period, we also measured the maternal mean arterial blood pressure (MAP) by automated devices (Poon *et al*., 2010b) and used transabdominal colour Doppler ultrasound to visualise the left and right uterine artery, measure the PI in each vessel and calculate the mean PI (Plasencia *et al*., 2007). Samples of serum and plasma are stored at −80 °C for subsequent biochemical analysis. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the King's College Hospital Ethics Committee.

The inclusion criteria for this study on screening for PE were singleton pregnancy delivering a phenotypically normal stillbirth or live birth at or after 24 weeks of gestation. We excluded pregnancies with major fetal abnormalities and those ending in termination, miscarriage or fetal death before 24 weeks.

In this study, we develop a model for predicting PE based on maternal characteristics in the whole screened population. We then expand this model for prediction of PE to include the addition of uterine artery PI, MAP and serum PAPP-A and free β-hCG, also derived from the screened population and serum or plasma PLGF, PP13, sEng, inhibin-A, activin-A, PTX3 and P-selectin derived from case-control studies. Data from these investigations were included in previous publications (Plasencia *et al*., 2007; Akolekar *et al*., 2008, 2009a, 2009b, 2009c, 2009d, 2010; Foidart *et al*., 2010; Poon *et al*., 2009, 2010b) but in this study we combine all data to develop an integrated algorithm for the early prediction of PE.

Maternal history and characteristics

Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, African, South Asian, East Asian and mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes or no), substance abuse during pregnancy (yes or no), history of chronic hypertension (yes or no), history of type 1 or 2 diabetes mellitus (yes or no), family history of PE in the mother of the patient (yes or no) and obstetric history including parity (parous or nulliparous if no previous pregnancies at or after 24 weeks) and previous pregnancy with PE (yes or no). The questionnaire was then reviewed by a doctor together with the patient, and the maternal weight and height were measured.

Outcome measures

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy (Brown *et al*., 2001). The systolic blood pressure should be 140 mm Hg or more and/or the diastolic blood pressure should be 90 mm Hg or more on at least two occasions 4 h apart developing after 20 weeks of gestation in previously normotensive women and there should be proteinuria of 300 mg or more in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection is available. In PE superimposed on chronic hypertension, significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks of gestation in the absence of trophoblastic disease).

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

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with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was chronic hypertension, PE or non-proteinuric gestational hypertension. The PE group was divided according to gestation at delivery into early PE (<34 weeks), intermediate PE (34–37 weeks) and late PE (≥38 weeks).

Case-control study for biochemical markers

The case-control study involved measurement of maternal serum concentration of PLGF, PP13, sEng, inhibin-A, activin-A, PTX3 and P-selectin at 11–13 weeks' gestation in pregnancies complicated by PE and unaffected controls. The cases were drawn from the screening study population on the basis of availability of stored serum. The controls were from pregnancies with no complications and normal outcome matched to the cases for storage time.

None of the samples were previously thawed and refrozen. Maternal serum PLGF was measured by a quantitative ELISA technique using Quantikine® human PLGF immunoassay (R&D Systems Europe Ltd., Abingdon, UK). Serum PP13 was measured by DELFIA® (Dissociation-Enhanced Lanthanide Fluorescent Immunoassay) using research reagents (Perkin Elmer Life and Analytical Sciences, Turku, Finland). Plasma sEng was measured by ELISA using DuoSet® human sEng immnoassay (R&D Systems Europe Ltd., Abington, UK). Plasma inhibin-A was measured by an ELISA technique using DSL-10-28100 inhibin-A immunoassay (Diagnostic systems laboratories, Inc. Webster, Texas, USA). Serum total activin-A concentration was measured by solid phase sandwich ELISA using Oxford Bio-Innovation total activin-A immunoassay kits (Oxford Bio-Innovation Limited, Oxfordshire, UK). Plasma PTX3 was measured by an ELISA kit (R&D Systems Europe Ltd, Abingdon, UK). Plasma P-selectin was measured by an ELISA technique using human soluble P-selectin/CD62P immunoassay (R&D Systems Europe Ltd., Abingdon, UK).

Statistical analysis

Comparison between the early, intermediate and late PE groups with the unaffected pregnancies was by chi-square test or Fisher's exact test for categorical variables and Mann Whitney-U test for continuous variables, both with *post hoc* Bonferroni correction (critical statistical significance $p < 0.0167$).

The following steps were used to develop a model for predicting early, intermediate and late PE based on maternal characteristics. First, the association of continuous variables, such as maternal age, weight and height, with PE was assessed to determine if this was linear or non-linear. Second, univariate analysis was performed to examine the individual variables contributing significantly to early, intermediate and late PE by assessing their odds ratios (ORs) and 95% confidence intervals. Third, logistic regression analysis with backward stepwise elimination of variables was used to develop the model. Fourth, to assess the predictive accuracy of our model we calculated the shrinkage factor using the equation $[\chi^2 - (df - 1)]/\chi^2$ where χ^2 is the model chi-square derived from the log-likelihood statistic and df is the degree of freedom. This shrinkage factor was then applied to all the parameters in the model to adjust for overfitting. Fifth, the patient-specific risk for early, intermediate and late PE was calculated from the formula: odds/(1 + odds), where odds $= e^Y$ and Y was derived from the logistic regression analysis. The distribution of risks was then used to calculate detection and FPRs at different risk cut-offs and the performance of screening was determined by receiver operating characteristic (ROC) curves analysis.

The following steps were used to develop a model for predicting early, intermediate and late PE based on the combination of maternal characteristics and biophysical and biochemical markers. First, the measured serum PAPP-A and free β-hCG were converted to multiples of the expected normal median (MoM) corrected for fetal CRL, maternal age, weight, smoking, parity, racial origin and method of conception as previously described (Kagan *et al.*, 2008b). Second, the values of uterine artery PI, MAP, PLGF, PP13, inhibin-A, activin-A, sEng, PTX3 and P-selectin were log transformed to make their distribution Gaussian. Third, in the unaffected pregnancies multiple regression analysis was used to determine which of the factors amongst the maternal characteristics and fetal CRL were significant predictors of each marker. In each case of PE and unaffected pregnancies, the measurements were converted into an MoM and the MoM values in different groups were compared. Fourth, Guassian distributions of markers in early, intermediate, late PE and unaffected pregnancies were fitted. These fitted distributions define the likelihood ratios for the screening tests that can be combined with the *a priori* maternal characteristics-derived risk to produce *a posteriori* risk. Fifth, the maternal factors-related *a priori* risks and $\log_{10}$ MoM values of the biophysical and biochemical markers were simulated for 500 000 pregnancies for each group of early, intermediate and late PE and 500 000 unaffected pregnancies. The maternal factors-related *a priori* risks for each of the PE groups were multiplied by the likelihood ratios of the biophysical and biochemical markers to derive the *a posteriori* risks in the simulated samples of 500 000 PE and 500 000 unaffected pregnancies. Fifth, the *a priori* and *a posteriori* risks in each of the PE groups and unaffected pregnancies were used to calculate the detection rates at fixed FPRs of 5 and 10%. The large size of the simulated population was chosen to ensure that the error resulting from simulation was negligible. The process of sampling with replacement from the screening data of PE and unaffected pregnancies ensured that the modelled screening performance reflects the screening population.

The statistical software package SPSS 16.0 (SPSS Inc., Chicago, IL) was used for data analyses. Monte-Carlo simulations were programmed in R (The R Foundation for Statistical Computing, R version 2.11.0, ISBN 3-900051-070-0, http://www.r-project.org).

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RESULTS

Characteristics of the study population

First-trimester combined screening for aneuploidies was carried out in 36 743 singleton pregnancies. We excluded 3141 cases because they had missing outcome data ($n = 2005$) or the pregnancies resulted in miscarriage, termination or the birth of babies with major defects ($n = 1136$). In the remaining 33 602 cases, there were 752 (2.2%) that developed PE and 32 850 that were unaffected by PE.

The maternal characteristics and history in each PE group and the unaffected pregnancies in the screening population and in the subgroups with measurements of uterine artery PI, MAP and serum PLGF are compared in Table 1 and Tables S1–S3.

Biophysical and biochemical markers in unaffected pregnancies

Multiple regression analyses in the unaffected pregnancies demonstrated that for each marker significant independent contributions were provided by certain maternal characteristics:

Log_{10} uterine artery PI expected = 0.438 (SE 0.017) − 0.001 (SE 0.0001) × maternal age in years − 0.002 (SE 0.0004) × maternal weight in kg + $5.96e^{-06}$ (SE $2.55e^{-06}$) × (maternal weight in kg)^2 + [0.009 (SE 0.003) if cigarette smoker, 0 if not] − 0.002 (SE 0.0001) × fetal CRL in mm + [0.028 (SE 0.002) if African, 0.016 (SE 0.005) if mixed and 0 if any other racial origin]; $R^2 = 0.034$, $p < 0.0001$.

Log_{10} MAP expected = 1.797 (SE 0.007) + 0.001 (SE $6.06e^{-05}$) × maternal age in years + 0.003 (SE $1.57e^{-04}$) × maternal weight in kg − $1.0e^{-04}$ (SE $1.01e^{-06}$) × (maternal weight in kg)^2 + [0.006 (SE $6.8e^{-04}$) if nulliparous and 0 if parous] − [0.008 (SE 0.001) if cigarette smoker and 0 if non-smoker] + [0.066 (SE 0.003) if chronic hypertension and 0 if not] − $1.68e^{-04}$ (SE $4.25e^{-05}$) × fetal CRL in mm + [0.011 (SE 0.005) if diabetes mellitus type 1 and 0 if not] − [0.002 (SE 0.001) if African, −0.004 (SE 0.002) if mixed and 0 if any other racial origin]; $R^2 = 0.161$, $p < 0.0001$.

Log_{10} PLGF expected = 0.932 (SE 0.042) + 0.002 (SE 0.001) × maternal age in years − 0.002 (SE $3.0e^{-04}$) × maternal weight in kg + [0.174 (SE 0.015) if cigarette smoker and 0 if non-smoker] + 0.009 (SE $5.1e^{-04}$) × fetal CRL in mm + [0.177 (SE 0.010) if African, 0.0871 (SE 0.020) if South Asian, 0.045 (SE 0.022) if mixed and 0 if any other racial origin]; $R^2 = 0.289$, $p < 0.0001$.

Log_{10} PP13 expected = 1.982 (SE 0.040) + 0.003 (SE 0.001) × maternal age in years − 0.004 (SE $3.9e^{-04}$) × maternal weight in kg − [0.214 (SE 0.019) if cigarette smoker and 0 if non-smoker] + [0.030 (SE 0.014) if African and 0 if any other racial origin]; $R^2 = 0.174$, $p < 0.0001$.

Log_{10} sEng expected = 4.312 (SE 0.060) − 0.002 (SE $8.6e^{-04}$) × maternal weight in kg; $R^2 = 0.029$, $p < 0.0001$.

Log_{10} inhibin-A expected = 2.546 (SE 0.047) − 0.002 (SE 0.001) × maternal weight in kg + [0.104 (SE 0.050) if use of ovulation induction drugs and 0 if spontaneous

Table 1—Maternal and pregnancy characteristics in the total screening population

Characteristic	Unaffected pregnancies ($n = 32\,850$)	Early PE ($n = 112$)	Intermediate PE ($n = 187$)	Late PE ($n = 453$)
Maternal age in years, median (IQR)	32.3 (27.9–36.0)	31.3 (25.7–36.2)	32.1 (28.1–36.8)	31.3 (27.2–36.3)
Maternal weight in kg, median (IQR)	65.0 (59.0–75.0)	72.0 (63.0–85.0)*	70.0 (61.0–85.0)*	72.0 (63.3–85.0)*
CRL in mm, median (IQR)	64.0 (59.2–69.5)	64.9 (58.1–72.1)	62.5 (57.4–68.2)	63.1 (58.9–69.4)
Racial origin				
Caucasian, *n* (%)	23,765 (72.3)	47 (42.0)	90 (48.1)	247 (54.5)
African, *n* (%)	6,051 (18.4)	53 (47.3)*	75 (40.1)*	165 (36.4)*
South Asian, *n* (%)	1,430 (4.4)	8 (7.1)	14 (7.5)	20 (4.4)
East Asian, *n* (%)	651 (2.0)	0	2 (1.1)	10 (2.2)
Mixed, *n* (%)	953 (2.9)	4 (3.6)	6 (3.2)	11 (2.4)
Parity				
Nulliparous, *n* (%)	15,698 (47.8)	65 (58.0)	104 (55.6)	291 (64.2)*
Parous with no previous PE, *n* (%)	16,196 (49.3)	27 (24.1)*	55 (29.4)*	105 (23.2)*
Parous with previous PE, *n* (%)	956 (2.9)	20 (17.9)*	28 (15.0)*	57 (12.6)*
Cigarette smoker, *n* (%)	2,695 (8.2)	2 (1.8)	12 (6.4)	29 (6.4)
Family history of PE, *n* (%)	1,480 (4.5)	13 (11.6)*	17 (9.1)*	34 (7.5)*
Conception				
Spontaneous, *n* (%)	31,618 (96.2)	104 (92.9)	174 (93.0)	435 (96.0)
Assisted, *n* (%)	1,232 (3.8)	8 (7.1)	13 (7.0)	18 (4.0)
History of chronic hypertension, *n* (%)	322 (1.0)	15 (13.4)*	18 (9.6)*	29 (6.4)*
History of pre-existing diabetes, *n* (%)	245 (0.7)	3 (2.7)	8 (4.3)*	2 (0.4)

Comparisons between each outcome group and unaffected controls (chi-square test and Fisher's exact test for categorical variables and Mann Whitney test with *post hoc* Bonferroni correction for continuous variables)
CRL, crown-rump length; IQR, interquartile range; PE, pre-eclampsia.
* Critical significance level $p < 0.0167$.

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Table 2—Multivariate logistic regression analysis to determine factors defining the *a priori* risk for the prediction of early, intermediate and late PE by maternal history and characteristics

	Early PE			Intermediate PE			Late PE		
Independent variable	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Weight (per kg)	1.021	1.009–1.033	0.001	1.022	1.012–1.031	<0.0001	1.028	1.022–1.034	<0.0001
Height (per cm)	0.949	0.921–0.978	0.001	0.957	0.936–0.980	<0.0001	0.964	0.950–0.978	<0.0001
Race									
Caucasian	1.000	—	—	1.000	—	—	1.000	—	—
African	3.644	2.431–5.463	<0.0001	2.662	1.938–3.657	<0.0001	2.123	1.735–2.598	<0.0001
South Asian	2.575	1.192–5.560	0.016	2.411	1.349–4.309	0.003	—	—	—
Assisted conception	2.225	1.061–4.670	0.034	2.131	1.198–3.790	0.010	—	—	—
Family history of PE	1.910	1.031–3.538	0.040	—	—	—	—	—	—
History of chronic hypertension	5.622	2.988–10.578	<0.0001	4.198	2.408–7.319	<0.0001	3.019	1.967–4.632	<0.0001
History of pre-existing diabetes	—	—	—	3.376	1.568–7.270	0.002	—	—	—
Parity									
Nulliparous (reference)	1.000	—	—	1.000	—	—	1.000	—	—
Parous with previous PE	2.235	1.259–3.966	0.006	2.411	1.521–3.823	<0.0001	1.815	1.325–2.485	<0.0001
Parous without previous PE	0.333	0.211–0.525	<0.0001	0.432	0.309–0.603	<0.0001	0.289	0.230–0.362	<0.0001

OR, odds ratio; CI, confidence interval; *p*, significance value; PE, pre-eclampsia.

conception] + [0.052 (SE 0.022) if African and 0 if any other racial origin]; $R^2 = 0.040$, $p < 0.0001$.

Log_{10} activin-A expected = 0.259 (SE 0.067) + 0.005 (SE 0.002) × maternal age in years − 0.003 (SE 0.001) × maternal weight in kg + [0.082 (SE 0.021) if African and 0 if any other racial origin]; $R^2 = 0.075$, $p < 0.0001$.

Log_{10} PTX3 expected = −0.078 (SE 0.085) − 0.003 (SE 0.001) × maternal weight in kg − [0.123 (SE 0.060) if South Asian and 0 if any other racial origin]; $R^2 = 0.042$, $p < 0.0001$.

Log_{10} P-selectin expected = 1.495 (SE 0.009) − [0.102 (SE 0.039) is use of ovulation induction drugs and 0 if spontaneous conception] − [0.063 (SE 0.019) if African, −0.152 (SE 0.076) if East Asian and 0 if any other racial origin]; $R^2 = 0.053$, $p < 0.0001$.

Patient-specific risks for early, intermediate and late PE

The patient-specific *a priori* risk for early, intermediate and late PE based on maternal characteristics was calculated from the formula: odds/(1 + odds), where odds = e^Y. The Y for each type of PE was derived from backward stepwise multivariate regression analysis. The results of this analysis are summarised in Table 2 and Tables S4–S6. The shrinkage coefficient for early, intermediate and late PE models w 0.95, 0.96 and 0.99, respectively, and all parameters in the model were adjusted accordingly.

The biophysical and biochemical results of each PE group and the unaffected pregnancies are compared in Table 3. The differences between the PE groups and unaffected pregnancies were sequentially greater in the early than intermediate or late disease, except for activin-A where the differences were greater for late than early disease. The inter-correlations between biophysical and biochemical markers in the PE and unaffected pregnancies are shown in Tables S7–S10.

Performance of screening for PE

The estimated detection rates of early, intermediate and late PE at fixed FPRs of 5 and 10% in screening by maternal factors only and by combinations of maternal factors with biophysical and biochemical markers are given in Table 4. ROC curves are given in Figure 1.

DISCUSSION

This prospective screening study in an inner city heterogeneous population of about 35 000 singleton pregnancies has found that the prevalence of early, intermediate and late PE is 0.3, 0.6 and 1.3%, respectively. We used logistic regression analysis to derive the a priori risk for each of the PE groups from maternal characteristics. The risk for PE increased with maternal weight and decreased with height: it was higher in women of African and South Asian racial origin than in Caucasians, and increased in women conceiving after the use of ovulation induction drugs, in those with a personal or family history of PE and in those with pre-existing chronic hypertension or diabetes mellitus. In parous women with no previous PE, the risk of developing PE in the current pregnancy was reduced by 60–70%. In general, the ORs for the factors in maternal history which defined the a priori risk for PE were inversely proportional to the gestation at delivery, with higher ratios for early disease compared with those in intermediate and late PE. Algorithms that combine the various maternal characteristics at 11–13 weeks could potentially identify 33, 28 and 25% of pregnancies that subsequently develop early, intermediate and late PE, at the FPR of 5%. The algorithm is freely accessible at the Fetal Medicine Foundation website www.fetalmedicine.com.

The patient-specific a posteriori risk for early, intermediate and late PE were calculated by multiplying the a priori patient characteristics-derived risk with the

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Table 3—Median and interquartile range (IQR) of pregnancy-associated plasma protein-A (PAPP-A), free β-human chorionic gonadotrophin (β-hCG), uterine artery pulsatility index (PI), mean arterial pressure (MAP), placental growth factor (PLGF), placental protein 13 (PP13), soluble endoglin (sEng), inhibin-A, activin-A, pentraxin 3 (PTX3) and P-selectin the unaffected group and in those subsequently developing early, intermediate and late pre-eclampsia (PE)

	Unaffected pregnancies		Early PE		Intermediate PE		Late PE	
Variables	*n*	MoM	*n*	MoM	*n*	MoM	*n*	MoM
PAPP-A, median (IQR)	32 850	1.02 (0.70–1.45)	112	0.63 (0.40–1.14)*	187	0.79 (0.53–1.11)*	453	0.90 (0.62–1.29)*
Free β-hCG, median (IQR)	32 850	0.97 (0.66–1.47)	112	0.99 (0.66–1.69)	187	0.92 (0.64–1.40)	453	0.99 (0.66–1.51)
Uterine artery PI, median (IQR)	21 090	1.02 (0.84–1.23)	86	1.47 (1.11–1.72)*	143	1.28 (1.06–1.51)*	354	1.11 (0.88–1.36)*
MAP, median (IQR)	13 515	1.00 (0.95–1.06)	69	1.10 (1.04–1.17)*	111	1.08 (1.03–1.13)*	251	1.06 (1.00–1.13)*
PLGF, median (IQR)	2 143	0.99 (0.77–1.27)	56	0.64 (0.46–0.82)*	104	0.72 (0.55–0.91)*	186	0.85 (0.68–1.12)*
PP13, median (IQR)	1 210	1.00 (0.76–1.33)	48	0.88 (0.57–1.23)	70	0.93 (0.70–1.30)	103	1.11 (0.89–1.49)
sEndoglin, median (IQR)	181	0.99 (0.78–1.31)	29	1.44 (1.03–1.92)*	28	0.89 (0.70–1.21)	32	0.99 (0.74–1.23)
Inhibin-A, median (IQR)	403	0.98 (0.75–1.33)	25	1.61 (0.90–1.94)**	37	1.13 (0.83–1.70)	62	1.32 (0.91–1.70)*
Activin-A, median (IQR)	398	1.00 (0.76–1.30)	26	1.25 (1.00–1.72)**	41	1.22 (0.97–1.74)**	61	1.36 (1.01–1.70)*
PTX3, median (IQR)	291	0.99 (0.76–1.31)	26	1.40 (0.82–2.04)	37	1.40 (0.93–1.89)**	60	1.02 (0.78–1.40)
P-Selectin, median (IQR)	294	1.01 (0.84–1.24)	26	1.21 (0.83–1.35)	36	1.18 (0.90–1.43)	62	1.16 (0.96–1.37)**

Comparisons between the outcome groups by Mann Whitney-U test with *post hoc* Bonferroni correction.
MoM, multiple of the unaffected median.
* $p < 0.0001$;
** $p < 0.01$.

Table 4—Performance of screening for early, intermediate and late pre-eclampsia (PE) by maternal factors only and maternal factors with pregnancy-associated plasma protein-A (PAPP-A), uterine artery pulsatility index (PI), mean arterial pressure (MAP), placental growth factor (PLGF), placental protein 13 (PP13), soluble endoglin (sEng), inhibin-A, activin-A, pentraxin 3 (PTX3), P-selectin and their combinations

	Detection rate (95% confidence interval) for fixed FPR					
	Early PE		Intermediate PE		Late PE	
Screening test	5%	10%	5%	10%	5%	10%
Maternal factors	33.0 (24.6–42.7)	46.4 (36.9–56.1)	27.8 (20.0–37.2)	37.4 (28.6–47.2)	24.5 (17.1–33.8)	34.7 (26.1–44.4)
Maternal factors plus						
PAPP-A	47.0 (37.5–56.7)	58.3 (49.5–67.5)	31.4 (23.1–41.0)	43.2 (33.2–53.0)	25.8 (17.7–34.5)	37.2 (28.4–47.0)
Uterine artery PI	54.1 (44.4–63.5)	66.1 (56.4–74.6)	36.9 (28.1–46.7)	48.9 (39.3–58.6)	27.1 (19.4–36.5)	38.6 (29.7–48.4)
MAP	49.7 (40.1–59.3)	62.6 (52.8–71.5)	41.1 (32.0–50.9)	53.7 (44.0–63.2)	33.1 (24.7–42.8)	44.6 (35.2–54.4)
PLGF	53.5 (43.8–63.0)	65.0 (55.3–73.6)	40.3 (31.2–40.1)	52.7 (43.0–62.2)	27.0 (19.3–36.4)	38.7 (29.7–48.5)
PP13	39.8 (30.8–49.6)	51.9 (42.2–61.4)	30.2 (22.1–39.8)	41.4 (32.2–51.2)	26.2 (18.6–35.6)	37.8 (28.9–47.6)
sEndoglin	46.2 (36.8–55.9)	58.8 (49.0–68.0)	31.0 (22.8–40.6)	42.2 (33.0–52.0)	25.7 (18.2–35.1)	37.1 (28.3–46.9)
Inhibin-A	44.4 (35.1–54.2)	56.7 (46.9–66.0)	32.6 (24.2–42.3)	44.2 (34.9–54.0)	30.8 (22.6–40.4)	42.5 (33.3–52.3)
Activin-A	40.4 (31.3–50.2)	53.1 (43.4–62.6)	33.7 (25.2–43.4)	46.0 (36.6–55.7)	34.1 (25.6–43.8)	47.0 (37.5–56.7)
PTX3	37.8 (28.9–47.6)	50.1 (40.5–59.7)	31.2 (23.0–40.8)	43.2 (33.9–53.0)	25.6 (18.1–35.0)	36.8 (28.0–46.6)
P-Selectin	38.5 (29.6–48.3)	50.5 (40.9–60.1)	31.1 (22.9–40.7)	42.6 (36.8–55.9)	28.5 (20.6–38.0)	40.5 (31.4–50.3)
Maternal factors plus biophysical markers	66.5 (56.8–75.0)	77.8 (68.7–84.8)	48.7 (39.1–58.4)	61.2 (51.4–70.2)	34.3 (25.7–44.0)	46.6 (37.1–56.3)
plus PAPP-A and PLGF	77.8 (68.7–84.8)	86.7 (78.7–92.0)	56.6 (46.8–65.9)	68.9 (59.3–77.1)	35.2 (26.6–45.0)	48.5 (38.9–58.2)
plus PAPP-A, PLGF, Inhibin-A and Activin-A	83.4 (74.9–89.4)	90.0 (82.6–94.5)	63.6 (53.8–72.4)	74.8 (65.5–82.3)	47.9 (38.4–57.6)	61.4 (51.6–70.4)
plus PAPP-A, PLGF, Inhibin-A, Activin-A and sEndoglin	86.7 (78.7–92.1)	92.1 (85.1–96.0)	68.6 (59.0–76.9)	79.5 (70.6–86.3)	50.5 (40.9–60.1)	64.2 (54.4–72.9)
Maternal factors plus all markers	91.0 (83.8–95.2)	95.2 (89.1–98.0)	79.4 (70.5–86.2)	88.3 (80.5–93.2)	60.9 (51.1–69.9)	71.1 (61.6–79.1)

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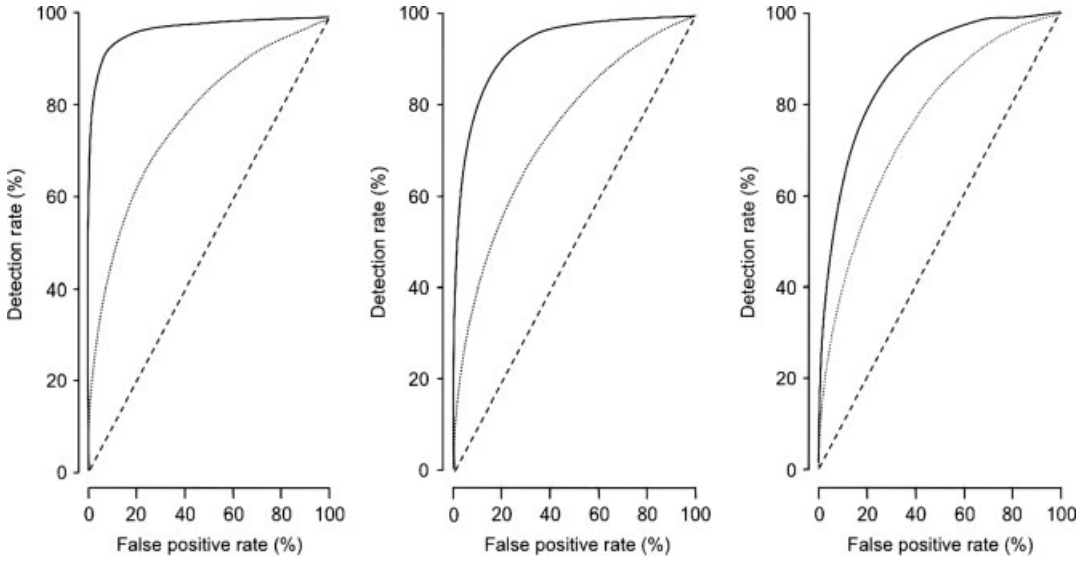

Figure 1—Receiver operating characteristic (ROC) curves in the prediction of early (left), intermediate (middle) and late pre-eclampsia (PE) (right) by maternal factors only (·····.) and by a combination of maternal factors, biochemical and biophysical markers (———)

likelihood ratio of a series of biophysical and biochemical markers after appropriate adjustments for the intercorrelations between these markers. As in the cases of maternal factors, the differences in biophysical and biochemical markers of impaired placentation between the PE and unaffected groups were, in general, more pronounced in those developing early disease compared with those in intermediate or late PE. Algorithms which combine maternal characteristics and biophysical and biochemical tests at 11–13 weeks could potentially identify about 90, 80 and 60% of pregnancies that subsequently develop early, intermediate and late PE, at the FPR of 5%.

An integrated first hospital visit at 11–13 weeks combining data from maternal characteristics and history with findings of biophysical and biochemical tests can define the patient-specific risk for a wide spectrum of pregnancy complications, including aneuploidies, fetal defects, miscarriage and fetal death, preterm delivery, fetal growth restriction and macrosomia, gestational diabetes, hypothyroidism and PE (Akolekar *et al*., 2011; Ashoor *et al*., 2010; Beta *et al*., 2011; Greco *et al*., 2011; Karagiannis *et al*., 2010; Nanda *et al*., 2011; Nicolaides, 2011; Poon *et al*, 2010c, 2011; Syngelaki *et al*., 2011). Early estimation of patient-specific risks for these pregnancy complications would improve pregnancy outcome by shifting prenatal care from a series of routine visits to a more individualised patient- and disease-specific approach both in terms of the schedule and content of such visits. In the case of PE, effective early identification of the high-risk group could potentially improve the outcome by directing such patients to specialist clinics for close surveillance and would be the basis for future studies investigating the potential role of pharmacological interventions, such as aspirin, starting from the first trimester to improve placentation and reduce the prevalence of the disease.

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