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Prediction of spontaneous preterm delivery from maternal factors, obstetric history and placental perfusion and function at 11–13 weeks

Jarek Beta[1,2], Ranjit Akolekar[1], Walter Ventura[1], Argyro Syngelaki[1,2] and Kypros H. Nicolaides[1,2]*

[1]*Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK*
[2]*Department of Fetal Medicine, University College Hospital, London, UK*

Objective To develop a model for prediction of spontaneous delivery before 34 weeks based on maternal factors, placental perfusion and function at 11–13 weeks' gestation.

Methods Two groups of studies: first, screening study of maternal characteristics, serum pregnancy-associated plasma protein-A (PAPP-A), free β-human chorionic gonadotrophin (β-hCG) and uterine artery pulsatility index (PI). Second, case-control studies of maternal serum or plasma concentration of placental growth factor (PlGF), placental protein 13 (PP13), a disintegrin and metalloprotease 12 (ADAM12), inhibin-A and activin-A. Regression analysis was used to develop a model for the prediction of spontaneous early delivery.

Results Spontaneous early delivery occurred in 365 (1.1%) of the 34 025 pregnancies. A model based on maternal factors could detect 38.2% of the preterm deliveries in women with previous pregnancies at or beyond 16 weeks and 18.4% in those without, at a false positive rate (FPR) of 10%. In the preterm delivery group, compared with unaffected pregnancies there were no significant differences in the markers of placental perfusion or function, except for PAPP-A which was reduced.

Conclusions Patient-specific risk of preterm delivery is provided by maternal factors and obstetric history. Placental perfusion and function at 11–13 weeks are not altered in pregnancies resulting in spontaneous early delivery. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS: first-trimester screening; preterm delivery; uterine artery Doppler; PAPP-A; PlGF; serum biochemistry

INTRODUCTION

Preterm birth is the leading cause of perinatal death and handicap in children and the vast majority of mortality and morbidity relates to early delivery before 34 weeks (Saigal and Doyle, 2008; CMACE, 2010). Cervical cerclage and prophylactic use of progesterone can reduce the risk of preterm delivery in high-risk pregnancies (Fonseca *et al*., 2003, 2007; Meis *et al*., 2003; Berghella *et al*., 2005). However, the rate of preterm delivery has not decreased in the past 30 years (Goldenberg *et al*., 2008), mainly because of failure to identify the high-risk group during routine prenatal care.

Delivery before 34 weeks occurs in about 2% of singleton pregnancies, and in two thirds of the cases this is due to spontaneous onset of labor or preterm pre-labor rupture of membranes and in the other one third it is iatrogenic, mainly due to pre-eclampsia (Celik *et al*., 2008). Effective screening for pre-eclampsia can be provided by a combination of maternal factors with biophysical and biochemical markers at 11–13 weeks (Akolekar *et al*., 2011). Screening for spontaneous preterm delivery relies on a combination of maternal factors and measurement of cervical length at 20–24 weeks (Iams *et al*., 1996; Heath *et al*., 1998; To *et al*., 2006; Celik *et al*., 2008). There is some evidence that in pregnancies delivering preterm the endocervical length is reduced at 11–13 weeks (Greco *et al*., 2011). Several studies have also investigated the potential value of uterine artery pulsatility index (PI) and maternal serum concentrations of pregnancy-associated plasma protein-A (PAPP-A), free β-human chorionic gonadotrophin (β-hCG), PlGF, placental protein 13 (PP13), a disintegrin and metalloprotease 12 (ADAM12), inhibin-A and activin-A and reported contradictory results (Strigini *et al*., 1995; Germain *et al*., 1999; Smith *et al*., 2002, 2007; Tul *et al*., 2003; Agarwal *et al*., 2004; Cobian-Sanchez *et al*., 2004; Dugoff *et al*., 2004, 2005; Krantz *et al*., 2004; Spencer *et al*., 2005, 2008; Farina *et al*., 2006; Fonseca *et al*., 2006; Chafetz *et al*., 2007; Cowans *et al*., 2007, 2008; Soares *et al*., 2007; Poon *et al*., 2008, 2009; Chaiworapongsa *et al*., 2009; Lain *et al*., 2009; Goetzinger *et al*., 2010; Huang *et al*., 2010).

The aims of this study are first, to develop a model for the calculation of patient-specific risk of spontaneous early preterm delivery by maternal characteristics and obstetric history and second, to determine whether the prediction is improved from the investigation of placental perfusion and function at 11–13 weeks.

*Correspondence to: Prof. Kypros H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London SE5 9RS. E-mail: kypros@fetalmedicine.com

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METHODS

Screening study population

The data for this study were derived from a prospective screening study for adverse obstetric outcomes in women attending their routine first hospital visit in pregnancy. In this visit, which is held between week 11 and 13 weeks and 6 days gestation, we record maternal characteristics and medical history and perform combined screening for aneuploidies by measurements of fetal crown-rump length (CRL), nuchal translucency (NT) thickness and maternal serum PAPP-A and free β-hCG (Robinson and Fleming, 1975; Snijders *et al*., 1998; Kagan *et al*., 2008a). During the second part of the study, we also measured the uterine artery PI (Plasencia *et al*., 2007). Samples of serum and plasma were stored at $-80\,^{\circ}$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 spontaneous delivery before 34 completed weeks (238 days) of gestation based on factors from maternal history and characteristics were singleton pregnancy delivering a phenotypically normal neonate at or after 24 weeks' gestation. We excluded pregnancies with major fetal abnormalities, those ending in termination, miscarriage or fetal death before 24 weeks and those with iatrogenic delivery before 34 weeks. The women were screened between March 2006 and September 2009.

Diagnosis of spontaneous early preterm delivery

Data on pregnancy outcome were obtained from the maternity computerized records or the general medical practitioners of the women and were also recorded in our database. The obstetric records of all patients delivering before 34 weeks were examined to determine if the preterm delivery was medically indicated or spontaneous. The latter included those with spontaneous onset of labor and those with preterm pre-labor rupture of membranes.

Case-control study for biochemical markers

The case-control study involved measurement of maternal serum concentration of PlGF, PP13, ADAM12, inhibin-A and activin-A at 11–13 weeks' gestation in pregnancies complicated by spontaneous early preterm delivery and controls delivering after 37 weeks. The cases were drawn at random from the screening study population with available 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. The biochemical markers were measured as previously described (Akolekar *et al*., 2008, 2009a,b,c; Poon *et al*., 2008).

STATISTICAL ANALYSIS

Comparisons between the spontaneous early preterm delivery group with those delivering at or after 34 weeks were by χ^2 test and Fisher's exact test for categorical variables and by Mann–Whitney U test for continuous variables. The following steps were used to develop a model for predicting spontaneous early preterm delivery. First, we assessed whether in case of continuous variables such as maternal age, weight and height, the association with preterm delivery was linear or non-linear. Second, we performed univariate analysis to examine the individual variables contributing significantly to preterm delivery by assessing their odds ratios (ORs) and 95% confidence intervals (CI). 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 $[\chi^2 - (\mathrm{df} - 1)]/\chi^2$, where χ^2 is the model chi-sqaure 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 preterm delivery was calculated from the formula: odds/(1 + odds), where odds $= e^Y$ and Y was derived from the multiple logistic regression analysis. The distribution of risks was then used to calculate detection and false positive rates (FPRs) at different risk cut-offs and the performance of screening was determined by receiver operating characteristic (ROC) curves analysis.

The measured serum PAPP-A, free β-hCG and uterine artery PI in the screening study and the measured serum PLGF, PP13, ADAM12, inhibin-A and activin-A in the case-control study 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; Akolekar *et al*., 2011). The Mann–Whitney test was used to compare median MoM values of each serum analyte and uterine artery PI between the outcome groups. Significant differences were observed only for PAPP-A (See Section on Results). Logistic regression analysis was used to determine if in the prediction of spontaneous early preterm delivery, the log 10 transformed risk based on maternal factors was significantly improved by log 10 PAPP-A MoM.

The statistical software package SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for data analyses.

RESULTS

Screening by maternal characteristics and obstetric history

First-trimester combined screening for aneuploidies was carried out in 36 743 singleton pregnancies. We excluded

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Table 1—Maternal characteristics and obstetric history in the screened population

Characteristics	Delivery ≥34 weeks ($n = 33\,017$)	Early preterm ($n = 353$)
Maternal age in years, median (IQR)	32.3 (27.9–36.0)	32.6 (28.0–36.5)
Maternal weight, median (IQR)	65.5 (59.0–75.0)	66.0 (58.0–77.0)
Maternal height in cm, median (IQR)	164 (160–168)	162.6 (158.0–167.6)*
Racial origin		
Caucasian, *n* (%)	23 804 (72.1)	217 (61.5)
African, *n* (%)	6170 (18.7)	100 (28.3)*
South Asian, *n* (%)	1436 (4.3)	23 (6.5)
East Asian, *n* (%)	651 (2.0)	7 (2.0)
Mixed, *n* (%)	956 (2.9)	6 (1.7)
Cigarette smoker, *n* (%)	2670 (8.1)	43 (12.2)*
History of substance abuse, *n* (%)	219 (0.7)	2 (0.6)
Conception		
Spontaneous, *n* (%)	31 790 (96.3)	331 (93.8)
Ovulation drugs, *n* (%)	1227 (3.7)	22 (6.2)*
Obstetric history		
Nulliparous—no pregnancy, *n* (%)	10 642 (32.2)	106 (30.0)
Nulliparous—fetal loss at <16 weeks, *n* (%)	5094 (15.4)	68 (19.3)
Nulliparous—miscarriage at 16–23 weeks, *n* (%)	116 (0.4)	10 (2.8)*
Parous preterm delivery 24–27 weeks, *n* (%)	170 (0.5)	12 (3.4)*
Parous preterm delivery 28–30 weeks, *n* (%)	125 (0.4)	7 (2.0)*
Parous preterm delivery 31–33 weeks, *n* (%)	153 (0.5)	6 (1.7)*
Parous preterm delivery 34–36 weeks, *n* (%)	775 (2.3)	23 (6.5)*
Parous term delivery >37 weeks, *n* (%)	15 752 (47.7)	118 (33.4)*
Parous iatrogenic preterm delivery, *n* (%)	190 (0.6)	3 (0.8)

IQR, interquartile range.
Comparisons between groups (χ^2-test and Fisher exact test for categorical variables and Mann–Whitney *U* test for continuous variables):
* $p < 0.05$.

3373 cases because they had missing outcome data ($n = 2005$), the pregnancies resulted in miscarriage, termination or the birth of babies with major defects ($n = 1,136$), or they were complicated by iatrogenic delivery before 34 weeks ($n = 232$).

The 33 370 singleton pregnancies fulfilling the entry criteria included 33 017 (98.9%) that delivered at or after 34 weeks and 353 (1.1%) that delivered before 34 weeks, either because of spontaneous onset of labor ($n = 178$) or preterm pre-labor rupture of membranes ($n = 175$). The maternal and pregnancy characteristics of the two groups are compared in Table 1. In the spontaneous early preterm delivery group, the median maternal height was lower and there was a higher prevalence of women of African racial origin, women who smoked cigarettes in pregnancy, those who conceived on ovulation induction drugs and women with previous spontaneous preterm deliveries.

In the regression analysis for prediction of spontaneous early preterm delivery, obstetric history was first classified into nulliparous and parous (Table 2). The nulliparous group was subdivided into first, no previous pregnancies; second, previous miscarriage or termination before 16 weeks; and third, at least one previous miscarriage between 16 weeks and 23 weeks and 6 days. The parous group was subdivided according to the earliest spontaneous delivery into first, 24 weeks to 27 weeks and six days; second, 28 weeks to 30 weeks and six days; third, 31 weeks to 33 weeks and six days; fourth, 34 weeks to 36 weeks and six days; fifth, only iatrogenic deliveries before 37 weeks and sixth, only deliveries at or after 37 weeks. Multiple regression analysis demonstrated that in the prediction of spontaneous early preterm delivery there were significant contributions from maternal age, height, racial origin, smoking status, method of conception and obstetric history (Table 2). The risk of preterm delivery in nulliparous women with previous fetal loss before 16 weeks was similar to that in nulliparous women with no previous pregnancies but in those with previous miscarriage at 16–23 weeks the risk was significantly increased. The ORs for parous women were inversely related to the gestation at previous spontaneous delivery (Figure 1).

To investigate the effect of more than one spontaneous preterm delivery and the protective effect of previous term delivery we reclassified the obstetric history into: first, nulliparous with or without previous fetal loss before 16 weeks; second, one or at least two spontaneous deliveries between 16 weeks and 30 weeks and six days with and without additional deliveries between 31 weeks and 36 weeks and six days or deliveries at or after 37 weeks; third, spontaneous delivery between 31 weeks and 36 weeks and six days with and without additional deliveries at or after 37 weeks and fourth, only deliveries at or after 37 weeks (Table 3, Figure 1). Multiple regression analysis demonstrated that in the prediction of spontaneous early preterm delivery, first, the ORs were increased if there was more than one spontaneous early preterm delivery and second, in women with a previous spontaneous early preterm delivery there was a protective effect against recurrennce if they also had a delivery at term.

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Table 2—Logistic regression analysis for the prediction of spontaneous preterm delivery before 34 weeks based on maternal characteristics and obstetric history

	Univariate			Multivariate		
Independent variable	OR	95% CI	*p*	OR	95% CI	*p*
Age (year)	1.009	0.991–1.028	0.320	1.025	1.005–1.045	0.012
Weight (kg)	1.004	0.997–1.011	0.260	—	—	—
Height (cm)	0.977	0.962–0.992	0.003	0.981	0.966–0.997	0.022
Racial origin			<0.0001			<0.0001
Caucasian (reference)	1			1		
African	1.778	1.401–2.257	<0.0001	1.803	1.404–2.315	<0.0001
South Asian	1.757	1.139–2.709	0.011	1.740	1.112–2.724	0.015
East Asian	1.180	0.533–2.514	0.669	1.183	0.551–2.542	0.666
Mixed	0.688	0.305–1.553	0.369	0.670	0.296–1.517	0.337
Smoking	1.577	1.143–2.174	0.005	1.763	1.262–2.462	0.001
Assisted conception	1.722	1.114–2.661	0.014	1.708	1.092–2.671	0.019
History of alcohol abuse	0.563	0.140–2.268	0.419	—	—	—
History of substance abuse	0.853	0.211–3.447	0.824	—	—	—
Obstetric history			<0.0001			<0.0001
Nulliparous—no pregnancy (reference) ($n = 10{,}748$)	1			1		
Nulliparous—fetal loss at <16 weeks, ($n = 5162$)	1.340	0.987–1.821	0.061	1.270	0.932–1.729	0.130
Nulliparous—miscarriage at 16–23 weeks, ($n = 126$)	8.655	4.412–16.976	<0.0001	7.214	3.647–14.270	<0.0001
Parous preterm delivery 24–27 weeks, ($n = 182$)	7.087	3.828–13.120	<0.0001	5.665	3.032–10.586	<0.0001
Parous preterm delivery 28–30 weeks, ($n = 132$)	5.622	2.565–12.235	<0.0001	4.496	2.030–9.956	<0.0001
Parous preterm delivery 31–33 weeks, ($n = 159$)	3.937	1.703–9.100	0.002	3.133	1.340–7.323	0.008
Parous preterm delivery 34–36 weeks, ($n = 798$)	2.980	1.887–4.704	<0.0001	2.478	1.555–3.949	<0.0001
Parous term delivery >37 weeks ($n = 15\,870$)	0.752	0.578–0.979	0.034	0.661	0.502–0.871	0.003
Parous iatrogenic preterm delivery, ($n = 193$)	1.585	0.499–5.039	0.435	1.362	0.427–4.347	0.601

OR, odds ratio; CI, confidence interval.

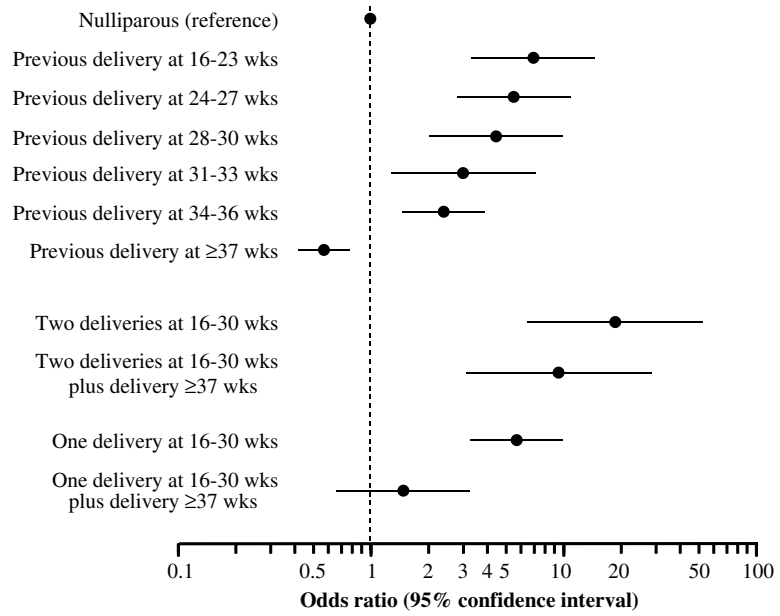

Figure 1—Odds ratios and 95% confidence interval (CI) for spontaneous delivery before 34 weeks according to previous obstetric history

Performance of screening by maternal characteristics and obstetric history

The shrinkage coefficient for the models in Tables 1 and 2 were 0.90 and 0.91, respectively, and all parameters in the model were adjusted accordingly. In each patient, the risk for spontaneous early preterm delivery was calculated using the model in Table 2. The estimated detection rate of preterm delivery at fixed FPR of 10% was 27.5% (AUROC 0.668, 95% CI 0.639–0.698). In the nulliparous women with no previous pregnancies or with fetal losses at <16 weeks the detection rate was 19.5% (AUROC 0.607, 95% CI 0.566–0.649). In women with previous pregnancies at or beyond 16 weeks the detection rate with the model in Table 2

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Table 3—Logistic regression analysis for the prediction of spontaneous preterm delivery before 34 weeks based on maternal characteristics and obstetric history subdivided according to number of previous preterm deliveries

	Univariate			Multivariate		
Independent variable	OR	95% CI	*p*	OR	95% CI	*p*
Age (year)	1.009	0.991–1.028	0.320	1.027	1.008–1.047	0.006
Weight (kg)	1.004	0.997–1.011	0.260	—	—	—
Height (cm)	0.977	0.962–0.992	0.003	0.981	0.966–0.997	0.022
Race origin			<0.0001			<0.0001
Caucasian (reference)	1			1		
African	1.778	1.401–2.257	<0.0001	1.765	1.372–2.272	<0.0001
South Asian	1.757	1.139–2.709	0.011	1.741	1.112–2.726	0.015
East Asian	1.180	0.533–2.514	0.669	1.161	0.540–2.496	0.701
Mixed	0.688	0.305–1.553	0.369	0.679	0.300–1.539	0.354
Smoking	1.577	1.143–2.174	0.005	1.813	1.297–2.534	<0.0001
Assisted conception	1.722	1.114–2.661	0.014	1.713	1.095–2.679	0.018
History of alcohol abuse	0.563	0.140–2.268	0.419	—	—	—
History of substance abuse	0.853	0.211–3.447	0.824	—	—	—
Obstetric history			<0.0001			<0.0001
No pregnancy at or beyond 16 weeks ($n = 16\,103$)	1			1		
Delivery at 16–30 weeks—one event ($n = 263$)	6.611	4.005–10.910	<0.0001	5.848	3.524–9.704	<0.0001
Delivery at 16–30 weeks—two events ($n = 24$)	23.678	8.744–64.120	<0.0001	18.725	6.789–51.748	<0.0001
Delivery at 16–30 weeks—one event plus 31–36 weeks ($n = 38$)	10.586	3.717–30.146	<0.0001	7.327	2.536–21.167	<0.0001
Delivery at 16–30 weeks—one event plus ≥37 weeks ($n = 322$)	1.999	0.932–4.290	0.075	1.548	0.715–3.349	0.267
Delivery at 16–30 weeks—two events plus ≥37 weeks ($n = 30$)	13.843	4.781–40.077	<0.0001	9.749	3.316–28.662	<0.0001
Delivery at 31–36 weeks ($n = 531$)	2.616	1.533–4.463	<0.0001	2.331	1.361–3.993	0.002
Delivery at 31–36 weeks plus ≥37 weeks ($n = 388$)	2.380	1.249–4.538	0.008	1.872	0.971–3.609	0.061
Delivery at ≥37 weeks ($n = 15\,671$)	0.654	0.516–0.828	<0.0001	0.583	0.456–0.747	<0.0001

OR, odds ratio; CI, confidence interval

was 35.8% (AUROC 0.706, 95% CI 0.663–0.749) and with the model in Table 3 was 38.0% (AUROC 0.712, 95% CI 0.669–0.756).

Uterine artery Doppler and biochemical markers

In the spontaneous early preterm delivery group, compared with those delivering at or after 34 weeks the median PAPP-A MoM was reduced but uterine artery PI, free β-hCG, PlGF, PP13, ADAM12, inhibin-A and activin-A were not significantly different (Table 4). In the early preterm delivery group and those delivering at or after 34 weeks, the median and interquartile range (IQR) PAPP-A MoM values in the women with no previous pregnancies at or beyond 16 weeks were 0.96 (0.63–1.37) and 1.02 (0.71–1.45), respectively, and the values in the women with previous pregnancies at or beyond 16 weeks were 0.95 (0.65–1.39) and 1.01 (0.69–1.43), respectively.

Logistic regression analysis demonstrated that in the prediction of spontaneous early preterm delivery the detection rate achieved by maternal characteristics and obstetric history was not significantly improved by addition of PAPP-A MoM (AUROC 0.668, 95% CI 0.639–0.698 vs 0.673, 95% CI 0.644–0.702; $p = 0.824$). This was also true in the subgroups of women with no previous pregnancies at or beyond 16 weeks (AUROC 0.607, 95% CI 0.566–0.649 vs 0.612, 95% CI 0.570–0.655; $p = 0.670$) and in those with previous pregnancies at or beyond 16 weeks (AUROC 0.706, 95% CI 0.663–0.749 vs 0.714, 95% CI 0.672–0.755; $p = 0.338$).

DISCUSSION

This study has established an algorithm for the calculation of patient-specific risk of spontaneous early preterm delivery by maternal characteristics and obstetric history and demonstrated that the prediction of preterm delivery is not improved by assessment of placental perfusion and function at 11–13 weeks.

The rate of spontaneous preterm delivery before 34 weeks in a heterogeneous inner city population was 1% and in half of the cases there was spontaneous onset of labor and in the other half there was preterm prelabor rupture of membranes. These rates are similar to those in our previous multicenter study of about 60 000 singleton pregnancies involving hospitals in and around London (Celik *et al*., 2008).

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Table 4—Median and interquartile range (IQR) of uterine artery pulsatility index (PI), pregnancy-associated plasma protein-A (PAPP-A), free β-human chorionic gonadotrophin (β-hCG), PlGF, placental protein 13, a disintegrin and metalloprotease 12 (ADAM12), inhibin-A and activin-A in pregnancies with spontaneous preterm delivery before 34 weeks and those delivering at or after 34 weeks

	Delivery ≥34 weeks		Early preterm	
Marker	*n*	MoM	*n*	MoM
Uterine artery pulsatility index, median (IQR)	21 252	1.02 (0.84–1.22)	257	1.07 (0.83–1.26)
Pregnancy-associated plasma protein, median (IQR)	33 017	1.02 (0.70–1.44)	353	0.95 (0.64–1.39)*
Free β-human chorionic gonadotrophin, median (IQR)	33 017	0.97 (0.66–1.47)	353	0.97 (0.63–1.45)
PlGF, median (IQR)	2366	0.96 (0.75–1.25)	60	1.12 (0.76–1.49)
Placental protein 13, median (IQR)	1322	1.01 (0.76–1.34)	63	0.90 (0.71–1.20)
ADAM12, median (IQR)	1049	0.98 (0.78–1.20)	58	1.03 (0.79–1.32)
Inhibin-A, median (IQR)	475	1.03 (0.76–1.44)	28	1.01 (0.83–1.33)
Activin-A, median (IQR)	475	1.06 (0.82–1.41)	28	0.96 (0.70–1.13)

MoM, multiple of the median.
Comparisons between the preterm and the unaffected groups were by Mann–Whitney *U* test.
* significance level $p < 0.05$.

The risk for spontaneous early preterm delivery increases with maternal age and decreases with height, it is higher in women of African and South Asian racial origin than Caucasians, in cigarette smokers and in those conceiving after the use of ovulation induction drugs. In a Caucasian nulliparous woman, 164 cm in height, who does not smoke and conceived spontaneously, the estimated risk for early delivery increases linearly from 0.6% at the age of 20 to 1.2% at 45 and the respective values for a woman of the same characteristics but of African racial origin are 1.1 and 2.1%.

Our findings on the association between maternal characteristics and preterm delivery are compatible with the results of previous studies. A population-based cohort study of 173 715 singleton pregnancies in Sweden reported that the incidence of delivery before 32 weeks increased from about 1% for women aged 20–24 to 2.4% at 40 and above (Cnattingius *et al.*, 1992). National statistics in the United States demonstrate that the risk of preterm delivery in women of African racial origin is 1.6 times higher than in Caucasians (Mathews and MacDorman, 2008). A population-based study of 585 291 singleton pregnancies from North London, UK, reported that after correcting for other confounders, the risk of spontaneous delivery before 37 weeks was higher by 1.6 and 1.4 times for women of African and South Asian racial origin, respectively, compared with Caucasians (Balchin and Steer, 2007). Racial disparities in preterm delivery have been attributed to genetic and environmental factors, including access to and quality of health care (Bryant *et al.*, 2010). However, in our study racial differences in outcome certainly persisted despite all women having the same quality of care within the National Heath Service and attended for prenatal care from early in pregnancy.

The risk of preterm delivery was inversely related to maternal height and increased from about 0.6% for a woman of 180 cm in height to 1.3% for one of 140 cm. Such an association was also reported in a population-based study of 791 532 singleton pregnancies and the increased risk in women with short stature was attributed to small uterine size, which may lead to membrane stretching, cervical shortening or other biomechanical factors that increase the likelihood of preterm delivery (Zhang *et al.*, 2007).

The risk of preterm delivery was higher in smokers than in non-smokers. A meta-analysis of 20 prospective studies reported that the risk of preterm delivery in smokers was increased by a factor of 1.3 (Shah and Bracken, 2000). A population-based cohort study of 1 219 159 singleton pregnancies reported that in smokers the risk of both spontaneous and iatrogenic delivery before 37 weeks was increased (Aliyu *et al.*, 2010). It has been suggested that cigarette smoke components may increase the risk of preterm pre-labor membrane rupture through impairment of immune function and promotion of inflammatory mechanisms (French and McGregor, 1996). As for the association between preterm delivery and the use of ovulation induction drugs, some studies suggest a method-related cause and others that infertility rather than its treatment is the cause because infertile women being older are more likely to suffer from chronic medical conditions (Filicori *et al.*, 2005; Wang *et al.*, 2005; Blickstein, 2006).

In nulliparous women with no previous pregnancies or with fetal losses at <16 weeks, screening using an algorithm combining maternal racial origin, age, height, smoking status and method of conception could detect about 20% of spontaneous early preterm deliveries at the FPR of 10%. In women with previous pregnancies at or beyond 16 weeks, the detection rate was doubled by incorporating obstetric history in the algorithm of maternal characteristics. We recorded prospectively detailed obstetric history and demonstrated that in women with previous pregnancies at or beyond 16 weeks the risk of preterm delivery in their current pregnancy was substantially influenced by the outcome of previous pregnancies. We found that the risk of spontaneous delivery before 34 weeks was inversely related to the gestation at previous spontaneous delivery decreasing from about 7% if the gestation was 16–24 weeks to 3% if 31–33 weeks and 0.6% if all deliveries were at term. In addition, the risk was affected by the number of previous spontaneous deliveries at 16–30 weeks and it increased from about

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6–19% if there were two rather than one such delivery. In women with previous preterm deliveries, there was a protective effect against recurrennce if they also had a delivery at term and for women with one or two deliveries at 16–30 weeks the risk of recurrence decreased from about 6 to 1.5% and from 19 to 10%, respectively.

A previous study of 8209 singleton pregnancies reported that the overall incidence of spontaneous delivery before 37 weeks was 3% and this was increased to 37, 63 and 100% if there were one, two or three previous deliveries at 28–37 weeks (Keirse *et al*., 1978). A study of 1711 multiparous women with singleton pregnancies with an overall 2% rate of spontaneous delivery before 32 weeks reported that the risk of such delivery was inversely related to the gestation of the previous earliest delivery decreasing from about 10% if the gestation was 23–27 weeks to 5% if 28–34 weeks, 4% if 32–36 weeks and 0.9% if at term (Mercer *et al*., 1999). A population-based, retrospective cohort study of 154 809 women with two consecutive singleton live births reported that the rate of spontaneous delivery before 35 weeks in the second pregnancy was about 3% and in those with a previous spontaneous delivery before 35 weeks the risk of recurrence was 13% (Ananth *et al*., 2006). A population-based, retrospective cohort study of 19 025 women with three consecutive singleton live births reported that the rate of delivery before 37 weeks in the third pregnancy was about 7% and in those with two, one or no previous preterm deliveries was 42, 17 and 5%, respectively (McManemy *et al*., 2007). Within the group with two previous preterm deliveries, the risk of recurrence was inversely related to the gestation of these preterm deliveries decreasing from 57% if the gestation was 21–31 weeks to 38% if 32–36 weeks (McManemy *et al*., 2007).

In the prediction of spontaneous early preterm delivery, we investigated the potential value of uterine artery PI and a series of biomarkers involved in placentation or in the cascade of events following impaired placentation. There is extensive evidence that altered levels of these markers are detectable at 11–13 weeks in pregnancies that subsequently develop pre-eclampsia (Akolekar *et al*., 2011). As many pregnancies with severe early-onset pre-eclampsia have iatrogenic preterm delivery failure, to distinguish between iatrogenic and spontaneous preterm delivery could lead to the erroneous conclusion that the markers are useful in the prediction of the condition irrespective of cause. Histological and Doppler studies in the second and third trimesters of pregnancies demonstrated that spontaneous preterm delivery may be associated with impaired placentation and placental ischemia (Arias *et al*., 1993, 1997; Strigini *et al*., 1995; Germain *et al*., 1999; Kim *et al*., 2002, 2003; Agarwal *et al*., 2004). A screening study involving the measurement of uterine artery PI at 22–24 weeks in 33 629 women with singleton pregnancies reported that although the PI was significantly increased in the 237 with spontaneous delivery before 33 weeks, multiple regression analysis demonstrated that the prediction of preterm delivery provided by maternal demographic characteristics and previous obstetric history was not significantly improved by the Doppler findings (Fonseca *et al*., 2006). A previous study investigating uterine artery impedance to flow at 11–13 weeks reported no significant differences between 19 pregnancies that subsequently delivered spontaneously before 34 weeks and 2417 pregnancies that delivered at term (Soares *et al*., 2007).

We found a small decrease in serum PAPP-A at 11–13 weeks in pregnancies that subsequently deliver spontaneously before 34 weeks but no significant differences in the levels of serum free β-hCG, PLGF, PP13, ADAM12, activin-A or inhibin-A. These results are compatible with findings in previous studies investigating maternal levels of these biomarkers at 11–13 weeks in the prediction of preterm delivery (Morssink *et al*., 1998; Ong *et al*., 2000; Smith *et al*., 2002, 2007; Tul *et al*., 2003; Dugoff *et al*., 2004; Krantz *et al*., 2004; Spencer *et al*., 2005, 2008; Cowans *et al*., 2007, 2008; She *et al*., 2007; Poon *et al*., 2008, 2009; Lain *et al*., 2009; Huang *et al*., 2010). However, one study of 46 women with subsequent spontaneous delivery before 37 weeks reported significantly increased serum PP13 at 9–12 weeks (Chafetz *et al*., 2007). A study examining serum activin-A in asymptomatic women at 30 weeks reported higher values in those who subsequently delivered before 37 weeks (1.27 MoM) compared with those delivering at term (Farina *et al*., 2006). A study of 33 145 pregnancies undergoing screening for trisomy 21 by the quadruple test at 15–18 weeks reported that high serum inhibin-A (>2.0 MoM) was associated with a 2.4-fold increased risk for delivery at or before 32 weeks (Dugoff *et al*., 2005). Another study reported elevated serum inhibin-A at 11–13 weeks (1.3 MoM) in 17 pregnancies that subsequently delivered before 34 weeks but the study did not specify if the deliveries were spontaneous or iatrogenic (Tul *et al*., 2003).

Screening at 11–13 weeks by maternal characteristics and obstetric history can identify, at an FPR of 10%, about 20% of spontaneous early preterm deliveries in nulliparous women and 38% in women with previous pregnancies at or after 16 weeks. Despite the overall low performance of such screening, an algorithm combining maternal characteristics and obstetric history can provide patient-specific risks which can be the basis of individualization of subsequent prenatal care. This is likely to constitute an improvement over the traditional approach of essentially classifying patients into high and low risk based on whether they had a previous preterm delivery or not. Future studies will define whether the overall performance of screening can be improved by combining maternal characteristics and obstetric history with the measurement of endocervical length at 11–13 weeks, because, unlike the biophysical and biochemical parameters investigated in this study, preliminary data suggest that this measurement is significantly reduced in pregnancies that will subsequently deliver preterm (Greco *et al*., 2011). This approach of combining maternal characteristics with biophysical and biochemical markers at 11–13 weeks can be evaluated in prospective studies to identify pregnancies at high risk of adverse pregnancy

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outcome, including aneuploidies, preterm delivery, pre-eclampsia, miscarriage, stillbirth, fetal growth restriction and macrosomia.

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