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Combined Screening for Preeclampsia and Small for Gestational Age at 11–13 Weeks

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Key Words
Birthweight percentiles · First-trimester screening · Preeclampsia · Small for gestational age · Pyramid of antenatal care

Abstract
Objective: To combine a specific algorithm for small for gestational age (SGA) without preeclampsia (PE) and another algorithm for PE in the prediction of SGA and PE. ***Methods:*** This was a screening study of singleton pregnancies at 11–13 weeks including 1,426 (2.3%) that subsequently developed PE, 3,168 (5.1%) that delivered SGA neonates and 57,458 that were unaffected by PE and SGA. We developed a prediction algorithm for SGA requiring delivery before 37 weeks' gestation (preterm-SGA) from maternal characteristics, uterine artery pulsatility index, mean arterial pressure, serum pregnancy-associated plasma protein-A and placental growth factor multiple of the median values. We then examined the performance of this algorithm individually and in combination with a previously reported algorithm for early-PE in the prediction of SGA and PE. ***Results:*** When screen positivity was defined by risk cutoff of 1:200 using the algorithm for early-PE and the risk cutoff of 1:150 using the algorithm for preterm-SGA, the false positive rate was 10.9% and the detection rates of early-PE, late-PE, preterm-SGA and term-SGA were 95.3, 45.6, 55.5 and 44.3%, respectively. ***Conclusions:*** Effective first-trimester screening for early-PE and preterm-SGA can be provided by the combined use of the specific algorithms.

Introduction

Preeclampsia (PE) and delivery of small for gestational age (SGA) neonates can be predicted at 11–13 weeks' gestation by a combination of maternal demographic characteristics, including medical and obstetric history, uterine artery pulsatility index (PI), mean arterial pressure (MAP) and maternal serum biochemical markers [1, 2]. The importance of first-trimester screening for these conditions is that their prevalence may be decreased by therapeutic interventions, such as the prophylactic use of low-dose aspirin [3, 4].

In previous studies we developed individual risk algorithms for PE and SGA without PE and reported on the performance of such algorithms for the condition under

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investigation [1, 2]. The two conditions share common pathophysiological mechanisms, as well as biophysical and biochemical markers, and it is therefore likely that the algorithm for PE would detect some of the cases of SGA and vice versa. We have recently developed a new approach to early screening for PE, based on a survival time model and the combination of maternal characteristics, uterine artery PI, MAP, serum pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) [5, 6]. Although several other biochemical markers have been proposed, PAPP-A and PlGF are the only two that have been investigated extensively in screening for PE, they have both been shown to be useful in screening for aneuploidies and they are now part of the platform of automated machines that provide reproducible results within 30–40 min of sampling [7, 8].

The aims of this study are, firstly, to derive an updated specific algorithm for SGA without PE by a combination of maternal characteristics, uterine artery PI, MAP, PAPP-A and PlGF, and secondly, to examine the performance of this SGA algorithm and the recently reported PE algorithm, individually and in combination, in the prediction of SGA and PE.

Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine first hospital visit in pregnancy at King's College Hospital, University College London Hospital and Medway Maritime Hospital between March 2006 and September 2010. In this visit, which is held at 11–13 weeks' gestation, we recorded maternal characteristics and performed combined screening for aneuploidies by the measurement of fetal crown-rump length (CRL) and nuchal translucency thickness and maternal serum free β-human chorionic gonadotropin (β-hCG) and PAPP-A [9, 10]. In women who agreed to participate in the study, we also measured the maternal MAP by automated devices [11], used transabdominal color Doppler ultrasound to visualize the left and right uterine artery, measured the PI in each vessel and calculated the mean PI [12] and measured maternal serum concentration of PlGF (DELFIA® Xpress system; PerkinElmer Life and Analytical Sciences, Waltham, Mass., USA). Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the ethics committee of the individual hospital.

The inclusion criteria for this study were singleton pregnancy undergoing first-trimester combined screening for aneuploidy and subsequently delivering a phenotypically normal live birth or stillbirth at or after 24 weeks' gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities and those ending in termination, miscarriage or fetal death before 24 weeks. The patients were subdivided into unaffected by PE or SGA (normal group), PE with or without SGA (PE group) and SGA without PE (SGA group).

Maternal History and Characteristics

Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, Afro-Caribbean, 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), history of chronic hypertension (yes or no), history of type 1 or 2 diabetes mellitus (yes or no), history of systemic lupus erythematosus or antiphospolipid syndrome (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), previous pregnancy with PE (yes or no) and previous history of SGA (yes or no). The questionnaire was then reviewed by a doctor together with the patient and the maternal weight (kg) and height (cm) were measured.

Outcome Measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women.

The definition of SGA was birthweight below the 5th percentile for gestational age of a normal range derived from our population [13]. The condition was classified as preterm-SGA if delivery occurred before 37 weeks' gestation.

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [14]. The condition was classified as early-PE if delivery occurred before 34 weeks' gestation.

Statistical Analysis

Comparisons between outcome groups were by the χ^2 or Fisher exact test for categorical variables and by the Mann-Whitney U test for continuous variables, both with post-hoc Bonferroni correction (critical statistical significance $p < 0.025$).

In each patient the measured uterine artery PI, MAP, PAPP-A and PlGF 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 [6–8].

The following steps were used to develop a specific algorithm for the calculation of patient-specific risk for preterm-SGA. First, in each patient in the preterm-SGA and normal groups the a priori risk for preterm-SGA was calculated using multivariate logistic regression analysis with backward stepwise elimination to determine which of the factors among maternal characteristics and obstetric history had a significant contribution in predicting preterm-SGA. Second, Gaussian distributions of markers in preterm-SGA and normal pregnancies were fitted. Third, the unpaired t test was used to compare the mean $\log_{10}$-value of each marker between the two outcome groups. Fourth, regression analysis was used to determine the significance of association between the markers in the two outcome groups. Fifth, given that uterine artery PI, MAP, PAPP-A and PlGF were not measured in every woman, the means and standard deviations of the Gaussian distributions in the preterm-SGA and normal groups were used to simulate the values for these markers in the screened population. Sixth, likelihood ratios for preterm-SGA were calculated from the fitted bivariate Gaussian distributions for each marker and these were combined with the a priori risk to produce an a posteriori risk. Seventh, the performance of screening for pre-

Table 1. Maternal characteristics in the study population

Characteristic	Normal (n = 57,458)	PE (n = 1,426)	SGA without PE (n = 3,168)
Maternal age, years	32.0 (27.7–35.6)	31.6 (27.0–36.4)	31.1 (25.7–35.4)*
Maternal weight, kg	65.5 (59.0–75.0)	71.6 (62.4–85.0)*	61.0 (55.0–70.0)*
Fetal crown-rump length, mm	63.4 (58.4–68.9)	62.6 (58.1–68.4)	62.3 (57.3–67.9)*
Racial origin			
Caucasian	42,514 (74.0)	751 (52.7)*	1,831 (57.8)*
Afro-Caribbean	9,268 (16.1)	525 (36.8)*	771 (24.3)*
South Asian	2,757 (4.8)	87 (6.1)*	325 (10.3)*
East Asian	1,462 (2.6)	27 (1.9)	120 (3.8)*
Mixed	1,457 (2.5)	36 (2.5)	121 (3.8)*
Parity			
Nulliparous	28,231 (49.1)	877 (61.5)*	1,992 (62.9)*
Parous with no previous PE or SGA	25,735 (44.8)	307 (21.5)*	800 (34.2)*
Parous with previous PE	1,618 (2.8)	203 (14.2)*	93 (2.9)
Parous with previous SGA	2,072 (3.6)	86 (6.0)*	316 (10.0)*
Cigarette smoker	4,498 (7.8)	86 (6.0)*	537 (17.0)*
Family history of PE	2,506 (4.4)	123 (8.6)*	162 (5.1)
Conception			
Spontaneous	55,358 (96.3)	1,347 (94.5)*	3,022 (95.4)*
Assisted	2,100 (3.7)	79 (5.5)*	146 (4.6)*
History of chronic hypertension	545 (0.9)	140 (9.8)*	53 (1.7)*
History of type 1 diabetes mellitus	237 (0.4)	14 (1.0)*	3 (0.1)*
History of type 2 diabetes mellitus	146 (0.3)	14 (1.0)*	16 (0.5)*
History of SLE or APS	117 (0.2)	8 (0.6)*	10 (0.3)

Figures are medians (interquartile range) or n (%). SLE or APS = Systemic lupus erythematosus or antiphospholipid syndrome. Comparisons between outcome groups were by the χ^2 or Fisher exact test for categorical variables and by the Mann-Whitney U test for continuous variables, with post hoc Bonferroni correction (* $p < 0.025$).

Table 2. Fitted regression model for the prediction of preterm-SGA

Independent variable	Coefficient	SE	OR	95% CI	p value
Intercept	–5.6446	0.0977			
Age, years – 30	0.0252	0.0084	1.026	1.009–1.042	0.003
(Age, years – 30)^2	0.0026	0.0010	1.003	1.001–1.005	0.011
Weight, kg – 69	–0.0117	0.0044	0.988	0.980–0.997	0.007
(Weight, kg – 69)^2	0.0004	0.0001	1.000	1.000–1.001	0.0002
Height, cm – 164	–0.0277	0.0082	0.973	0.957–0.988	0.001
Racial origin					
Afro-Caribbean	0.8750	0.1240	2.399	1.881–3.059	<0.0001
South Asian	0.5697	0.2068	1.768	1.179–2.651	0.006
Previous history					
Parous with SGA	0.7401	0.1615	2.096	1.527–2.877	<0.0001
Parous with no SGA	–0.6965	0.1171	0.498	0.396–0.627	<0.0001
Conception by ovulation drugs	0.9247	0.2764	2.521	1.467–4.334	0.001
Smoking	1.2578	0.1271	3.518	2.742–4.513	<0.0001
Chronic hypertension	1.4432	0.2481	4.234	2.604–6.886	<0.0001
Type 2 diabetes mellitus	1.3275	0.4226	3.772	1.648–8.634	0.002
SLE or APS	1.5778	0.7366	4.844	1.143–20.422	0.032

SLE = Systemic lupus erythematosus; APS = antiphospholipid syndrome; SE = standard error; OR = odds ratio; CI = confidence interval.

Table 3. Mean and SD of log_{10}-MoM values for markers in normal and preterm-SGA groups

	Normal			Preterm-SGA			p value
	n	mean	SD	n	mean	SD	
Uterine artery PI	44,640	–0.0010805	0.1242215	334	0.076690	0.142728	<0.0001
MAP	34,236	0.0001946	0.0386549	231	0.007551	0.041265	0.011
PAPP-A	57,458	0.0084481	0.2368016	397	–0.179599	0.294323	<0.0001
PlGF	15,695	0.0011573	0.1764965	134	–0.094828	0.261815	<0.0001

SD = Standard deviation. Comparisons were made by unpaired t test.

Table 4. Covariance matrix between log_{10}-MoM marker values in the normal and preterm-SGA groups

	PAPP-A	Uterine artery PI	MAP	PlGF
Normal				
PAPP-A	0.056075	–0.0046174	–0.000063776	0.012577
Uterine artery PI	–0.0046174	0.015431	–0.00034804	–0.0029002
MAP	–0.000063776	–0.00034804	0.0014942	–0.00023628
PlGF	0.012577	–0.0029002	–0.00023628	0.031151
Preterm-SGA				
PAPP-A	0.086626	–0.0080457	0.00020759	0.027947
Uterine artery PI	–0.0080457	0.020371	0.00020513	–0.0063989
MAP	0.00020759	0.00020513	0.00170276	–0.0012196
PlGF	0.027947	–0.0063989	–0.0012196	0.068547

term-SGA by maternal characteristics, uterine artery PI, MAP, PAPP-A and PlGF, individually and in various combinations was determined by receiver operating characteristic (ROC) curve analysis.

The algorithms for preterm-SGA and PE [6] were applied to the whole population (normal, PE and SGA) and the proportions with risks above a given risk threshold were used to calculate the false positive rate (FPR) and detection rates of preterm-SGA, term-SGA, early-PE and late-PE (requiring delivery at or after 34 weeks).

The statistical software package SPSS 20.0 (SPSS, Inc., Chicago, Ill., USA) and MedCalc (MedCalc Software, Mariakerke, Belgium) were used for all data analyses.

Results

Characteristics of the Study Population

First-trimester combined screening for aneuploidies was carried out in 65,960 singleton pregnancies. We excluded 3,908 cases because they had missing outcome data (n = 2,133), the pregnancies resulted in miscarriage, termination or the birth of babies with major defects (n = 1,775).

In the remaining 62,052 cases there were 57,458 that were unaffected by PE or SGA (normal group), 1,426 (2.3%) that developed PE and 3,168 (5.1%) that were SGA in the absence of PE. In the SGA group there were 397 (12.5%) with preterm-SGA and 2,771 with term-SGA.

Serum PAPP-A was available in all cases. Uterine artery PI was available in 48,500 of the 62,052 pregnancies, including 1,245 (2.6%) that developed PE and 2,615 (5.4%) that delivered SGA neonates, MAP was available in 37,141 of the 62,052 pregnancies, including 979 (2.6%) that developed PE and 1,926 (5.2%) that delivered SGA neonates, and serum PlGF was available in 15,001 of the 62,052 pregnancies, including 385 (2.6%) that developed PE and 749 (5.0%) that delivered SGA neonates.

The maternal characteristics and history in the outcome groups are presented in table 1. In the PE group, compared to the normal group, there was a higher median maternal weight and prevalence of Afro-Caribbean and South Asian racial origin, women who had assisted conception, family and personal history of PE, previous pregnancies with SGA neonates, chronic hypertension, diabetes mellitus and systemic lupus erythematosus or

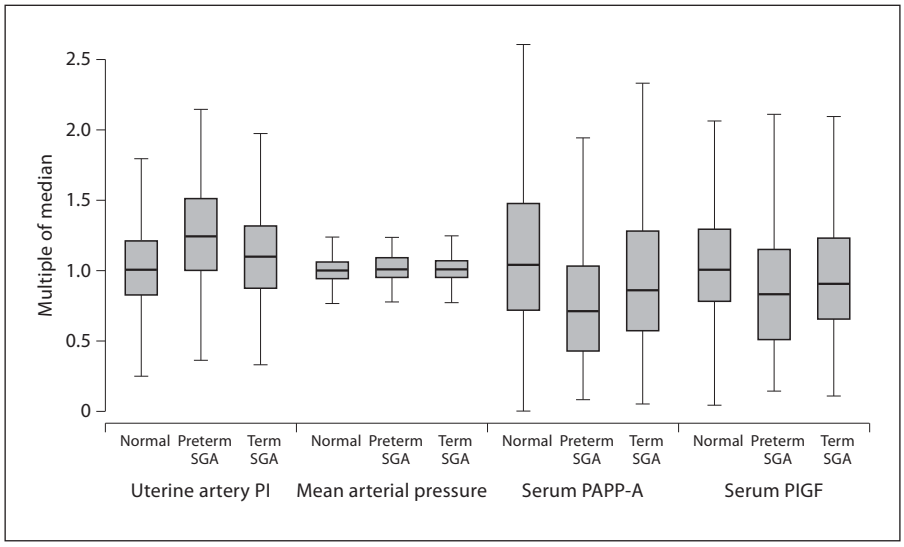

Fig. 1. Box-and-whisker plots of multiple of median values of uterine artery PI, MAP, PAPP-A and PlGF in the preterm-SGA, term-SGA and normal groups.

antiphospholipid syndrome and a lower prevalence of cigarette smokers. In the SGA group, compared to the normal group, there was a lower median maternal age and weight and fetal CRL and a higher prevalence of racial origins other than Caucasian, cigarette smokers, women who had assisted conception, previous pregnancies with SGA neonates, chronic hypertension, type 2 diabetes mellitus and a lower prevalence of type 1 diabetes mellitus.

Iatrogenic delivery was carried out in 63.2% of the preterm-SGA group compared to 28.9% in the term-SGA group ($p < 0.0001$).

Algorithm for Preterm-SGA

Regression coefficients and adjusted odds ratios of each of the maternal factors in the prediction algorithm for preterm-SGA, derived from a multivariate logistic regression analysis, is presented in table 2. The likelihood of preterm-SGA increased with maternal age and decreased with weight and height, the risk was higher in women of Afro-Caribbean and South Asian racial origin compared to Caucasian women, in parous women with prior SGA, in cigarette smokers, in women with a history of chronic hypertension, type 2 diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome, and in those who conceived with ovulation drugs.

In SGA pregnancies there was an inverse correlation between $\log_{10}$-MoM values of uterine artery PI ($r = -0.103$, $p < 0.0001$) and MAP ($r = -0.045$, $p = 0.048$) with gestational age at delivery. Similarly, there was a significant correlation between $\log_{10}$-MoM values of PAPP-A ($r = 0.125$, $p < 0.0001$) and PlGF ($r = 0.107$, $p < 0.0001$) with gestational age at delivery in SGA pregnancies.

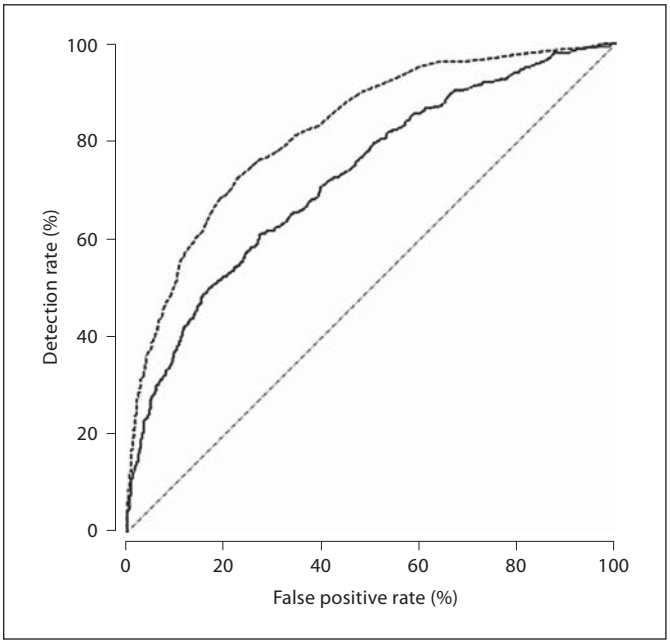

Fig. 2. ROC curves of maternal factors only (——) and a combination of maternal factors with biophysical and biochemical markers (– – –) in the prediction of preterm-SGA neonates.

In the preterm-SGA group, compared to the normal group, mean $\log_{10}$-MoM of uterine artery PI and MAP were significantly higher, and mean $\log_{10}$-MoM of PAPP-A and PlGF were significantly lower (table 3). Box-and-

Table 5. Performance of screening for preterm-SGA neonates by maternal factors and various combinations of maternal factors with biophysical and biochemical markers

	Area under ROC curve (95% CI)	
Maternal factors	0.727 (0.724–0.731)	
Maternal factors plus		
PAPP-A	0.770 (0.766–0.773)	
PlGF	0.777 (0.773–0.780)	
PAPP-A and PlGF	0.801 (0.798–0.804)	
Uterine artery PI	0.758 (0.755–0.762)	
MAP	0.730 (0.727–0.734)	
Uterine artery PI and MAP	0.759 (0.756–0.763)	
Uterine artery PI and PAPP-A	0.796 (0.793–0.799)	
Uterine artery PI and PlGF	0.798 (0.795–0.801)	
MAP and PAPP-A	0.772 (0.768–0.775)	
MAP and PlGF	0.779 (0.776–0.783)	
Uterine artery PI, PAPP-A and PlGF	0.823 (0.819–0.826)	
Uterine artery PI, MAP and PAPP-A	0.796 (0.792–0.799)	
Uterine artery PI, MAP and PlGF	0.799 (0.796–0.802)	
MAP, PAPP-A and PlGF	0.802 (0.799–0.805)	
Maternal factors plus all markers	0.822 (0.819–0.825)	
	Detection rate for fixed FPR (95% CI)	
	5%	10%
Maternal factors	26.1 (21.7–31.6)	37.4 (32.1–43.0)
Maternal factors plus		
PAPP-A	32.4 (27.3–37.8)	44.3 (38.8–50.0)
PlGF	31.5 (26.4–36.9)	43.4 (37.9–49.0)
PAPP-A and PlGF	37.4 (32.7–42.1)	50.0 (44.7–55.3)
Uterine artery PI	32.1 (27.0–37.5)	43.4 (37.9–49.0)
MAP	27.0 (21.2–32.3)	38.7 (33.3–44.3)
Uterine artery PI and MAP	30.3 (25.9–34.7)	44.8 (40.2–49.4)
Uterine artery PI and PAPP-A	36.2 (30.9–41.7)	49.4 (43.7–55.0)
Uterine artery PI and PlGF	33.7 (28.5–39.1)	49.4 (43.7–55.0)
MAP and PAPP-A	33.0 (27.9–38.5)	45.9 (40.3–51.6)
MAP and PlGF	32.1 (27.0–37.5)	43.1 (37.6–48.7)
Uterine artery PI, PAPP-A and PlGF	37.1 (31.8–42.7)	51.6 (45.9–57.2)
Uterine artery PI, MAP and PAPP-A	35.9 (30.6–41.4)	49.4 (43.7–55.0)
Uterine artery PI, MAP and PlGF	33.3 (28.2–38.8)	47.8 (42.2–53.4)
MAP, PAPP-A and PlGF	35.5 (30.3–41.1)	49.7 (44.1–55.3)
Maternal factors plus all markers	38.1 (32.8–43.4)	52.3 (47.3–57.3)

whisker plots of these markers in the preterm-SGA, term-SGA and normal groups are shown in figure 1. The covariance matrices between $\log_{10}$-MoM values of biophysical and biochemical markers in the normal and preterm-SGA groups are shown in table 4.

Performance of Screening for Preterm-SGA

The estimated detection rates at fixed FPR 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 5. The ROC curves for preterm-SGA are illustrated in figure 2.

Combined Screening for Preterm-SGA and Early-PE

Tables 6–8 show the detection rates of early-PE, late-PE, preterm-SGA, and term-SGA for given FPR in screening by the individual risk algorithm for early-PE and preterm-SGA based on maternal characteristics, uterine artery PI and MAP (biophysical testing; table 6), maternal characteristics and serum PAPP-A and PlGF (biochemi-

Table 6. Total FPRs and detection rates of early-PE, late-PE, preterm-SGA, and term-SGA by the combined use of the algorithm for early-PE and the algorithm for preterm-SGA based on maternal characteristics, uterine artery PI and MAP (biophysical testing)

Algorithm for preterm-SGA: FPR and (risk cutoff)	Outcome	Algorithm for early-PE: FPR and (risk cutoff)						
		0%	5% (1:96)	6% (1:116)	7% (1:134)	8% (1:154)	9% (1:175)	10% (1:197)
0%	Normal	–	5.0	6.1	7.0	8.0	9.0	**10.0**
	Early-PE	–	79.9	84.1	86.4	88.3	89.3	**89.7**
	Late-PE	–	27.3	31.4	35.8	40.0	43.8	**48.3**
	Preterm-SGA	–	21.9	23.9	25.8	27.1	29.0	**30.3**
	Term-SGA	–	26.3	28.0	29.2	30.5	32.0	**33.1**
1% (1:66)	Normal	1.0	5.7	6.7	7.6	8.6	9.6	10.5
	Early-PE	16.8	81.3	85.0	87.4	89.3	90.2	90.7
	Late-PE	6.2	28.1	32.1	36.4	40.6	44.2	48.8
	Preterm-SGA	10.3	26.8	28.1	30.0	31.3	33.2	34.2
	Term-SGA	6.2	29.4	31.0	32.2	33.4	34.8	35.8
2% (1:90)	Normal	2.0	6.5	7.5	8.3	9.3	10.2	11.2
	Early-PE	23.4	81.8	85.5	87.9	89.7	90.7	91.1
	Late-PE	9.0	29.0	32.9	37.0	41.0	44.6	49.1
	Preterm-SGA	20.0	32.9	33.5	35.2	36.1	37.7	38.7
	Term-SGA	11.0	32.0	33.4	34.5	35.7	37.0	38.0
3% (1:108)	Normal	3.0	7.3	8.2	9.1	**10.0**	10.9	11.9
	Early-PE	27.1	82.2	86.0	88.3	**90.2**	91.1	91.6
	Late-PE	11.7	29.7	33.6	37.5	**41.5**	45.0	49.5
	Preterm-SGA	22.6	34.8	35.5	37.1	**38.1**	39.7	40.6
	Term-SGA	14.3	33.7	35.0	36.0	**37.1**	38.4	39.3
4% (1:124)	Normal	4.0	8.1	9.0	9.8	10.8	11.6	12.6
	Early-PE	31.8	83.6	87.4	89.3	91.1	92.1	92.5
	Late-PE	14.3	31.0	34.7	38.5	42.5	46.0	50.3
	Preterm-SGA	26.5	38.1	38.4	40.0	41.0	42.3	43.2
	Term-SGA	17.3	35.7	36.9	37.9	39.0	40.2	41.1
5% (1:139)	Normal	5.0	8.9	9.8	10.6	11.5	12.4	13.2
	Early-PE	36.4	83.6	87.4	89.3	91.1	92.1	92.5
	Late-PE	17.7	32.7	36.3	40.0	43.8	47.2	51.2
	Preterm-SGA	30.3	41.3	41.6	43.2	44.2	45.5	46.5
	Term-SGA	20.7	37.6	38.8	39.7	40.8	42.1	42.8
10% (1:199)	Normal	**10.0**	13.1	13.8	14.5	15.3	16.1	16.9
	Early-PE	**57.0**	85.5	88.3	89.7	91.6	92.5	93.0
	Late-PE	**28.1**	39.0	41.7	44.6	47.7	50.7	53.9
	Preterm-SGA	**44.8**	51.3	51.3	52.6	53.5	54.8	55.8
	Term-SGA	**34.7**	46.9	47.9	48.7	49.4	50.4	51.0

Bold values indicate the performance of screening.

cal testing; table 7) and maternal characteristics, uterine artery PI, MAP, PAPP-A and PlGF (combined testing; table 8).

In combined testing by the algorithm for early-PE, at FPR of 10% (risk cutoff of 1:269), the detection rates of early-PE, late-PE, preterm-SGA and term-SGA were 96.3, 51.6, 41.6 and 37.0%, respectively (table 8). In combined testing by the algorithm for preterm-SGA, at FPR of 10% (risk cutoff of 1:224), the detection rates of early-PE, late-PE, preterm-SGA and term-SGA were 59.8, 26.1, 52.3 and 37.9%, respectively (table 8).

When the algorithms for early-PE and preterm-SGA are combined and screen positivity is defined by 8% FPR using the algorithm for early-PE (risk cutoff of 1:214) and

Table 7. Total FPRs and detection rates of early-PE, late-PE, preterm-SGA, and term-SGA by the combined use of the algorithm for early-PE and the algorithm for preterm-SGA based on maternal characteristics, serum PAPP-A and serum placental growth factor (biochemical testing)

Algorithm for preterm-SGA: FPR and (risk cutoff)	Outcome	Algorithm for early-PE: FPR and (risk cutoff)						
		0%	5% (1:101)	6% (1:117)	7% (1:134)	8% (1:150)	9% (1:166)	10% (1:181)
0%	Normal	–	5.0	6.0	7.0	8.0	9.0	**10.0**
	Early-PE	–	60.3	65.9	70.1	72.0	72.9	**74.3**
	Late-PE	–	24.4	27.1	29.7	32.3	35.2	**37.3**
	Preterm-SGA	–	31.6	32.6	34.5	35.8	38.1	**40.3**
	Term-SGA	–	12.4	14.8	17.1	19.0	21.0	**22.5**
1% (1:69)	Normal	1.0	5.7	6.6	7.6	8.6	9.6	10.5
	Early-PE	13.6	62.1	67.3	71.5	73.4	74.3	75.7
	Late-PE	4.9	25.3	27.7	30.4	32.8	35.8	37.9
	Preterm-SGA	16.1	39.0	39.7	41.0	41.9	43.9	45.8
	Term-SGA	5.4	16.0	18.4	20.6	22.4	24.1	25.5
2% (1:95)	Normal	2.0	6.4	7.4	8.3	9.3	10.2	11.2
	Early-PE	20.1	62.6	67.8	72.0	73.8	74.8	76.2
	Late-PE	6.9	25.7	28.0	30.6	33.1	36.1	38.1
	Preterm-SGA	23.2	41.9	42.6	43.9	44.8	46.8	48.7
	Term-SGA	10.3	19.5	21.8	23.9	25.5	27.3	28.6
3% (1:115)	Normal	3.1	7.2	8.2	9.1	**10.0**	10.9	11.9
	Early-PE	26.6	64.5	69.2	73.4	**75.2**	76.2	77.6
	Late-PE	9.7	26.7	28.9	31.5	**33.7**	36.7	38.7
	Preterm-SGA	30.3	45.8	46.1	47.4	**48.4**	50.3	51.9
	Term-SGA	13.8	21.9	24.1	26.1	**27.6**	29.4	30.7
4% (1:132)	Normal	4.0	8.0	8.9	9.8	10.7	11.6	12.5
	Early-PE	30.4	65.9	70.6	74.3	76.2	77.1	78.5
	Late-PE	12.4	27.8	29.7	32.3	34.6	37.5	39.5
	Preterm-SGA	33.9	48.1	48.4	49.7	50.6	52.3	53.9
	Term-SGA	17.2	24.5	26.6	28.5	30.0	31.6	33.0
5% (1:148)	Normal	5.0	8.8	9.7	10.5	11.4	12.3	13.2
	Early-PE	32.2	65.9	70.6	74.3	76.2	77.1	78.5
	Late-PE	14.4	28.6	30.5	33.2	35.3	38.1	40.0
	Preterm-SGA	37.4	50.0	50.3	51.3	52.3	53.9	55.2
	Term-SGA	19.9	26.5	28.4	30.2	31.6	33.2	34.5
10% (1:215)	Normal	**10.0**	12.9	13.7	14.4	15.1	15.9	16.7
	Early-PE	**44.9**	69.2	72.0	75.7	77.1	78.0	79.4
	Late-PE	**23.0**	33.0	34.3	36.2	38.2	40.8	42.6
	Preterm-SGA	**50.0**	57.7	58.1	58.7	59.7	61.0	62.3
	Term-SGA	**31.8**	35.8	37.4	38.8	39.9	41.1	42.3

Bold values indicate the performance of screening.

3% FPR using the algorithm for preterm-SGA (risk cutoff of 1:119), the total FPR was 10% and the detection rates of early-PE, late-PE, preterm-SGA and term-SGA were 95.3, 47.1, 52.6 and 42.1%, respectively (table 8).

Table 9 shows the detection rates of early-PE, late-PE, preterm-SGA, and term-SGA for given risk cutoffs in screening by the individual risk algorithm for early-PE and preterm-SGA based on maternal characteristics, uterine artery PI, MAP, PAPP-A and PlGF (combined testing). When screen positivity is defined by the risk cut-off of 1:200 using the algorithm for early-PE and the risk cutoff of 1:150 using the algorithm for preterm-SGA the

Table 8. Total FPRs and detection rates of early-PE, late-PE, preterm-SGA, and term-SGA by the combined use of the algorithm for early-PE and the algorithm for preterm-SGA based on maternal characteristics, uterine artery PI, MAP, serum PAPP-A and serum placental growth factor (combined testing)

Algorithm for preterm-SGA: FPR and (risk cutoff)	Outcome	Algorithm for early-PE: FPR and (risk cutoff)						
		0%	5% (1:128)	6% (1:157)	7% (1:184)	8% (1:214)	9% (1:241)	10% (1:269)
0%	Normal	–	5.0	6.0	7.0	8.0	9.0	**10.0**
	Early-PE	–	93.4	89.7	93.0	94.9	94.9	**96.3**
	Late-PE	–	30.0	35.4	39.9	45.7	48.6	**51.6**
	Preterm-SGA	–	29.7	33.5	35.2	38.7	40.3	**41.6**
	Term-SGA	–	28.2	30.6	32.2	34.3	35.7	**37.0**
1% (1:71)	Normal	1.0	5.7	6.7	7.6	8.6	9.6	10.6
	Early-PE	18.7	87.9	90.7	93.5	94.9	94.9	96.3
	Late-PE	5.7	30.7	36.1	40.6	46.4	49.3	52.1
	Preterm-SGA	16.5	38.1	41.3	42.6	45.2	46.8	47.4
	Term-SGA	7.1	31.7	33.9	35.4	37.4	38.7	40.0
2% (1:97)	Normal	2.0	6.5	7.4	8.4	9.3	10.3	11.2
	Early-PE	26.2	88.3	91.1	93.5	94.9	94.9	96.3
	Late-PE	7.9	30.9	36.3	40.7	46.5	49.3	52.1
	Preterm-SGA	25.8	43.2	45.8	47.1	49.4	51.0	51.6
	Term-SGA	12.7	34.6	36.7	38.1	39.9	41.1	42.4
3% (1:119)	Normal	3.0	7.3	8.2	9.1	**10.0**	11.0	11.9
	Early-PE	32.2	89.7	92.5	94.9	**95.3**	95.3	96.7
	Late-PE	11.6	32.3	37.5	41.4	**47.1**	49.9	52.6
	Preterm-SGA	31.9	47.4	49.7	51.0	**52.6**	54.2	54.8
	Term-SGA	17.0	37.2	39.2	40.4	**42.1**	43.3	44.5
4% (1:136)	Normal	4.0	8.1	8.9	9.8	10.7	11.7	12.6
	Early-PE	37.4	89.7	92.5	94.9	95.3	95.3	96.7
	Late-PE	14.0	33.3	38.4	42.2	47.8	50.6	53.2
	Preterm-SGA	35.5	49.4	51.6	52.6	53.9	55.5	56.1
	Term-SGA	20.6	39.4	41.2	42.4	43.9	45.0	46.1
5% (1:153)	Normal	5.0	8.9	9.7	10.6	11.5	12.4	13.2
	Early-PE	42.1	89.7	92.5	94.9	95.3	95.3	96.7
	Late-PE	16.9	34.3	39.0	42.6	48.1	50.9	53.5
	Preterm-SGA	38.1	51.3	53.5	54.5	55.8	57.4	58.1
	Term-SGA	23.6	40.9	42.8	43.8	45.2	46.3	47.3
10% (1:224)	Normal	**10.0**	13.0	13.8	14.5	15.3	16.1	16.9
	Early-PE	**59.8**	90.2	93.0	94.9	95.3	95.3	96.7
	Late-PE	**26.1**	39.4	43.5	46.5	51.0	53.5	55.9
	Preterm-SGA	**52.3**	60.0	61.9	62.6	63.5	64.8	65.5
	Term-SGA	**37.9**	49.8	51.3	52.2	53.4	54.3	55.2

Bold values indicate the performance of screening.

total FPR was 10.9% and the detection rates of early-PE, late-PE, preterm-SGA and term-SGA were 95.3, 45.6, 55.5 and 44.3%, respectively.

Table 10 shows the performance of the combined algorithms for early-PE and preterm-SGA in women of Caucasian and Afro-Caribbean racial origin and according to their obstetric history. In women of Afro-Caribbean racial origin, compared to Caucasians, and in nulliparous, compared to parous women, both the FPR and detection rates for PE and SGA are higher.

Table 9. Total FPRs at fixed risk cutoffs and detection rates of early-PE, late-PE, preterm-SGA, and term-SGA by the combined use of the algorithm for early-PE and the algorithm for preterm-SGA based on maternal characteristics, uterine artery PI, MAP, serum PAPP-A and serum placental growth factor (combined testing)

Algorithm for preterm-SGA: FPR at fixed risk cutoffs	Outcome	Algorithm for early-PE: FPR at fixed risk cutoffs						
		0%	1:50	1:100	1:150	1:200	1:250	1:300
0%	Normal	0.0	1.8	3.9	5.8	7.6	9.3	**11.0**
	Early-PE	0.0	73.4	83.6	89.3	94.4	95.3	**97.2**
	Late-PE	0.0	14.4	24.2	34.6	43.2	49.3	**54.9**
	Preterm-SGA	0.0	19.7	27.1	33.2	37.4	40.6	**42.9**
	Term-SGA	0.0	18.9	25.8	30.0	33.4	36.4	**38.4**
1:50	Normal	0.5	2.1	4.2	6.1	7.8	9.6	11.3
	Early-PE	11.7	74.8	84.6	90.2	94.4	95.3	97.2
	Late-PE	2.8	14.9	24.3	34.6	43.2	49.3	54.9
	Preterm-SGA	9.0	24.8	31.6	37.1	41.0	44.2	45.5
	Term-SGA	4.0	21.1	27.9	31.8	35.1	38.0	40.0
1:100	Normal	2.2	3.6	5.5	7.3	9.0	10.7	12.3
	Early-PE	26.6	76.2	85.5	91.1	94.4	95.3	97.2
	Late-PE	8.3	17.0	25.8	35.6	44.0	50.1	55.4
	Preterm-SGA	27.1	38.4	43.2	46.8	50.0	52.6	53.9
	Term-SGA	13.1	27.0	33.0	36.5	39.4	42.0	43.8
1:150	Normal	4.8	6.0	7.8	9.4	**10.9**	12.5	14.0
	Early-PE	40.7	77.6	86.4	92.1	**95.3**	95.8	97.7
	Late-PE	16.3	22.0	29.5	38.3	**45.6**	51.4	56.4
	Preterm-SGA	38.1	46.8	50.6	53.2	**55.5**	57.7	58.7
	Term-SGA	23.0	33.8	39.0	41.9	**44.3**	46.5	48.1
1:200	Normal	8.2	9.1	10.6	12.1	13.5	14.9	16.4
	Early-PE	55.6	79.4	86.9	92.5	95.3	95.8	97.7
	Late-PE	22.9	27.2	33.3	41.0	47.5	53.1	57.7
	Preterm-SGA	48.7	53.9	56.8	59.4	61.0	62.9	63.5
	Term-SGA	32.9	41.0	45.3	47.9	49.9	51.8	53.1
1:250	Normal	**12.1**	12.9	14.1	15.3	16.6	17.9	19.2
	Early-PE	**66.4**	82.7	88.8	93.0	95.8	96.3	97.7
	Late-PE	**29.8**	33.4	38.4	44.6	49.9	54.7	58.9
	Preterm-SGA	**56.8**	60.3	62.3	64.5	65.8	67.4	68.1
	Term-SGA	**42.0**	47.5	50.9	53.3	55.1	56.8	57.9

Bold values indicate the performance of screening.

Discussion

This study has established a risk algorithm for preterm-SGA by a combination of maternal characteristics, uterine artery PI, PAPP-A and PlGF. With such combined screening at 11–13 weeks' gestation the detection rates of preterm-SGA were 38 and 52% at FPRs of 5 and 10%, respectively. A beneficial consequence of early screening for preterm-SGA is the detection of some cases of term-SGA and both early- and late-PE. Similarly, the use of an algorithm for the prediction of early-PE can identify some of the cases of late-PE and both preterm- and term-SGA. The study has demonstrated an approach for combining the two specific algorithms for preterm-SGA and early-PE to maximize the performance of screening for these pregnancy complications.

The risk for SGA decreased with maternal weight and height, and increased with maternal age and in cigarette smokers, in women with previous history of SGA, in women of Afro-Caribbean and South Asian racial origin, in those with a medical history of chronic hypertension, diabetes mellitus and systemic lupus erythematosus or

Table 10. Performance of the combined algorithm for early-PE at risk cutoff of 1:200 and algorithm for preterm-SGA at risk cutoff of 1:150 for women of Caucasian and Afro-Caribbean racial origin and according to their obstetric history

	Caucasian					Afro-Caribbean				
	all	nulliparous	parous	previous PE	no previous PE	all	nulliparous	parous	previous PE	no previous PE
Normal	3,291/42,514 (7.7)	2,102/21,785 (9.6)	1,189/20,729 (5.7)	378/1,144 (33.0)	811/19,585 (4.1)	2,311/9,268 (24.9)	1,121/3,638 (30.8)	1,190/5,630 (21.1)	221/345 (64.1)	969/5,285 (18.3)
Early-PE	88/97 (90.7)	65/68 (95.6)	23/29 (79.3)	15/15 (100.0)	8/14 (57.1)	92/92 (100.0)	46/46 (100.0)	46/46 (100.0)	23/23 (100.0)	23/23 (100.0)
Late-PE	209/654 (32.0)	135/464 (29.1)	74/190 (38.9)	61/78 (78.2)	13/112 (11.6)	293/433 (67.7)	149/204 (73.0)	144/229 (62.9)	65/67 (97.0)	79/162 (48.8)
Preterm-SGA	92/220 (41.8)	92/220 (41.8)	30/79 (38.0)	6/7 (85.7)	24/72 (33.3)	91/124 (73.4)	46/59 (78.0)	45/65 (69.2)	10/11 (90.9)	35/54 (64.8)
Term-SGA	637/1,611 (39.5)	637/1,611 (39.5)	207/529 (39.1)	27/44 (61.4)	180/485 (37.1)	350/647 (54.1)	197/365 (54.0)	153/282 (54.3)	17/21 (80.1)	136/261 (52.1)

In the total population the FPR was 10.9% and the detection rates of early-PE, late-PE, preterm-SGA and term-SGA were 95.3, 45.6, 55.5 and 44.3%, respectively (cf. table 9).

antiphospholipid syndrome and in women who had assisted conception. The associations between birthweight and maternal characteristics such as age, weight, height, racial origin, cigarette smoking and assisted conception have been extensively reported [15–20]. Large retrospective population-based studies of pregnant women with chronic hypertension reported an associated four- to five-fold increase in the risk of SGA [20, 21]. The association between pre-pregnancy diabetes mellitus and SGA is less well described. A prospective cohort study of 682 consecutive diabetic pregnancies reported a two-fold increase in the rate of SGA in type 2 diabetes compared to type 1 diabetes (11.4 vs. 4.9%) [22]. A retrospective study of 336 patients with pre-pregnancy diabetes mellitus has shown that pregnancies complicated by the delivery of SGA neonates could be the result of maternal vascular disease, such as diabetic retinopathy [23]. Population-based studies and case series of women with systemic lupus erythematosus or antiphospholipid syndrome have consistently demonstrated a significant increase in the risk of SGA [24–26].

Our findings that in the preterm-SGA group uterine artery PI and MAP at 11–13 weeks are increased and serum PAPP-A and PlGF are decreased provide indirect evidence that preterm-SGA, like early-onset PE, are the consequence of impaired placentation. The intrinsic failure in trophoblast differentiation at different time points of ontogeny may lead to late-onset PE or SGA with or without maternal symptoms [27]. The magnitude of the deviations in biophysical and biochemical markers from normal in the SGA pregnancies was lower than in PE presumably because unlike PE, which is a pathological disorder, SGA is a heterogeneous condition which in addition to fetal growth restriction (FGR) due to impaired placentation it includes many constitutionally small fetuses. The proportion of FGR to constitutional SGA is likely to be higher in the preterm-SGA rather than the term-SGA group and this is reflected in the higher deviation from normal in the biophysical and biochemical markers as well as the higher incidence of iatrogenic delivery in the preterm-SGA group.

We have proposed that maternal factors and biomarkers can be assessed in the same medical visit as in combined first-trimester screening for aneuploidies and that such assessment could form the basis for a new approach to pregnancy care [28]. It would be important to provide detailed counselling to the women before such complex visit. There is evidence that such early assessment of risk for PE and SGA is beneficial because the prophylactic use of low-dose aspirin started in early pregnancy can potentially halve the incidence of PE but also that of SGA in the absence of PE [3]. The approach proposed in this study whereby the specific algorithms for preterm-SGA and early-PE are combined keeps the screen positive rate to a minimum and at the same time achieves a high detection rate for both pregnancy complications. This approach of combining different specific algorithms is analogous to screening for aneuploidies by the combined use of specific algorithms for trisomies 21, 18 and 13 [29].

The FPR and detection rates of PE and SGA are influenced by the characteristics of the study population and for given risk cutoffs they are both higher in nulliparous than in parous women and in those of Afro-Caribbean than Caucasian racial origin. This is analogous to combined screening for trisomy 21 where both the FPR and detection rate increase with maternal age. Consequently, care should be taken in comparing the performance of screening of these algorithms reported in different studies. The data presented here can form the basis for planning future studies on therapeutic interventions in different population groups to reduce the prevalence of pregnancy complications related to impaired placentation.

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