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Reference range of birth weight with gestation and first-trimester prediction of small-for-gestation neonates

Leona C. Y. Poon, George Karagiannis, Ismini Staboulidou, Akram Shafiei and Kypros H. Nicolaides*

Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London, UK

Objective Firstly, to establish a reference range of birth weight with gestation at delivery; secondly, to identify maternal characteristics that are significantly associated with birth weight; and thirdly, to determine if combinations of maternal characteristics, fetal nuchal translucency thickness (NT), and serum concentrations of free beta-human chorionic gonadotrophin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) are significant predictors of small-for-gestational-age (SGA) neonates in the absence of preeclampsia.

Method Maternal characteristics were recorded; fetal NT, maternal serum free β-hCG and PAPP-A were measured at 11 weeks to 13 weeks 6 days in 33,602 women with singleton pregnancies. Regression analysis was used to determine the association of birth weight with gestation at delivery and to establish a reference range with gestation. Logistic regression analysis was used to determine if maternal factors, fetal NT, free β-hCG, and PAPP-A contribute significantly in predicting SGA in the absence of preeclampsia.

Results Birth weight increased with maternal weight and height; it was higher in parous than in nulliparous women and in those with a medical history of pre-pregnancy diabetes mellitus, and it was lower in cigarette smokers, in all racial groups other than in Caucasian women, and in those with a medical history of chronic hypertension and in those who previously delivered SGA neonates. In the SGA group compared with the unaffected group, there were lower median delta NT (0.10 vs 0.12 mm), free β-hCG [0.9 vs 1.0 MoM (multiples of median)], and PAPP-A (0.8 vs 1.0 MoM). The prediction of SGA provided by maternal factors was significantly improved by the addition of fetal NT and PAPP-A (34.0 vs 37.0% at a false-positive rate of 10%).

Conclusion Prediction of the birth of SGA neonates in the absence of preeclampsia can be provided in the first trimester of pregnancy by a combination of maternal characteristics and measurements of parameters used in early screening for aneuploidies. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS: birth weight for gestation; reference range; small for gestation; screening; PAPP-A; nuchal translucency

INTRODUCTION

Birth weight is affected by gestational age at delivery and several maternal characteristics, including racial origin, age, body mass index, parity, and cigarette smoking (Wen *et al*., 1990; Gardosi *et al*., 1995a,b; Clausson *et al*., 1998; Gardosi, 2006). There is also some evidence that birth weight is related to placental function in early pregnancy, reflected in the maternal serum concentration of the pregnancy-associated plasma protein-A (PAPP-A) at 11 to 13 weeks of gestation. Several studies reported that in pregnancies delivering small-for-gestational-age (SGA) neonates, serum PAPP-A at 11 to 13 weeks was decreased (Ong *et al*., 2000; Smith *et al*., 2002; Yaron *et al*., 2002; Tul *et al*., 2003; Dugoff *et al*., 2004; Smith *et al*., 2006; Canini *et al*., 2008; Spencer *et al*., 2008; Fox *et al*., 2009; Law *et al*., 2009; Montanari *et al*., 2009; Pihl *et al*., 2009). In these studies, the definition of SGA was based on previously established birth weight percentiles derived from examination of different populations than the ones under investigation. One study has raised the possibility for an association between fetal nuchal translucency thickness (NT) and birth weight; however, the available published data regarding this possible association is limited (Kelecki *et al*., 2005).

The aims of this study in a population of more than 30,000 singleton pregnancies attending for routine care at 11 to 13 weeks of gestation were, firstly, to establish a reference range of birth weight with gestation at delivery; secondly, to identify maternal characteristics that were significantly associated with birth weight; and thirdly, to determine if combinations of maternal characteristics, fetal NT, serum concentrations of free β-hCG and PAPP-A were significant predictors of SGA neonates.

METHODS

This was a prospective screening study for adverse obstetric outcomes in women attending for their routine first hospital visit in pregnancy. In this visit, which is held at 11 weeks to 13 weeks 6 days of gestation, we recorded maternal characteristics and performed a transabdominal ultrasound scan to confirm gestational

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

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age from the measurement of the fetal crown-rump length (CRL), to diagnose any major fetal abnormalities, and to measure fetal NT (Snijders *et al*., 1998). Automated machines that provide reproducible results within 30 min were used to measure PAPP-A and free β-hCG (DELFIA Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, MA, USA) as part of screening for chromosomal abnormalities (Kagan *et al*., 2008). Data on pregnancy outcome were collected from the hospital maternity records or their general medical practitioners. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by King's College Hospital Ethics Committee.

Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, African, South Asian, East Asian, and mixed), cigarette smoking during pregnancy (yes or no), parity (nulliparous if there were no previous pregnancies beyond 23 completed weeks or parous), birth weight of previous neonates (only SGA, only non-SGA, or mixture of SGA and non-SGA), method of conception (spontaneous or assisted), and medical history of chronic hypertension and pre-pregnancy diabetes mellitus. The maternal weight in kilogram and height in centimeter were measured.

During the study period (March 2006 to September 2009) first-trimester combined screening for aneuploidies was carried out in 36,743 singleton pregnancies. We excluded 3,141 cases because the outcome data were missing ($n = 2,005$) or there was a major fetal defect or aneuploidy or the pregnancies resulted in fetal death or miscarriage before 24 weeks of gestation or the pregnancies were terminated for social reasons ($n = 1{,}136$). Statistical analysis was performed in the remaining 33,602 pregnancies.

Statistical analysis

Statistical analysis was performed in the remaining 28 268 pregnancies. The measured NT was expressed as a difference from the expected normal mean for gestation (δ value). Similarly, the measured concentrations of maternal serum free β-hCG and PAPP-A were converted to multiples of the expected normal median (MoM) corrected for fetal CRL, maternal weight, smoking status, racial origin, parity, and method of conception (Kagan *et al*., 2008). The distribution of birth weight was made Gaussian after logarithmic$_{10}$ transformation. Regression analysis was used to determine the association of birth weight with gestation at delivery (GA) and to establish a reference range with gestation. Multivariate linear regression analysis was used to determine which of the factors amongst maternal characteristics, fetal NT, free β-hCG, and PAPP-A were significant predictors of $\log_{10}$ birth weight corrected for GA. A neonate was considered to be SGA if the birth weight was less than the 5th percentile for GA. In the pregnancies not complicated by preeclampsia, the Mann–Whitney U-test was used to compare the delta NT, MoM β-hCG, and MoM PAPP-A between the SGA and the unaffected group. Multivariate logistic regression analysis was used to determine the factors amongst the maternal characteristics with significant contributions in predicting SGA and the extent to which such a prediction is improved by the addition of fetal NT, free β-hCG, and PAPP-A. The performance of screening was estimated using receiver operating characteristic (ROC) curves. The performance of different methods of screening was compared using the areas under the ROC curves (AUROC) (Zweig and Campbell, 1993).

The statistical software package SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for the data analyses.

RESULTS

Birth weight corrected for gestation at delivery

In the total population of 33,602 pregnancies there was a significant association between birth weight and gestation at delivery (Figure 1):

Expected $\log_{10}$ birth weight $= -0.6329 + 0.1873 \times (\mathrm{GA}) - 0.0021 \times (\mathrm{GA})^2$; $R^2 = 0.574$, SD $= 0.0581$, $p < 0.0001$.

Birth weight and maternal characteristics

Multivariate linear regression analysis demonstrated that for $\log_{10}$ birth weight, significant independent contributions were provided by GA, weight, height, smoking status, parity, racial origin, and medical history of chronic hypertension and pre-pregnancy diabetes mellitus ($R^2 = 0.625$, SD $= 0.0544$, $p < 0.0001$; Table 1).

Birth weight and maternal characteristics, fetal nuchal translucency, serum free β-hCG and PAPP-A

Multivariate linear regression analysis demonstrated that in the prediction of birth weight, fetal NT and maternal serum free β-hCG and PAPP-A contributed significantly in addition to the contribution of maternal characteristics ($R^2 = 0.636$, SD $= 0.0535$; $p < 0.0001$; Table 1).

Prediction of small-for-gestational-age neonates

In 752 (2.2%) of the 33,602 pregnancies, there was preeclampsia and these were excluded from further analysis. In 1,536 (4.7%) of the 32,850 pregnancies, the birth weight was below the 5th percentile corrected for GA. The maternal characteristics of the SGA and unaffected pregnancies are shown in Table 2.

Median fetal delta NT, MoM β-hCG, and MoM PAPP-A were significantly lower in the SGA than in the unaffected group ($p < 0.0001$) (Table 3). Pearson

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Table 1—Linear regression analysis for the prediction of $\log_{10}$ birth weight by gestational age at delivery (GA), maternal factors, fetal nuchal translucency (NT), free beta-human chorionic gonadotrophin (β–hCG) and pregnancy associated plasma protein-A (PAPP-A)

	Maternal factors only			Maternal factors, NT, β–hCG, PAPP-A		
Independent variable	*b*	SE	*p*	*b*	SE	*p*
Intercept	−0.935219	0.042717	<0.0001	−0.921268	0.042155	<0.0001
GA	0.186853	0.002072	<0.0001	0.186631	0.002047	<0.0001
$(GA)^2$	−0.002078	0.000028	<0.0001	−0.002081	0.000027	<0.0001
Weight	0.003726	0.000622	<0.0001	0.004009	0.000612	<0.0001
$(Weight)^2$	−0.000030	0.000008	<0.0001	−0.000034	0.000007	<0.0001
$(Weight)^3$	$8.820640e^{-08}$	$2.926274e^{-08}$	0.003	$1.037589e^{-07}$	$2.878720e^{-08}$	0.0003
Height	0.000965	0.000048	<0.0001	0.000926	0.000047	<0.0001
Age	0.001466	0.000441	0.0009	0.001468	0.000434	0.0007
$(Age)^2$	−0.000026	0.000007	0.0002	−0.000026	0.000007	0.0002
Parous	0.016986	0.000631	<0.0001	0.016890	0.000621	<0.0001
Smoking	−0.024867	0.001116	<0.0001	−0.024689	0.001099	<0.0001
Racial origin						
Caucasian	0			0		
African	−0.021769	0.000809	<0.0001	−0.021869	0.000802	<0.0001
South Asian	−0.017824	0.001503	<0.0001	−0.017817	0.001479	<0.0001
East Asian	−0.005543	0.002176	0.011	−0.005956	0.002143	0.005
Mixed	−0.009063	0.001788	<0.0001	−0.010920	0.001762	<0.0001
Chronic hypertension	−0.020995	0.002834	<0.0001	−0.020235	0.002791	<0.0001
Diabetes	0.031430	0.003438	<0.0001	0.033839	0.003381	<0.0001
Assisted conception	−0.004015	0.001581	0.011	−0.003494	0.001561	0.025
Delta NT	—	—	—	0.011710	0.001040	<0.0001
$(Delta\ NT)^2$	—	—	—	−0.003680	0.000847	<0.0001
$(Delta\ NT)^3$	—	—	—	0.000241	0.000110	0.029
$Log_{10}MoM$ PAPP-A	—	—	—	0.036798	0.001472	<0.0001
$(Log_{10}MoM\ PAPP\text{-}A)^2$	—	—	—	−0.033580	0.003837	<0.0001
$(Log_{10}MoM\ PAPP\text{-}A)^3$	—	—	—	−0.024000	0.004335	<0.0001
$Log_{10}MoM\ \beta$-hCG	—	—	—	0.005561	0.001147	<0.0001
$(Log_{10}MoM\ \beta\text{-}hCG)^2$	—	—	—	−0.011596	0.002600	<0.0001

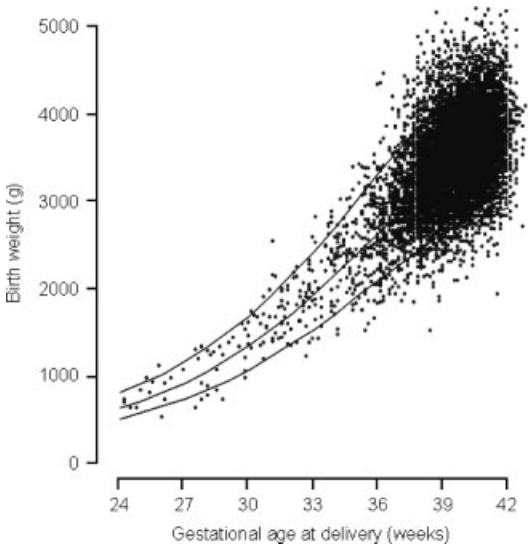

Figure 1—Relationship between birth weight and gestational age at delivery with 95th, 50th, and 5th percentiles

correlation between delta NT, $\log_{10}$MoM β-hCG, and $\log_{10}$MoM PAPP-A in the unaffected and SGA groups is shown in Table 4.

In the SGA group, there was a significant association between $\log_{10}$MoM PAPP-A and $\log_{10}$MoM β-hCG ($r = 0.174$, $p < 0.0001$), GA ($r = 0.132$, $p < 0.0001$) and birth weight centile ($r = 0.130$, $p < 0.0001$). There was a significant association between $\log_{10}$MoM β-hCG and birth weight centile ($r = 0.058$, $p = 0.023$) but not GA ($r = -0.006$, $p = 0.818$). Delta NT was not significantly associated with $\log_{10}$MoM β-hCG ($r = -0.023$, $p = 0.370$), $\log_{10}$MoM PAPP-A ($r = 0.016$, $p = 0.536$), GA ($r = -0.009$, $p = 0.715$) and birth weight centile ($r = 0.012$, $p = 0.640$).

In the unaffected group there was a significant association between $\log_{10}$MoM PAPP-A and $\log_{10}$MoM β-hCG ($r = 0.215$, $p < 0.0001$), GA ($r = 0.052$, $p < 0.0001$) and birth weight centile ($r = 0.110$, $p < 0.0001$) but not delta NT ($r = 0.010$, $p = 0.082$). There was a significant association between $\log_{10}$MoM β-hCG and delta NT ($r = -0.024$, $p < 0.0001$), GA ($r = 0.035$, $p < 0.0001$) and birth weight centile ($r = 0.045$, $p < 0.0001$). Delta NT was significantly associated with birth weight centile ($r = 0.067$, $p < 0.0001$) but not GA ($r = -0.01$, $p = 0.063$).

The risk for SGA was calculated from the formula: odds/(1 + odds), where odds $= e^Y$. Y was derived from multivariate logistic regression analysis of, firstly, maternal factors only (Table 5) and, secondly, maternal factors, delta NT, $\log_{10}$MoM β-hCG, and $\log_{10}$MoM PAPP-A (Table 5).

The relationship between the risk for SGA with serum PAPP-A and the effects of maternal factors

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Table 2—Maternal characteristics in the unaffected and in those delivering small for gestational age (SGA) neonates

Variables	Unaffected (n = 31,314)	SGA (n = 1,536)
Maternal age in yrs, median (IQR)	32.3 (28.0–36.0)	31.4 (26.3–35.7)‡
Weight in kg, median (IQR)	66.0 (59.0–75.0)	61.1 (55.0–70.0)‡
Height in cm, median (IQR)	165.0 (160.0–169.0)	161.8 (157.0–166.0)‡
Racial origin		
Caucasian, n (%)	22,898 (73.1)	867 (56.4)‡
African, n (%)	5,635 (18.0)	416 (27.1)‡
South Asian, n (%)	1,290 (4.1)	140 (9.1)‡
East Asian, n (%)	600 (1.9)	51 (3.3)†
Mixed, n (%)	891 (2.8)	62 (4.0)*
Parity		
Nulliparous, n (%)	14,746 (47.1)	952 (62.0)‡
Parous with previous non-SGA neonate, n (%)	15,302 (48.9)	409 (26.6)‡
Parous with previous SGA and non-SGA neonate, n (%)	586 (1.9)	62 (4.0)‡
Parous with previous SGA neonate, n (%)	680 (2.2)	113 (7.4)‡
Cigarette smoker, n (%)	2,483 (7.8)	257 (16.7)‡
Conception		
Spontaneous, n (%)	30,163 (96.3)	1,455 (94.7)
Assisted conception, n (%)	1,151 (3.7)	81 (5.3)*
Chronic hypertension, n (%)	297 (0.9)	25 (1.6)*
Pre-pregnancy diabetes mellitus, n (%)	235 (0.8)	10 (0.7)

Comparisons between the SGA and the unaffected groups were by Chi square or Fisher exact test for categorical variables and Mann Whitney-U test for continuous variables: * $p < 0.05$, † $p < 0.001$, ‡ $p < 0.0001$.

Table 3—The measurement of fetal nuchal translucency thickness (NT), free beta-human chorionic gonadotrophin (β-hCG) and pregnancy associated plasma protein-A (PAPP-A) in the unaffected group and in those delivering small for gestational age (SGA) neonates

Variables	Unaffected (n = 31,314)	SGA (n = 1,536)	*p*
Delta NT, median (IQR)	0.123 (−0.076 to 0.341)	0.097 (−0.124 to 0.302)	<0.0001
MoM β-hCG, median (IQR)	0.974 (0.663 to 1.467)	0.886 (0.582 to 1.397)	<0.0001
MoM PAPP-A, median (IQR)	1.027 (0.706 to 1.454)	0.819 (0.550 to 1.213)	<0.0001

Comparisons between the SGA and the unaffected groups were by Mann Whitney-U test.
Multiple of median—MoM.

Table 4—Pearson Correlation between delta NT, $\log_{10}$MoM β-hCG and $\log_{10}$MoM PAPP-A in the unaffected and in those delivery small for gestational age (SGA) neonates

		Delta NT		$\log_{10}$MoM β-hCG		$\log_{10}$MoM PAPP-A	
		Unaffected	SGA	Unaffected	SGA	Unaffected	SGA
Delta NT	Pearson Correlation	1	1	−0.024	−0.023	0.010	0.016
	p	—	—	<0.0001	0.370	0.082	0.536
$\log_{10}$MoM β-hCG	Pearson Correlation	−0.024	−0.023	1	1	0.215	0.174
	p	<0.0001	0.370	—	—	<0.0001	<0.0001
$\log_{10}$MoM PAPP-A	Pearson Correlation	0.010	0.016	0.215	0.174	1	1
	p	0.082	0.536	<0.0001	<0.0001	—	—

for Caucasian and those of African racial origin are illustrated in Figure 2.

Performance of screening

The AUROC and the detection rates of SGA in screening by maternal factors only and by combinations of maternal factors, fetal NT, and PAPP-A are given in Table 6 and Figure 3. There was significant improvement in the AUROC by the addition of NT, PAPP-A and free β-hCG to maternal factors ($p < 0.0001$).

DISCUSSION

This study has established a reference range of birth weight for gestation in a large heterogeneous inner-city

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Table 5—Logistic regression analysis for the prediction of small for gestational age by maternal factors, fetal nuchal translucency (NT), pregnancy associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotrophin (β-hCG)

	Maternal factors only			Maternal factors, NT, β-hCG, PAPP-A		
Independent variable	OR	95% CI	p	OR	95% CI	p
Age (per year)	1.659	1.152-2.389	0.006	1.632	1.129-2.339	0.009
$(Age)^2$	0.983	0.971-0.994	0.004	0.983	0.971-0.995	0.006
$(Age)^3$	1.000	1.000–1.000	0.002	1.000	1.000–1.000	0.003
Weight (per kg)	0.781	0.696-0.876	<0.0001	0.767	0.683-0.862	<0.0001
$(Weight)^2$	1.003	1.001–1.004	0.001	1.003	1.001–1.004	<0.0001
$(Weight)^3$	1.000	1.000–1.000	0.005	1.000	1.000–1.000	0.002
Height (per cm)	0.968	0.960-0.977	<0.0001	0.969	0.961-0.978	<0.0001
Racial origin			<0.0001			<0.0001
Caucasian (reference)	1			1		
African	2.292	2.010-2.615	<0.0001	2.364	2.067-2.703	<0.0001
South Asian	2.129	1.742-2.602	<0.0001	2.214	1.809-2.709	<0.0001
East Asian	1.456	1.070-1.982	0.017	1.497	1.097-2.042	0.011
Mixed	1.702	1.296-2.237	<0.0001	1.931	1.467-2.543	<0.0001
Cigarette smoking	2.736	2.350-3.186	<0.0001	2.696	2.311-3.145	<0.0001
Assisted conception	1.481	1.160-1.893	0.002	1.384	1.078-1.776	0.011
History of chronic hypertension	1.683	1.087-2.605	0.020	1.658	1.060-2.593	0.027
Parity			<0.0001			<0.0001
Nulliparous (reference)	1			1		
Parous with previous SGA	1.823	1.464-2.270	<0.0001	1.680	1.345-2.100	<0.0001
Parous with previous SGA and non-SGA	1.054	0.795-1.398	0.715	1.040	0.782-1.382	0.787
Parous with previous non-SGA	0.392	0.346-0.444	<0.0001	0.381	0.336-0.432	<0.0001
Delta NT	—	—	—	0.743	0.633-0.873	<0.0001
$(Delta\ NT)^2$	—	—	—	1.053	1.013-1.095	0.010
$Log_{10}MoM\ PAPP\text{-}A$	—	—	—	0.189	0.146-0.245	<0.0001
$(Log_{10}MoM\ PAPP\text{-}A)^2$	—	—	—	2.817	1.381-5.747	0.004
$(Log_{10}MoM\ PAPP\text{-}A)^3$	—	—	—	2.855	1.338-6.092	0.007
$Log_{10}MoM$ free β-hCG	—	—	—	0.768	0.631-0.935	0.009
$(Log_{10}MoM\ free\ \beta\text{-}hCG)^2$	—	—	—	1.555	1.110-2.179	0.010
R^2		0.095			0.122	

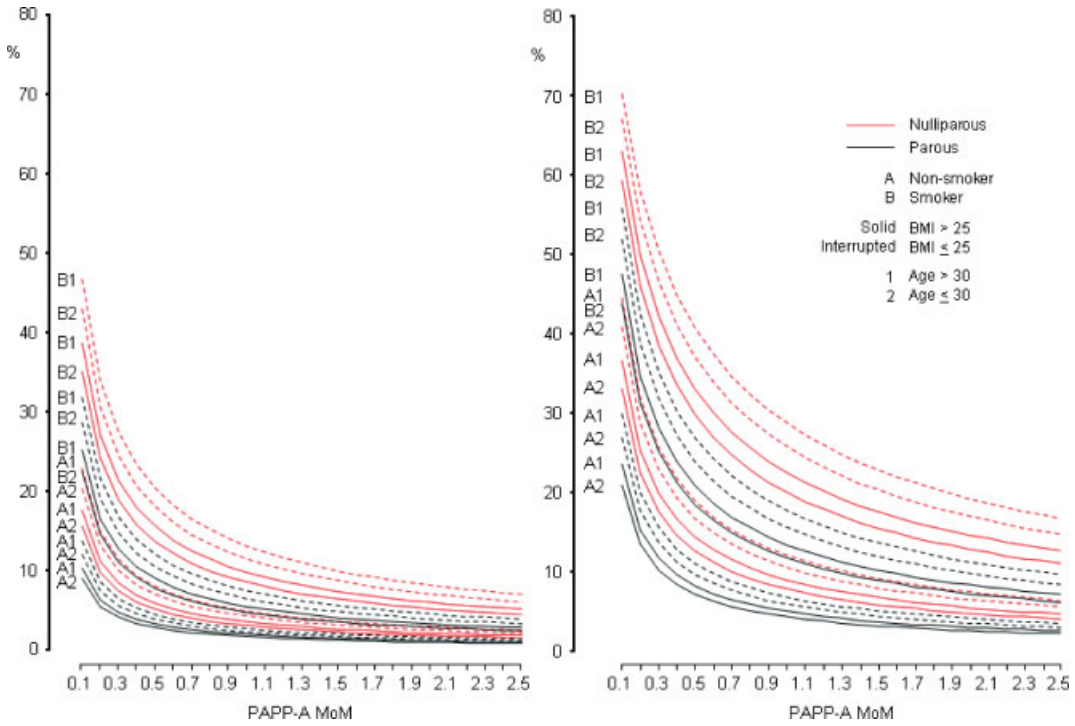

Figure 2—Risks of small for gestational age (<5th percentile corrected for gestational age at delivery) for Caucasian women (left) and African women (right). The red lines are for nulliparous and the black lines are for parous women; A = non-smoker, B = smoker; interrupted lines = body mass index (BMI) >25 kg/m^2; solid lines = BMI <25 kg/m^2; 1 = age >30 years, and 2 = age <30 years

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Table 6—Performance of screening for small for gestational age neonates by maternal factors only, maternal factors with fetal nuchal translucency thickness (NT) and pregnancy associated plasma protein-A (PAPP-A)

Screening test	Area under receiver operating curve (95% CI)
Maternal factors	0.719 (0.706–0.732)
Maternal factors plus	
NT	0.720 (0.707–0.734)
Free β-hCG	0.724 (0.711–0.737)
PAPP-A	0.745 (0.733–0.758)
NT, PAPP-A and free β-hCG	0.747 (0.735–0.760)

	Detection rate for fixed false positive rate	
	5%	10%
Maternal factors	21.0	34.0
Maternal factors plus		
NT	21.2	35.3
Free β-hCG	21.9	34.9
PAPP-A	24.5	37.2
NT, PAPP-A and free β-hCG	25.2	37.0

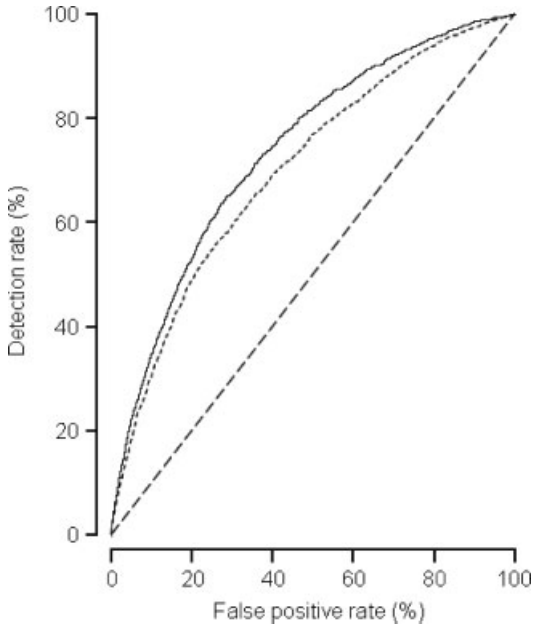

Figure 3—Receiver operating characteristics curves of maternal factors only (· · · · · ·) and by a combination of maternal factors, fetal NT, and maternal serum PAPP-A and free β-hCG (———) in the prediction of small for gestational age

population of singleton pregnancies in which gestational age was determined by an ultrasound scan in early pregnancy. Birth weight is significantly influenced by maternal characteristics such as racial origin, weight, height, parity, cigarette smoking, and medical history of chronic hypertension and pre-pregnancy diabetes mellitus. The prediction of SGA in euploid pregnancies provided by maternal characteristics is improved by the addition of fetal NT and maternal serum PAPP-A and free β-hCG and the combined model could detect about 37% of women who deliver SGA neonates at a false-positive rate of 10%.

Birth weight increased with maternal weight and height; it was higher in parous than in nulliparous women and in those with a medical history of pre-pregnancy diabetes mellitus, and it was lower in cigarette smokers, in all racial groups other than in Caucasian women, and in those with a medical history of chronic hypertension. The risk for SGA decreased with maternal weight and height, and increased with maternal age and in cigarette smokers, nulliparous women, in women of all racial groups other than Caucasians, in those with a medical history of chronic hypertension, and in women who had assisted conception. The associations between birth weight and maternal characteristics such as age, weight, parity, racial origin, and cigarette smoking have been extensively reported (Wen *et al*., 1990; Gardosi *et al*., 1995a,b; Clausson *et al*., 1998; Gardosi, 2006). It is recognized that it is necessary to adjust birth weight for these maternal variables to establish appropriate growth standards to define growth abnormalities (Gardosi *et al*., 1992, 1995a,b).

Previous studies have reported that maternal serum PAPP-A below the 5th percentile in early pregnancy could detect 10 to 18% of pregnancies delivering SGA neonates, and the reported odds ratios varied between 1.7 and 3.3 (Ong *et al*., 2000; Smith *et al*., 2002; Yaron *et al*., 2002; Tul *et al*., 2003; Dugoff *et al*., 2004; Smith *et al*., 2006; Canini *et al*., 2008; Spencer *et al*., 2008; Fox *et al*., 2009; Law *et al*., 2009; Montanari *et al*., 2009; Pihl *et al*., 2009). The findings of this study confirm the results of these reports that the levels of maternal serum PAPP-A during the first trimester are low in women who subsequently deliver small babies. Additionally, serum free β-hCG was low in the SGA group. The finding of such an association implies that birth weight is predetermined by placental development during the first trimester of pregnancy. It is uncertain to what extent genetic factors affect fetal growth through placentation, although there is some evidence that imprinted genes play a role in regulating the supply of nutrients to the fetus (Angiolini *et al*., 2006). The gene encoding for insulin-like growth factor (IGF) is imprinted and IGF is thought to have a key role in the control of placental growth and ability to transfer nutrients (Reik *et al*., 2003). PAPP-A has been shown to be a syncytiotrophoblast-derived protease for IGF binding proteins, and the cleavage of these proteins by PAPP-A increases the bioavailability of IGF (Bonno *et al*., 1994; Irwin *et al*., 1999; Lawrence *et al*., 1999). It is therefore not surprising that low serum PAPP-A is associated with a higher incidence of SGA.

This study has also demonstrated that birth weight increases with increasing fetal NT and that a small fetal NT is associated with an increased risk of delivering small babies. Published data on the association between fetal NT and birth weight are confined to only one study, which reported that an increased fetal NT in euploid pregnancies is associated with macrosomia (Kelecki *et al*., 2005). The suggested underlying pathophysiology for this association is that enhanced capillary permeability, resulting in an increase in fetal NT, may

be a result of maternal hyperglycemia, which by itself may increase birth weight (Bartha *et al*., 2003; Kelecki *et al*., 2005). Whether the reverse of this hypothesis may provide a possible reason for our findings remains to be established.

In our screening study of over 30,000 singleton pregnancies for SGA in the absence of preeclampsia, we chose 11 to 13 weeks as the gestation for screening because this is often the period of first hospital visit of pregnant women at which combined sonographic and biochemical testings for chromosomal and other major defects are carried out (Snijders *et al*., 1998; Kagan *et al*., 2008). At this visit, maternal characteristics are recorded; an ultrasound scan is carried out to confirm the gestation, screen for major defects, and measure fetal NT; and maternal blood is taken for the measurement of free β-hCG and PAPP-A. Combining maternal characteristics with sonographic and maternal serum biochemical markers provides effective early screening for both chromosomal abnormalities and the development of pre-eclampsia, with a detection rate of about 90% at a false-positive rate of 5% (Poon *et al*., 2009). There is currently no effective method of early screening for SGA in the absence of pre-eclampsia. In this respect, the improvement in sensitivity from 34 to 37% by the addition of PAPP-A, free β-hCG and fetal NT to maternal characteristics is not negligible. The extent to which a substantial increase in the performance of screening for SGA can be achieved by a combinaton of maternal factors with a series of additional biochemical and biophysical parameters remains to be determined in future studies.

Measurement of maternal serum PAPP-A in early pregnancy is in itself not an effective method of screening for SGA neonates. Nevertheless, the observation of low levels of PAPP-A in euploid pregnancies in the first trimester has led to recommendations that such pregnancies should have follow-up scans for monitoring fetal growth (Ong *et al*., 2000; Smith *et al*., 2002; Yaron *et al*., 2002; Tul *et al*., 2003; Dugoff *et al*., 2004; Smith *et al*., 2006; Canini *et al*., 2008; Spencer *et al*., 2008; Fox *et al*., 2009; Law *et al*., 2009; Montanari *et al*., 2009; Pihl *et al*., 2009). Our study has demonstrated that the PAPP-A-related patient-specific risk for SGA is substantially affected by various maternal factors and is modifiable by the addition of the measurement of fetal NT. These variables should be taken into account in calculating the patient-specific risk and therefore in defining the real need and frequency of subsequent growth scans.

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