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First-Trimester Prediction of Macrosomia

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Key Words
Macrosomia · Screening · Free β-human chorionic gonadotrophin · Pregnancy-associated plasma protein-A · Nuchal translucency

Abstract
Objective: To determine if combinations of maternal characteristics and measurements of parameters used in screening for aneuploidies at 11–13 weeks provide significant prediction of macrosomia. ***Method:*** Maternal characteristics, fetal nuchal translucency (NT), free β-human chorionic gonadotrophin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) were recorded at 11^{+0}–13^{+6} weeks in 36,743 singleton pregnancies. Regression analysis was used to determine if in predicting macrosomia significant contributions are provided by maternal factors, fetal NT, free β-hCG and PAPP-A. ***Results:*** The risk for macrosomia increased with maternal weight and height and was higher in parous women with previous delivery of a macrosomic baby and in those with diabetes mellitus; the risk was lower in women of African and South Asian racial origins, in cigarette smokers and in those with chronic hypertension. In the macrosomic group compared to the unaffected group there were higher Δ-NT (0.167 vs. 0.116 mm), free β-hCG (1.010 vs. 0.964 MoM) and PAPP-A (1.103 vs. 1.003 MoM). Prediction of macrosomia provided by maternal factors was significantly improved by fetal NT, free β-hCG and PAPP-A (34.4 vs. 33.1% at a false-positive rate of 10%). ***Conclusion:*** Prediction of macrosomia is provided in the first trimester of pregnancy by a combination of maternal characteristics and measurements of parameters used in screening for aneuploidies.

Introduction

Fetal macrosomia, commonly defined as a birth weight above the 90th centile for gestational age (GA), is associated with increased risks for the mother, including cesarean section and trauma to the birth canal, and for the baby, including shoulder dystocia and consequent brachial plexus or facial nerve injuries, fractures of the humerus or clavicle and birth asphyxia [1–6].

Birth weight is affected by GA at delivery and several maternal characteristics, including racial origin, age, body mass index, parity and cigarette smoking, and medical conditions, such as pre-pregnancy diabetes mellitus [7–10]. 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 11–13 weeks of gestation. Several studies reported that in pregnancies delivering small for gestational age (SGA) neonates se-

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rum PAPP-A at 11–13 weeks was decreased and that in those delivering macrosomic neonates PAPP-A was increased [11–18]. One study reported that neonatal macrosomia was more common in 389 fetuses with nuchal translucency (NT) thickness above the 95th centile than in 386 fetuses with NT within the normal range [19].

The aims of this study in a population of more than 30,000 singleton pregnancies attending for routine care at 11–13 weeks was to firstly determine if combinations of maternal characteristics, fetal NT, serum concentrations of PAPP-A and free β-human chorionic gonadotrophin (β-hCG) are significant predictors of macrosomia and secondly to estimate the performance of first-trimester combined screening in the prediction of macrosomia.

Materials and Methods

The study reports the development of an algorithm for neonatal macrosomia using data from an ongoing 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^{+0}–13^{+6} weeks of gestation, we recorded maternal characteristics and performed a transabdominal ultrasound scan to confirm GA from the measurement of the fetal crown-rump length, to diagnose any major fetal abnormalities, and to measure fetal NT [20]. Automated machines that provide reproducible results within 40 min were used to measure PAPP-A and free β-hCG (DELFIA Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, Mass., USA) as part of screening for chromosomal abnormalities [21]. 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 the King's College Hospital Ethics Committee.

Maternal characteristics recorded were 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), previous delivery of a macrosomic baby (yes or no), method of conception (spontaneous or assisted) and medical history of chronic hypertension and pre-pregnancy diabetes mellitus (yes or no). The maternal weight in kilograms (kg) and height in centimetres (cm) were measured.

Statistical Analysis

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 crown-rump length, maternal weight, smoking status, racial origin, parity and method of conception [21]. The birth weights were expressed as centiles corrected for GA derived from the same dataset as in the current study [22]. The neonate was considered to be macrosomic if the birth weight was more than the 90th centile for GA. The Mann-Whitney U test was used to compare the δ-NT, MoM β-hCG and MoM PAPP-A between the macrosomic and the unaffected groups. Multivariate logistic regression analysis was used to determine the factors amongst the maternal characteristics with significant contributions in predicting macrosomia and the extent to which such prediction is improved by the addition of fetal NT, free β-hCG and PAPP-A. The performance of screening was estimated by receiver operating characteristic (ROC) curves. The performance of different methods of screening was compared by the areas under the ROC curves (AUROC) [23].

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

Results

During the study period (March 2006 to September 2009) first-trimester combined screening for chromosomal defects was carried out in 36,743 singleton pregnancies. We excluded 3,141 cases because they had missing outcome data (n = 2,005), the pregnancies resulted in miscarriage before 24 weeks of gestation, they were terminated for fetal abnormalities or maternal psychosocial indications or they resulted in the birth of babies with major defects (n = 1,136). Statistical analysis was performed in the remaining 33,602 pregnancies.

Maternal Characteristics

In 3,353 (10%) of the neonates the birth weight was above the 90th centile corrected for GA. The maternal characteristics of the study population are shown in table 1.

Multiple regression analysis demonstrated that in the prediction of macrosomia there were significant contributions from maternal racial origin, weight, height, previous delivery of macrosomic neonates, smoking and history of chronic hypertension and diabetes mellitus (table 2).

The AUROC of macrosomia in screening by maternal factors was 0.715 and the detection rates at false-positive rates of 5 and 10% were 22.4 and 33.1%, respectively (fig. 1; table 3).

Fetal NT, Maternal Serum Free β-hCG and PAPP-A

There was a significant linear association between Δ-NT and birth weight centile (Δ-NT = 0.106424 + 0.001076 × birth weight centile; $r = 0.071$, $p < 0.0001$). There was a significant linear association between $\log_{10}$MoM β-hCG and birth weight centile ($\log_{10}$MoM β-hCG = −0.026587 + 0.000487 × birth weight centile; r =

Table 1. Maternal characteristics in the unaffected group and in those delivering macrosomic neonates

Variables	Unaffected (n = 30,249)	Macrosomia (n = 3,353)
Maternal age, years, median (IQR)	32.2 (27.8–35.9)	33.2 (29.2–36.7)[c]
Weight, kg, median (IQR)	65.0 (59.0–74.0)	73.0 (64.0–84.0)[c]
Height, cm, median (IQR)	164.0 (160.0–168.0)	167.0 (162.6–170.2)[c]
Racial origin, n (%)		
White	21,498 (71.1)	2,651 (79.1)[c]
Black	5,837 (19.3)	507 (15.1)[c]
South Asian	1,394 (4.6)	78 (2.3)[c]
East Asian	620 (2.0)	43 (1.3)[b]
Mixed	900 (3.0)	74 (2.2)[a]
Parity, n (%)		
Nulliparous	14,989 (49.5)	1,171 (34.9)[c]
Parous, no previous macrosomic baby	14,002 (46.3)	1,572 (46.9)
Parous, previous macrosomic baby	1,258 (4.2)	610 (18.2)[c]
Cigarette smoker, n (%)	2,578 (8.5)	160 (4.8)[c]
Conception, n (%)		
Spontaneous	29,117 (96.3)	3,214 (95.9)
Assisted conception	1,132 (3.7)	139 (4.1)
Chronic hypertension, n (%)	349 (1.2)	35 (1.0)
Pre-pregnancy diabetes, n (%)	170 (0.6)	88 (2.6)[c]

Comparisons between the macrosomic and the unaffected groups were by χ^2 or Fisher's exact test for categorical variables and by Mann-Whitney U test for continuous variables: [a] $p < 0.05$, [b] $p < 0.001$, [c] $p < 0.0001$.

0.052, $p < 0.0001$). There was a significant quadratic association between $\log_{10}$MoM PAPP-A and birth weight centile ($\log_{10}$MoM PAPP-A = −0.083243 + 0.002241 × birth weight centile − 1.075818 × birth weight centile^2; $r = 0.140$, $p < 0.0001$).

Fetal Δ-NT, maternal serum MoM β-hCG and MoM PAPP-A were significantly higher in the macrosomic than in the unaffected group ($p < 0.0001$) (fig. 2; table 4). Pearson's correlation between Δ-NT, $\log_{10}$MoM β-hCG and $\log_{10}$MoM PAPP-A in the unaffected and macrosomic groups are shown in table 5.

Multiple regression analysis demonstrated that in the prediction of macrosomia there were significant contributions from Δ-NT, $\log_{10}$MoM β-hCG and $\log_{10}$MoM PAPP-A in addition to maternal factors (table 2).

The relations between the risk for macrosomia with serum PAPP-A and the effects of maternal factors for women of Caucasian and African racial origin are illustrated in figure 3.

In screening for macrosomia the addition of fetal NT, β-hCG and PAPP-A to maternal factors improved the prediction provided by maternal factors alone (AUROC 0.727 vs. 0.715, $p < 0.001$; fig. 1; table 3).

Discussion

This study has demonstrated that the birth of macrosomic neonates is related to certain maternal characteristics and the results of first-trimester markers used in screening for fetal aneuploidies. The combined model could detect about 34% of women who delivered macrosomic neonates at a false-positive rate of 10%.

The findings that the risk for macrosomia increases with maternal weight and height and is higher in parous women with previous delivery of a macrosomic infant and in those with a medical history of diabetes mellitus and that the risk is lower in women of African and South Asian racial origins, in cigarette smokers and in those with a medical history of chronic hypertension are compatible with previous reports [1, 5, 24–38]. Parous women are 2–3 times more likely than nulliparous women to have macrosomic neonates [24, 25]. Furthermore, population-based studies have reported that parous women with previous delivery of a macrosomic neonate are 7–15 times more likely to deliver another macrosomic neonate in a subsequent pregnancy [26–28]. Racial differences in the rate of macrosomia have been observed, with the re-

Table 2. Logistic regression analysis for the prediction of macrosomia by maternal factors, fetal NT, free β-hCG and PAPP-A

Independent variable	Maternal factors only			Maternal factors, NT, β-hCG, PAPP-A		
	adjusted OR	95% CI	p	adjusted OR	95% CI	p
Weight	1.092	1.074–1.110	<0.0001	1.091	1.073–1.110	<0.0001
(Weight)^2	1.000	1.000–1.000	<0.0001	1.000	1.000–1.000	<0.0001
Height	1.030	1.025–1.036	<0.0001	1.030	1.024–1.036	<0.0001
Parity						
Nulliparous	1			1		
Parous, no previous macrosomic baby	1.439	1.327–1.560	<0.0001	1.435	1.323–1.557	<0.0001
Parous, previous macrosomic baby	4.937	4.382–5.562	<0.0001	4.901	4.346–5.526	<0.0001
Smoking	0.482	0.407–0.572	<0.0001	0.477	0.402–0.566	<0.0001
Racial origin						
Caucasian	1			1		
African	0.516	0.464–0.574	<0.0001	0.510	0.458–0.568	<0.0001
South Asian	0.695	0.547–0.884	0.003	0.707	0.555–0.899	0.005
Mixed	0.687	0.535–0.882	0.003	0.656	0.510–0.844	0.001
Chronic hypertension	0.555	0.384–0.801	0.002	0.568	0.392–0.821	0.003
Pre-pregnancy diabetes	3.194	2.405–4.242	<0.0001	3.534	2.655–4.703	<0.0001
Δ-NT	–	–	–	1.509	1.338–1.703	<0.0001
(Δ-NT)^2	–	–	–	0.924	0.878–0.971	0.002
$\log_{10}$MoM PAPP-A	–	–	–	2.798	2.319–3.376	<0.0001
($\log_{10}$MoM PAPP-A)^2	–	–	–	0.464	0.283–0.761	0.002
($\log_{10}$MoM PAPP-A)^3	–	–	–	0.398	0.258–0.612	<0.0001
$\log_{10}$MoM β-hCG	–	–	–	1.205	1.040–1.396	0.013
	$R^2 = 0.121$			$R^2 = 0.132$		

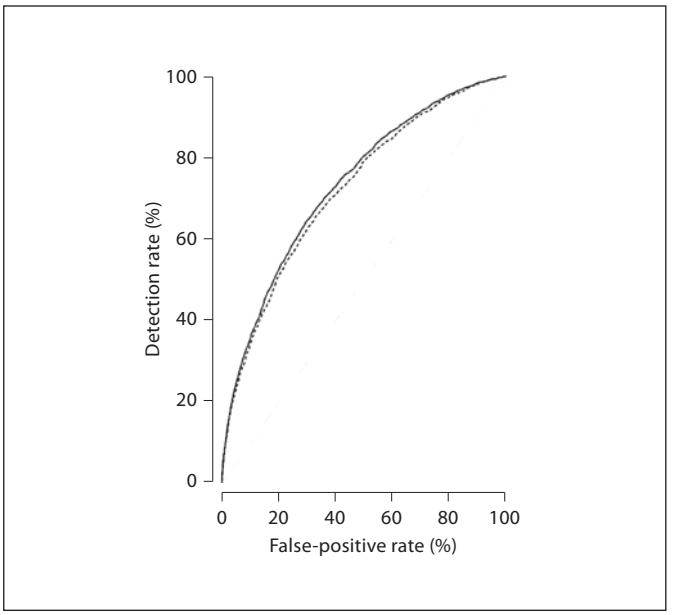

Fig. 1. ROC curves of maternal factors only (------) and a combination of maternal factors, fetal NT, maternal serum β-hCG and PAPP-A (——) in the prediction of macrosomia.

Table 3. Performance of screening for macrosomia by maternal factors only, maternal factors with fetal NT thickness, free β-hCG and PAPP-A

Screening test	AUROC (95% CI)	
Maternal factors	0.715 (0.710–0.719)	
Maternal factors plus		
Fetal NT	0.718 (0.713–0.723)	
Serum β-hCG	0.716 (0.712–0.721)	
Serum PAPP-A	0.723 (0.718–0.728)	
NT, β-hCG, PAPP-A	0.727 (0.722–0.732)	
	Detection rate with 95% CI for fixed false-positive rate	
	5%	10%
Maternal factors	22.4 (21.0–23.8)	33.1 (31.5–35.7)
Maternal factors plus		
Fetal NT	22.6 (21.2–24.1)	33.6 (32.0–35.2)
Serum β-hCG	22.6 (21.2–24.1)	33.5 (31.9–35.1)
Serum PAPP-A	23.4 (22.0–24.9)	34.2 (32.6–35.9)
NT, β-hCG, PAPP-A	23.5 (22.1–25.0)	34.4 (32.8–36.0)

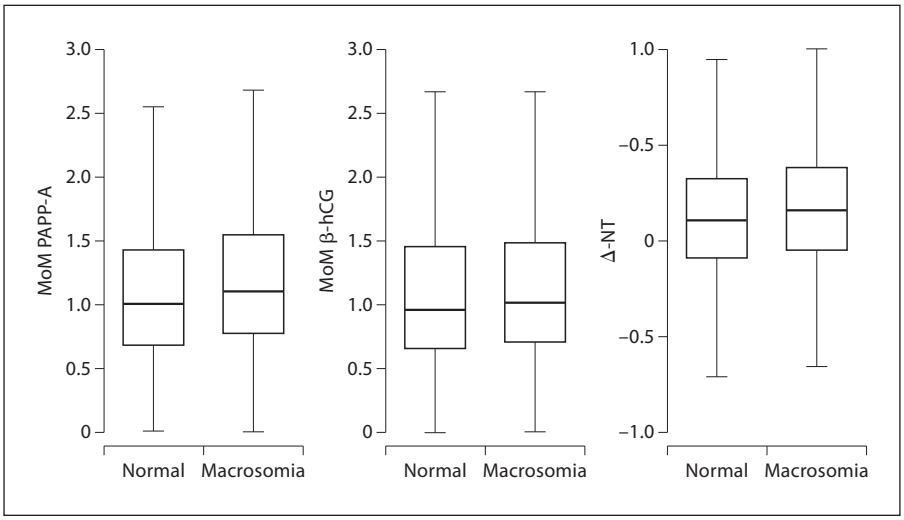

Fig. 2. Box-whisker plots of maternal serum PAPP-A, β-hCG and fetal NT in the macrosomic and unaffected groups.

Table 4. Measurement of fetal NT thickness, free β-hCG and PAPP-A in the unaffected group and in those delivering macrosomic neonates

Variables	Unaffected (n = 30,249)	Macrosomia (n = 3,353)	p
Δ-NT, median (IQR)	0.116 (–0.084 to 0.331)	0.167 (–0.036 to 0.387)	<0.0001
MoM β-hCG, median (IQR)	0.964 (0.654 to 1.463)	1.010 (0.710 to 1.493)	<0.0001
MoM PAPP-A, median (IQR)	1.004 (0.685 to 1.430)	1.103 (0.769 to 1.539)	<0.0001

Comparisons between the macrosomic and the unaffected groups were by Mann-Whitney U test.

ported risk being lower in African than in Caucasian women [24, 29, 30]. However, the results on South Asian women are contradictory, with the risk of macrosomia being reduced or increased [29, 30].

The association between maternal obesity and macrosomia is well documented [24, 29, 31, 32]. A similar trend is found for maternal height, which has also been shown to be an independent determinant of high birth weight [33, 34]. The mechanisms by which maternal overweight induces fetal macrosomia remain to be determined, but its effect on fetal weight appears independent of that of diabetes or glucose intolerance [39]. Thus, there appears to be additional metabolic factors related to maternal overweight that influence fetal growth [40–42]. Insulin resistance increases with maternal weight and this may cause metabolic disturbances that result in an increased flux of nutrients across the placenta, causing fetal hyperinsulinemia and accelerated fetal growth [43–46]. Diabetes in pregnancy is associated with a significant risk of fetal macrosomia, even when good metabolic control is achieved [35]. The mother develops an insulin-resistant state induced by hormones produced by the placenta [47], which in turn results in hyperinsulinemia leading to asymmetrical macrosomia with a high proportion of fat relative to length [48]. The restricting effects of chronic hypertension and smoking in pregnancy are well known and they both reduce the risk of neonatal macrosomia [29, 36–38].

Maternal serum free β-hCG and PAPP-A increase with birth weight centile. The association between low PAPP-A and birth of SGA neonates has been well documented in several studies [11–18]. These and two previous studies have demonstrated that at the other end of the spectrum high serum PAPP-A is associated with macrosomia [12, 18]. A possible mechanism for this association is related to the proteolytic properties of PAPP-A which cleaves insulin-like growth factor (IGF)-binding proteins, thereby increasing the bioavailability of IGF which

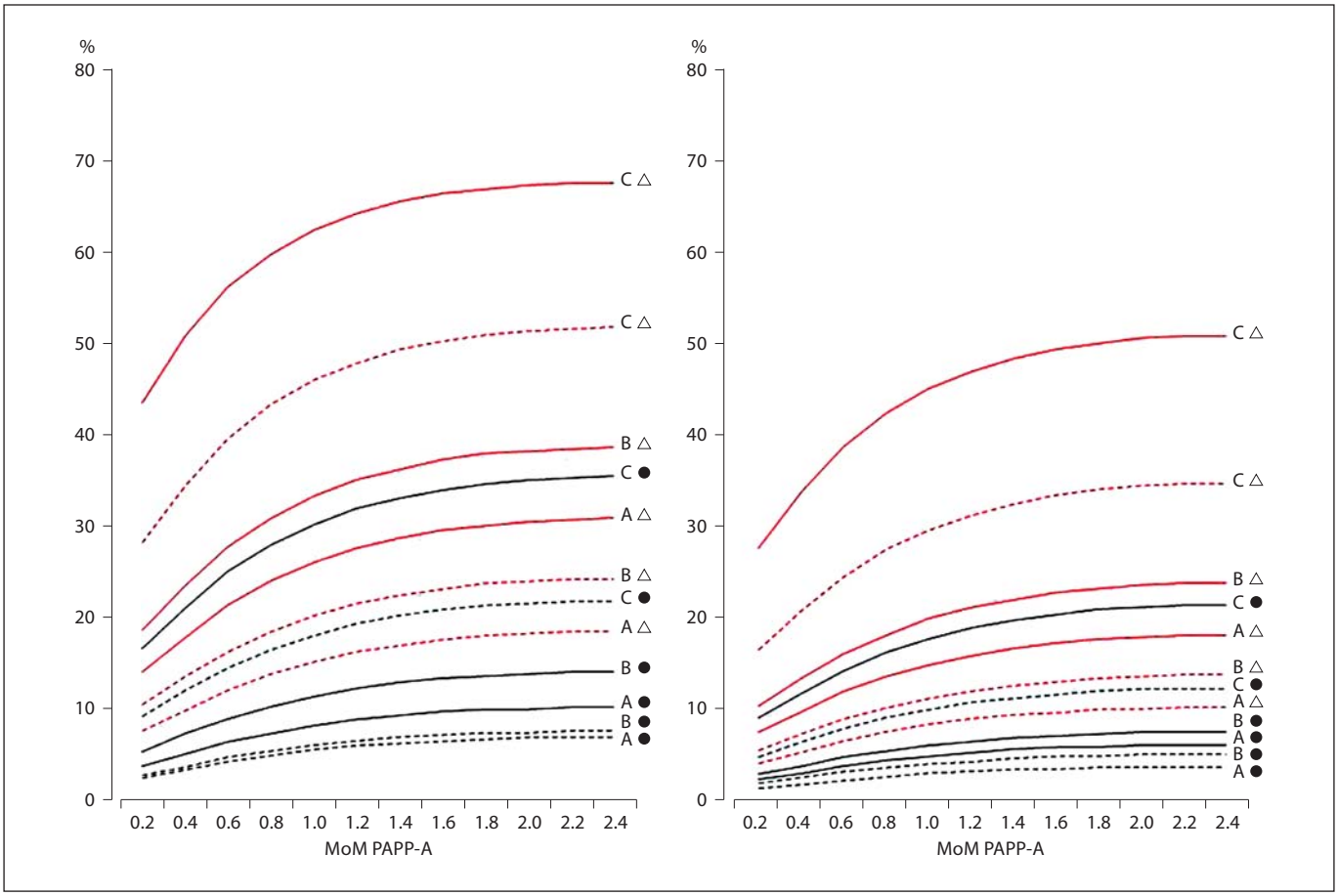

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Fig. 3. Risks of macrosomia (>90th centile corrected for GA at delivery) for women of Caucasian (left) and African (right) racial origin. △ = History of diabetes mellitus, ● = non-diabetic. A = Nulliparous, B = parous with no previous macrosomic neonate, C = parous with previous macrosomic neonate; interrupted lines = body mass index (BMI) ≤25, solid lines = BMI >25.

Table 5. Pearson's correlation between Δ-NT, $\log_{10}$MoM β-hCG and $\log_{10}$MoM PAPP-A in the unaffected group and in those delivering macrosomic neonates

	Δ-NT		$\log_{10}$MoM β-hCG		$\log_{10}$MoM PAPP-A	
	unaffected	macrosomia	unaffected	macrosomia	unaffected	macrosomia
Δ-NT						
Pearson's correlation	1	1	–0.030	–0.003	0.009	0.025
p	–	–	<0.0001	0.871	0.111	0.143
$\log_{10}$MoM β-hCG						
Pearson's correlation	–0.030	–0.003	1	1	0.213	0.192
p	<0.0001	0.871	–	–	<0.0001	<0.0001
$\log_{10}$MoM PAPP-A						
Pearson's correlation	0.009	0.025	0.213	0.192	1	1
p	0.111	0.143	<0.0001	<0.0001	–	–

is thought to play a key role in the control of placental growth and transfer of nutrients to the fetus [49–51]. Studies examining free β-hCG have reported that there is no significant association between low first-trimester serum levels and subsequent birth of SGA neonates [17, 22]. Our study has shown that although the relation between birth weight centile and serum free β-hCG is weaker than that with PAPP-A, the relation is statistically significant and the first-trimester serum levels are increased in pregnancies delivering macrosomic neonates.

This study has also demonstrated that birth weight increases with increasing fetal NT and that a large fetal NT is associated with an increased risk of delivering macrosomic neonates. Kelekci et al. [19] reported that the incidence of developing gestational diabetes and delivering macrosomic neonates in 389 pregnancies with increased fetal NT was significantly higher than in 386 pregnancies with normal fetal NT, and it was concluded that increased fetal NT was predictive of gestational diabetes. It was also suggested that maternal hyperglycemia causes enhanced capillary permeability which results in an increase in fetal NT. However, Leipold et al. [52] reported that the fetal NT was not significantly different in 135 women who developed gestational diabetes compared to 329 women with normal glucose tolerance. Similarly, Spencer et al. [53] examined 79 pregnancies with pre-pregnancy insulin-dependent diabetes mellitus and reported that the fetal NT was not significantly different from non-diabetic pregnancies. Bartha et al. [54] examined 65 women with pre-pregnancy insulin-dependent diabetes mellitus and reported that fetal NT thickness was not related to years of diabetes, dose of insulin, glycosylated hemoglobin concentration or capillary glucose profiles.

The 11- to 13-week approach to combining factors from the maternal history with sonographic and serum biochemical measurements for effective early screening for aneuploidies and other fetal abnormalities is now well accepted [55, 56]. There is increasing evidence that the same approach of combining maternal characteristics with the results of biophysical and biochemical tests can be used for early identification of pregnancies at high risk for subsequent development of preeclampsia, fetal death and fetal growth restriction [22, 57, 58]. This study expands on this concept in the prediction of macrosomia. Although the performance of early screening for macrosomia is poor compared to that of screening for aneuploidies and preeclampsia, our findings can form the basis of future research to improve screening by the addition of potentially new markers. Similarly, the extent to which knowledge of the individual patient-specific risk for macrosomia by first-trimester combined screening can improve antenatal surveillance and prevention of macrosomia itself or the intrapartum complications related to macrosomia remains to be determined by future studies.

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References

1 Berkus MD, Conway D, Langer O: The large fetus. Clin Obstet Gynecol 1999;42:766–784.
2 Bromwich P: Big babies. Br Med J (Clin Res Ed) 1986;293:1387–1388.
3 Ferber A: Maternal complications of fetal macrosomia. Clin Obstet Gynecol 2000;43:335–339.
4 Grassi AE, Giuliano MA: The neonate with macrosomia. Clin Obstet Gynecol 2000;43:340–348.
5 Spellacy WN, Miller S, Winegar A, Peterson PQ: Macrosomia – maternal characteristics and infant complications. Obstet Gynecol 1985;66:158–161.
6 Henriksen T: The macrosomic fetus: a challenge in current obstetrics. Acta Obstet Gynecol Scand 2008;87:134–145.
7 Gardosi J, Mongelli M, Mul T: Intrauterine growth retardation; in Steegers EAP, Eskes TKAB, Symonds EM (eds): Preventive care in obstetrics and gynaecology. Baillieres Clin Obstet Gynaecol 1995;9:445–643.
8 Gardosi J: New definition of small for gestational age based on fetal growth potential. Horm Res 2006;65(suppl 3):15–18.
9 Wen SW, Goldenberg RL, Cutter GR, Hoffman HJ, Cliver SP, Davis RO, DuBard MB: Smoking, maternal age, fetal growth, and gestational age at delivery. Am J Obstet Gynecol 1990;162:53–58.
10 Clausson B, Cnattingius S, Axelsson O: Preterm and term births of small for gestational age infants: a population-based study of risk factors among nulliparous women. BJOG 1998;105:1011–1017.
11 Ong CYT, Liao AW, Spencer K, Munim S, Nicolaides KH: First trimester maternal serum free β-human chorionic gonadotrophin and pregnancy-associated plasma protein A as predictors of pregnancy complications. BJOG 2000;107:1265–1270.
12 Tul N, Pusenjak S, Osredkar J, Spencer K, Novak-Antolic Z: Predicting complications of pregnancy with first-trimester maternal serum free-β-hCG, PAPP-A and inhibin-A. Prenat Diagn 2003;23:990–996.
13 Yaron Y, Heifetz S, Ochshorn Y, Lehavi O, Orr-Urtreger A: Decreased first trimester PAPP-A is a predictor of adverse pregnancy outcome. Prenat Diagn 2002;22:778–782.

14 Smith GCS, Stenhouse EJ, Crossley JA, Aitken DA, Cameron AD, Connor JM: Early pregnancy levels of pregnancy associated plasma protein A and the risk of intrauterine growth restriction, premature birth, pre-eclampsia and stillbirth. J Clin Endocrinol Metab 2002;87:1762–1767.
15 Dugoff L, Hobbins JC, Malone FD, Porter TF, Luthy D, Comstock CH, Hankins G, Berkowitz RL, Merkatz I, Craigo SD, Timor-Tritsch IE, Carr SR, Wolfe HM, Vidaver J, D'Alton ME: First trimester maternal serum PAPP-A and free β-subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (The FASTER Trial). Am J Obstet Gynecol 2004;191:1446–1451.
16 Smith GC, Shah I, Crossley JA, Aitken DA, Pell JP, Nelson SM, Cameron AD, Connor MJ, Dobbie R: Pregnancy-associated plasma protein A and α-fetoprotein and prediction of adverse perinatal outcome. Obstet Gynecol 2006;107:161–166.
17 Spencer K, Cowans NJ, Avgidou K, Molina F, Nicolaides KH: First-trimester biochemical markers of aneuploidy and the prediction of small-for-gestational age fetuses. Ultrasound Obstet Gynecol 2008;31:15–19.
18 Canini S, Prefumo F, Pastorino D, Crocetti L, Afflitto CG, Venturini PL, De Biasio P: Association between birth weight and first-trimester free β-human chorionic gonadotropin and pregnancy-associated plasma protein A. Fertil Steril 2008;89:174–178.
19 Kelekci S, Yilmaz B, Savan K, Sonmez S: Can increased nuchal translucency in the first trimester of pregnancy predict gestational diabetes mellitus. J Obstet Gynecol 2005;25:579–582.
20 Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH: UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10–14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. Lancet 1998;352:343–346.
21 Kagan KO, Wright D, Baker A, Sahota D, Nicolaides KH: Screening for trisomy 21 by maternal age, fetal NT, free β-hCG and PAPP-A. Ultrasound Obstet Gynecol 2008;31:618–624.
22 Poon LC, Karagiannis G, Staboulidou I, Shafiei A, Nicolaides KH: Reference range of birth weight with gestation and first-trimester prediction of small for gestation neonates. Prenat Diagn 2010 (in press).
23 Zweig MH, Campbell G: Receiver-operating characteristic plots: a fundamental evaluation tool in clinical medicine. Clin Chem 1993;39:561–577.
24 Boulet SL, Alexander GR, Salihu HM, Pass M: Macrosomic births in the United States: determinants, outcomes, and proposed grades of risk. Am J Obstet Gynecol 2003;188:1372–1378.
25 Modanlou HD, Dorchester WL, Thorosian A, Freeman RK: Macrosomia – maternal, fetal, and neonatal implications. Obstet Gynecol 1980;55:420–424.
26 Davis R, Woelk G, Mueller BA, Daling J: The role of previous birthweight on risk for macrosomia in a subsequent birth. Epidemiology 1995;6:607–611.
27 Walsh CA, Mahony RT, Foley ME, Daly L, O'Herlihy C: Recurrence of fetal macrosomia in non-diabetic pregnancies. J Obstet Gynaecol 2007;27:374–378.
28 Mahony R, Walsh C, Foley ME, Daly L, O'Herlihy C: Outcome of second delivery after prior macrosomic infant in women with normal glucose tolerance. Obstet Gynecol 2006;107:857–862.
29 Jolly MC, Sebire NJ, Harris JP, Regan L, Robinson S: Risk factors for macrosomia and its clinical consequences: a study of 350,311 pregnancies. Eur J Obstet Gynecol Reprod Biol 2003;111:9–14.
30 Ramos GA, Caughey AB: The interrelationship between ethnicity and obesity on obstetric outcomes. Am J Obstet Gynecol 2005;193:1089–1093.
31 Mardones-Santander F, Salazar G, Rosso P, Villarroel L: Maternal body composition near term and birth weight. Obstet Gynecol 1998;91:873–877.
32 Lim JH, Tan BC, Jammal AE, Symonds EM: Delivery of macrosomic babies: management and outcomes of 330 cases. J Obstet Gynaecol 2002;22:370–374.
33 Bergmann RL, Richter R, Bergmann KE, Plagemann A, Brauer M, Dudenhausen JW: Secular trends in neonatal macrosomia in Berlin: influences of potential determinants. Paediatr Perinat Epidemiol 2003;17:244–249.
34 Kramer MS, Morin I, Yang H, Platt RW, Usher R, McNamara H, Joseph KS, Wen SW: Why are babies getting bigger? Temporal trends in fetal growth and its determinants. J Pediatr 2002;141:538–542.
35 Susa JB, Langer O: Diabetes and fetal growth; in Reece EA, Coustan DR (eds): Diabetes Mellitus in Pregnancy. New York, Churchill Livingstone, 1995, pp 79–92.
36 Maulik D: Fetal growth restriction: the etiology. Clin Obstet Gynecol 2006;49:228–235.
37 Gardosi J: The application of individualised fetal growth curves. J Perinat Med 1998;26:137–142.
38 Floyd RL, Rimer BK, Giovino GA, Mullen PD, Sullivan SE: A review of smoking in pregnancy: effects on pregnancy outcomes and cessation efforts. Annu Rev Public Health 1993;14:379–411.
39 Ehrenberg HM, Mercer BM, Catalano PM: The influence of obesity and diabetes on the prevalence of macrosomia. Am J Obstet Gynecol 2004;191:964–968.
40 Clausen T, Burski TK, Oyen N, Godang K, Bollerslev J, Henriksen T: Maternal anthropometric and metabolic factors in the first half of pregnancy and risk of neonatal macrosomia in term pregnancies. A prospective study. Eur J Endocrinol 2005;153:887–894.
41 Bo S, Menato G, Gallo ML, Bardelli C, Lezo A, Signorile A, Gambino R, Cassader M, Massobrio M, Pagano G: Mild gestational hyperglycemia, the metabolic syndrome and adverse neonatal outcomes. Acta Obstet Gynecol Scand 2004;83:335–340.
42 Kitajima M, Oka S, Yasuhi I, Fukuda M, Rii Y, Ishimaru T: Maternal serum triglyceride at 24–32 weeks' gestation and newborn weight in nondiabetic women with positive diabetic screens. Obstet Gynecol 2001;97:776–780.
43 Freinkel N, Metzger B: Pregnancy as a tissue culture experience: the critical implications of maternal metabolism for fetal development. Ciba Found Symp 1978;63:3–28.
44 Soltani KH, Bruce C, Fraser RB: Observational study of maternal anthropometry and fetal insulin. Arch Dis Child Fetal Neonatal Ed 1999;81:F122–F124.
45 Robinson S, Viira J, Learner J, Chan SP, Anyaoku V, Beard RW, Johnston DG: Insulin insensitivity is associated with a decrease in postprandial thermogenesis in normal pregnancy. Diabet Med 1993;10:139–145.
46 Thomas CR: Placental transfer of non-esterified fatty acids in normal and diabetic pregnancy. Biol Neonate 1987;51:94–101.
47 Ryan EA, Enns L: Role of gestational hormones in the induction of insulin resistance. J Clin Endocrinol Metab 1988;67:341–347.
48 Ktorza A, Bihoreau MT, Nurjhan N, Picon L, Girard J: Insulin and glucagon during the perinatal period: secretion and metabolic effects on the liver. Biol Neonate 1985;48:204–220.
49 Lawrence JB, Oxvig C, Overgaard MT, Sottrup-Jensen L, Gleich GJ, Hays LG, Yates JR 3rd, Conover CA: The insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease secreted by human fibroblasts is pregnancy-associated plasma protein-A. Proc Natl Acad Sci USA 1999;96:3149–3153.
50 Bonno M, Oxvig C, Kephart GM, Wagner JM, Kristensen T, Sottrup-Jensen L, Gleich GJ: Localization of pregnancy-associated plasma protein-A and colocalization of pregnancy-associated plasma protein-A messenger ribonucleic acid and eosinophil granule major basic protein messenger ribonucleic acid in placenta. Lab Invest 1994;71:560–566.
51 Irwin JC, Suen LF, Martina NA, Mark SP, Giudice LC: Role of the IGF system in trophoblast invasion and pre-eclampsia. Hum Reprod 1999;14(suppl 2):90–96.

52 Leipold H, Worda C, Ozbal A, Husslein P, Krampl E: First-trimester nuchal translucency screening in pregnant women who subsequently developed gestational diabetes. J Soc Gynecol Investig 2005;12:529–532.
53 Spencer K, Cicero S, Atzei A, Otigbah C, Nicolaides KH: The influence of maternal insulin-dependent diabetes on fetal nuchal translucency thickness and first-trimester maternal serum biochemical markers of aneuploidy. Prenat Diagn 2005;25:927–929.
54 Bartha JL, Wood J, Kyle PM, Soothill PW: The effect of metabolic control on fetal nuchal translucency in women with insulin-dependent diabetes: a preliminary study. Ultrasound Obstet Gynecol 2003;21:451–454.
55 National Collaborating Centre for Women's and Children's Health: Commissioned by the National Institute for Health and Clinical Excellence. Antenatal care: routine care for the healthy pregnant woman. CG62: full guidance. March 2008 (corrected June 2008).
56 ACOG Committee on Practice Bulletins: ACOG Practice Bulletin No. 77: Screening for fetal chromosomal abnormalities. Obstet Gynecol 2007;109:217–227.
57 Maiz N, Valencia C, Emmanuel EE, Staboulidou I, Nicolaides KH: Screening for adverse pregnancy outcome by ductus venosus Doppler at $11–13^{+6}$ weeks of gestation. Obstet Gynecol 2008;112:598–605.
58 Poon LC, Akolekar R, Lachmann R, Beta J, Nicolaides KH: Hypertensive disorders in pregnancy: screening by biophysical and biochemical markers at 11–13 weeks. Ultrasound Obstet Gynecol 2010;35:662–670.