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Prediction of large-for-gestational-age neonates: screening by maternal factors and biomarkers in the three trimesters of pregnancy

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KEYWORDS: fetal biometry; large-for-gestational age; maternal history; pyramid of antenatal care; screening

ABSTRACT

Objective *To develop a model based on maternal characteristics and medical history (maternal factors) for the prediction of delivery of large-for-gestational-age (LGA) neonates, and to examine the potential value of first-, second- and third-trimester fetal biometry and biomarkers in improving such a model.*

Methods *This was a screening study in 76 300, 54 999, 25 727 and 6181 singleton pregnancies at 11–13, 19–24, 30–34 and 35–37 weeks' gestation, respectively. The* a-priori *risk for LGA with birth weight > 95th percentile (LGA > 95th) was calculated using multivariable logistic regression analysis to determine which of the maternal factors had a significant contribution. Regression analysis was then used to determine whether screening by a combination of maternal factors, fetal biometry and various biophysical and biochemical markers had significant contribution in predicting delivery of LGA neonates.*

Results *The likelihood of LGA > 95th increased with increasing maternal weight and height and was lower in women of Afro-Caribbean and South Asian racial origins, in cigarette smokers and in nulliparous women. The risk was higher in women with pre-existing diabetes mellitus Type I and lower in those with chronic hypertension. In parous women, the risk increased with birth-weight* Z*-score in previous pregnancy and prior history of gestational diabetes and decreased with interpregnancy interval. Screening by maternal factors at 11–13 weeks predicted 32%, 44% and 60% of LGA > 95th at false-positive rates (FPRs) of 5%, 10% and 20%, respectively. With the addition of fetal biometry, the detection rates improved to 37%, 51% and 68% at 19–24 weeks, 50%, 65% and 81% at 30–34 weeks and 60%, 73% and 85% at 35–37 weeks at FPRs of 5%, 10% and 20%, respectively. The addition of biomarkers did not improve the detection rates achieved when screening by a combination of maternal factors and fetal biometry.*

Conclusion *Combined screening by maternal factors and fetal biometry can predict a high proportion of pregnancies that will deliver LGA neonates. Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Fetal macrosomia is associated with adverse perinatal outcome[1,2]. For the mother, this includes an increased incidence of emergency Cesarean section, operative vaginal delivery, anal sphincter injury, and postpartum hemorrhage[3–8]. The macrosomic neonate is at increased risk of shoulder dystocia, brachial plexus injury, fracture of the clavicle or humerus, birth asphyxia, stillbirth and increased peripartum mortality[3–6,9–12]. Long-term complications for the neonate include increased risk of obesity, Type 2 diabetes mellitus and asthma[2,13–15]. The definition of macrosomia varies between studies, but there is consistency in the trend that the higher the birth weight the greater the risk of adverse outcome. The majority of the associated harm to both mother and neonate is due to traumatic vaginal delivery. Elective delivery by Cesarean section or early induction of labor in suspected macrosomia should reduce this harm. Unfortunately, previous studies and guidelines assessing the effectiveness of elective delivery for a suspected macrosomic fetus are hampered by the poor performance of current models to predict macrosomia[16–18].

An accurate model that could predict prospectively which pregnancies are at risk of delivering a large-for-gestational-age (LGA) baby would be useful in

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counseling women on the risks surrounding attempted vaginal delivery as well as providing the basis for future research on timing of delivery in cases of suspected LGA. The aim of this study was to develop such a model that combined maternal history, fetal biometry and maternal biophysical and biochemical markers.

METHODS

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending their routine hospital visit in the first, second and/or third trimester of pregnancy at King's College Hospital, London, between March 2006 and December 2014 and Medway Maritime Hospital, Kent, between February 2007 and December 2014.

We examined 76 300 singleton pregnancies at 11 + 0 to 13 + 6 weeks' gestation, 54 999 at 19 + 0 to 24 + 6 weeks, 25 727 at 30 + 0 to 34 + 6 weeks and 6181 at 35 + 0 to 37 + 6 weeks. The first-trimester dataset was used to derive the prior risk, based on maternal factors, and all datasets were used to investigate the potential value of combined screening by maternal factors and biophysical or biochemical markers in the three trimesters of pregnancy. In all three trimesters we measured uterine artery pulsatility index (UtA-PI)[19] and obtained maternal blood samples for measurement of serum biochemical markers. In the second and third trimesters, we estimated fetal weight from measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL)[20]. Gestational age was determined from the measurement of fetal crown–rump length (CRL) at 11–13 weeks or the fetal HC at 19–24 weeks[20,21].

The pregnancies included in the study all resulted in the live birth or stillbirth of phenotypically normal babies, delivered at or after 24 weeks' gestation. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the National Health Service research ethics committee.

Maternal history and characteristics

Patient characteristics that were recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous/assisted conception requiring the use of ovulation drugs/*in-vitro* fertilization), cigarette smoking during pregnancy (yes/no), medical history including diabetes mellitus Type 1 or 2, family history of diabetes mellitus (first-, second- or third-degree relative with diabetes mellitus Type 1 or 2), obstetric history including parity (parous/nulliparous if no previous pregnancies ≥ 24 weeks' gestation), previous pregnancy with gestational diabetes (GDM), neonatal birth-weight *Z*-score (corrected for gestational age at delivery[22]) of previous pregnancy and the time interval between the last delivery and conception of the current pregnancy in years. The maternal weight and height were also measured. At the 30–34 and 35–37-week visits, the diagnosis of GDM in the index pregnancy was recorded.

Outcome measures

Details of maternal characteristics, medical and obstetric history and the findings of the assessments at 11–13, 19–24, 30–34 and 35–37 weeks were recorded in our secured database. Data on pregnancy outcome were obtained from the maternity computerized records or the general medical practitioners of the women and were also recorded in our secured database. The primary outcome of the study was delivery of a LGA neonate. The newborn was considered to be LGA if the birth weight was > 95th percentile (LGA > 95th) after correcting for gestational age at delivery[22].

Statistical analysis

The *a-priori* risk for LGA > 95th was calculated using multivariable logistic regression analysis with backward stepwise elimination to determine which maternal factors had significant contribution to LGA > 95th. The observed measurements of biomarkers were $\log_{10}$ transformed to make their distributions Gaussian. Each measured value in the outcome groups was expressed as a multiple of the normal median (MoM) after adjustment for those characteristics found to provide a substantial contribution to the $\log_{10}$ transformed value[23–26]. The observed measurements of fetal nuchal translucency thickness (NT) were expressed as delta values corrected for gestational age[27]. The observed measurements of HC, AC and FL were expressed as *Z*-scores, corrected for gestational age[22]. Mann–Whitney *U*-test was used to compare the biometric *Z*-scores and biomarkers between the outcome groups. Regression analysis was used to determine the significance of association between the $\log_{10}$ MoM values of biomarkers.

Multivariable logistic regression analysis was used to determine if the maternal factor-derived logit (*a-priori* risk), fetal biometry and biomarkers had significant contribution in predicting LGA > 95th. The performance of screening was determined by receiver–operating characteristics (ROC) curves. Similarly, the algorithm was used to determine the performance of screening for LGA defined by birth weight > 90th percentile (LGA > 90th) and > 97th percentile (LGA > 97th) and birth weight > 4000 g (LGA > 4000 g) and > 4500 g (LGA > 4500 g).

The statistical software package SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for data analyses.

RESULTS

Maternal and pregnancy characteristics of the study populations examined at 11–13, 19–24, 30–34 and 35–37 weeks' gestation are presented in Table S1. The Pearson correlations between each of the biomarkers assessed at different stages in pregnancy in

Table 1 Fitted regression model with maternal characteristics and history for prediction of large-for-gestational-age neonates with birth weight > 95th percentile

Variable	*Coefficient*	*SE*	*OR (95% CI)*	P
Intercept	−0.25972	0.05289		
Weight (−69*)	0.04236	0.00180	1.043 (1.040–1.047)	< 0.0001
(Weight (−69*))^2	−0.00071	0.00009	0.999 (0.999–0.999)	< 0.0001
(Weight (−69*))^3	0.000005	0.000001	1.000 (1.000–1.000)	< 0.0001
Height (−164†)	0.03130	0.00261	1.032 (1.027–1.037)	< 0.0001
Cigarette smoking	−0.66881	0.06726	0.512 (0.449–0.585)	< 0.0001
Racial origin				
Caucasian/East Asian/mixed (reference)	0		1	
Afro-Caribbean	−0.66249	0.04993	0.516 (0.468–0.569)	< 0.0001
South Asian	−0.59866	0.12449	0.550 (0.431–0.701)	< 0.0001
Obstetric history and pregnancy interval				
Nulliparous	−0.36238	0.03600	0.696 (0.649–0.747)	< 0.0001
Parous				
No previous GDM (reference)	−2.35162	0.03734		
Previous GDM	0.47894	0.09988	1.730 (1.423–2.104)	< 0.0001
Interpregnancy interval in years	−0.02272	0.00725	0.974 (0.961–0.988)	< 0.0001
Neonatal birth-weight *Z*-score	0.80699	0.01962	2.519 (2.424–2.618)	< 0.0001
Medical disorder				
Chronic hypertension	−0.38936	0.14505	0.677 (0.510–0.900)	0.007
Diabetes mellitus Type 1	1.65817	0.13284	5.250 (4.046–6.811)	< 0.0001

*Subtracted from weight in kg. †Subtracted from height in cm. GDM, gestational diabetes; OR, odds ratio; SE, standard error.

LGA > 95th and those without LGA are demonstrated in Tables S2–S5.

Large-for-gestational age

Prior risk

The *a-priori* risk for LGA > 95th is calculated from the following formula: odds/(1 + odds), where odds = e^Y and Y is derived from multivariable logistic regression analysis. Regression coefficients and adjusted odds ratios of each of the maternal factors in the prediction algorithms are presented in Table 1 ($R^2 = 0.174$, $P < 0.0001$). The likelihood of LGA > 95th increased with increasing maternal weight and height. In parous women, the risk increased with neonatal birth weight *Z*-score in previous pregnancy and decreased with interpregnancy interval and was higher in women with a previous history of gestational diabetes. The risk was higher in women with pre-existing diabetes mellitus Type 1 and lower in women of Afro-Caribbean and South Asian racial origins, in cigarette smokers, in nulliparous women and in women with chronic hypertension. The likelihood of LGA > 95th was not altered significantly by maternal age ($P = 0.128$), method of conception ($P = 0.337$), personal history of systemic lupus erythematosus/antiphospholipid syndrome ($P = 0.813$) or family history of diabetes mellitus ($P = 0.692$).

Performance of screening for LGA > 95th with modifiable maternal risk factors, such as pre-existing diabetes, increased body mass index, previous pregnancy with LGA neonate and previous or current gestational diabetes, that were treated as an individual screening test is demonstrated in Table 2.

11–13-week combined test

At 11–13 weeks, the delta NT, and MoM values for pregnancy-associated plasma protein-A (PAPP-A), free beta-human chorionic gonadotropin (β-hCG) and placental growth factor (PlGF) were significantly higher and UtA-PI MoM was significantly lower ($P < 0.0001$; Table S6) in the LGA > 95th group compared to the non-LGA group. Multivariable logistic regression analyses demonstrated that, in the prediction of LGA > 95th, there were significant independent contributions from maternal factors and combinations of delta NT, $\log_{10}$ MoM values of PAPP-A, free β-hCG and UtA-PI (Table S7), however PlGF MoM did not contribute significantly to this prediction ($P = 0.063$).

Screening by maternal factors at 11–13 weeks predicted 38.3%, 43.6%, 46.8%, 32.0% and 43.9% of LGA > 90th, LGA > 95th, LGA > 97th, LGA > 4000 g and LGA > 4500 g, respectively, at a false-positive rate (FPR) of 10%. The respective detection rates for combined screening with maternal factors, delta NT, PAPP-A, free β-hCG and UtA-PI were 39.8%, 45.8%, 49.2%, 33.6% and 47.7% (Figure 1, Table S8 and Table 3).

19–24-week combined test

At 19–24 weeks, all *Z*-scores of fetal biometric measurements and MoM values for PAPP-A, free β-hCG, PlGF and sFlt-1 were significantly higher and UtA-PI MoM was significantly lower ($P < 0.0001$; Tables S6 and S9) in the LGA > 95th group compared to the non-LGA group. At 19–24 weeks, multivariable logistic regression analyses demonstrated that, in the prediction of LGA > 95th, there were significant independent contributions from maternal factors, fetal biometry and combinations of $\log_{10}$ MoM

Table 2 Performance of screening for large-for-gestational-age neonate with birth weight > 95th percentile (LGA > 95th) using modifiable maternal risk factors

	All		*Non-LGA**		*LGA > 95th*	
Risk factors	n	*DR (% (95% CI))*	n	*DR (% (95% CI))*	n	*DR (% (95% CI))*
11–13 weeks	76 300		68 439		4468	
Type 1 diabetes	367	0.5 (0.4–0.5)	229	0.4 (0.3–0.4)	110	2.5 (2.0–3.0)
Previous GDM	945	1.2 (1.2–1.3)	707	1.0 (1.0–1.1)	161	3.6 (3.1–4.2)
BMI ≥ 30 kg/m^2	13 542	17.7 (17.5–18.0)	11 316	16.5 (16.3–16.8)	1432	32.1 (30.7–33.4)
Previous LGA > 95th	2516	3.3 (3.2–3.4)	1491	2.2 (2.1–2.3)	721	16.1 (15.1–17.2)
At least one	15 849	20.8 (20.5–21.1)	12 867	18.8 (18.5–19.1)	1928	43.2 (41.7–44.6)
35–37 weeks	6181		5520		381	
Type 1 diabetes	39	0.6 (0.5–0.9)	37	0.7 (0.5–0.9)	11	2.9 (1.6–5.1)
GDM in index pregnancy	221	3.6 (3.1–4.1)	176	3.2 (2.8–3.7)	24	6.3 (4.3–9.2)
BMI ≥ 30 kg/m^2	1099	17.8 (16.8–18.8)	878	15.9 (15.0–16.9)	131	34.4 (29.8–39.3)
Previous LGA > 95th	257	4.2 (3.7–4.7)	139	2.5 (2.1–3.0)	82	21.5 (17.7–25.9)
At least one	1418	22.9 (21.9–24.0)	1101	19.9 (18.9–21.0)	191	50.1 (45.1–55.1)

*Non-LGA defined as birth weight < 90th percentile. BMI, body mass index; DR, detection rate; GDM, gestational diabetes.

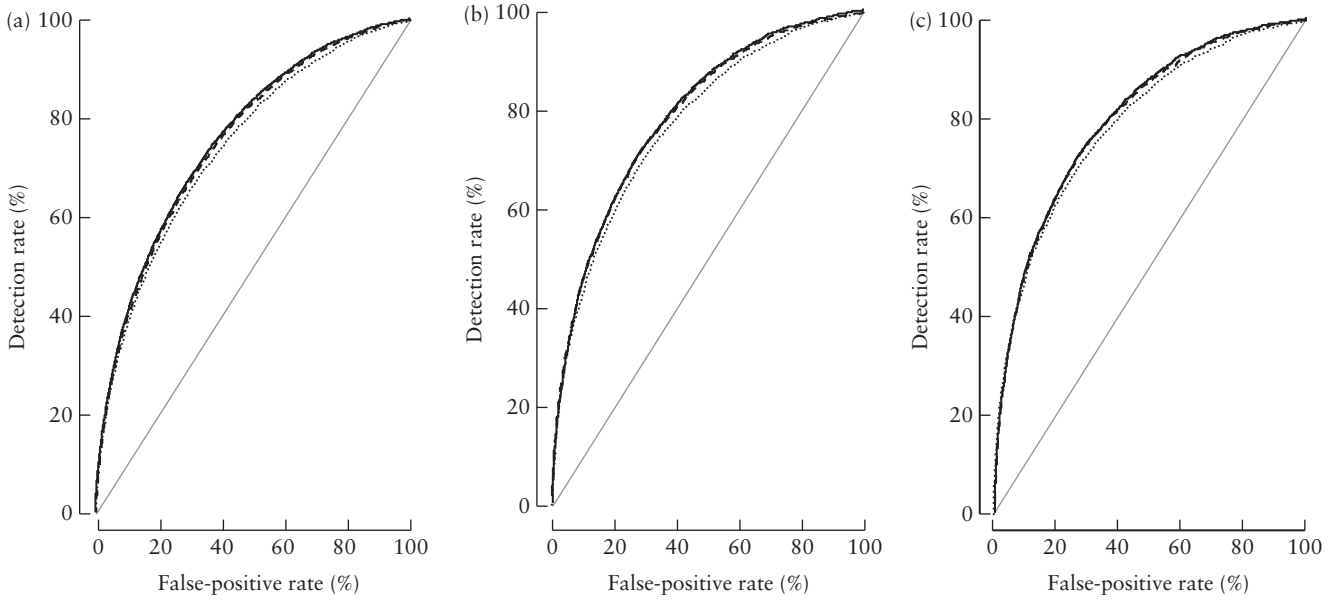

Figure 1 Receiver–operating characteristics curves of maternal factors (·····), maternal factors with fetal nuchal translucency (NT), pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotropin (β-hCG) (– – – –) and maternal factors with fetal NT, PAPP-A, β-hCG and uterine artery pulsatility index (——), at 11–13 weeks, in the prediction of large-for-gestational-age neonates with birth weight > 90th (a), > 95th (b) and > 97th (c) percentiles.

values of PAPP-A and UtA-PI (Table S10), however maternal serum free β-hCG ($P = 0.058$), PlGF ($P = 0.469$) and sFlt-1 ($P = 0.592$) did not contribute significantly to this prediction.

Combined screening by maternal factors and fetal biometry at 19–24 weeks predicted 43.9%, 50.5%, 54.3%, 36.0% and 52.2% of LGA > 90th, LGA > 95th, LGA > 97th, LGA > 4000 g and LGA > 4500 g, respectively, at a FPR of 10%. The respective detection rates for combined screening with maternal factors, fetal biometry, maternal serum PAPP-A and UtA-PI were 45.7%, 53.7%, 55.9%, 40.6% and 57.3% (Figure 2, Table S11 and Table 3).

30–34-week combined test

At 30–34 weeks, all *Z*-scores of fetal biometric measurements and MoM values for PAPP-A, PlGF and sFlt-1 were significantly higher and UtA-PI MoM was significantly lower ($P < 0.0001$; Table S6 and S9) in the LGA > 95th group compared to the non-LGA group; free β-hCG MoM was not significantly different between outcome groups. At 30–34 weeks, multivariable logistic regression analyses demonstrated that, in the prediction of LGA > 95th, there were significant independent contributions from maternal factors, fetal biometry and combinations of $\log_{10}$ MoM values of PlGF and UtA-PI (Table S12), however a diagnosis of GDM in the index pregnancy ($P = 0.846$), maternal serum PAPP-A ($P = 0.469$) and sFlt-1 ($P = 0.131$) did not contribute significantly to this prediction.

Combined screening by maternal factors and fetal biometry at 30–34 weeks predicted 56.9%, 65.2%, 70.4%, 46.0% and 70.3% of LGA > 90th, LGA > 95th, LGA > 97th, LGA > 4000 g and LGA > 4500 g, respectively, at a FPR of 10%. The respective detection rates for

Table 3 Performance of screening for large-for-gestational-age neonates with birth weight > 95th percentile by a combination of maternal characteristics, medical and obstetric history, fetal biometry and biomarkers

	DR (95% CI)(%) for fixed FPR			*FPR (95% CI)(%) for fixed DR*		
Screening test	*FPR = 5%*	*FPR = 10%*	*FPR = 20%*	*DR = 80%*	*DR = 90%*	*DR = 100%*
11–13 weeks						
Maternal characteristics and history	31.7 (30.4–33.1)	43.6 (42.1–45.0)	59.7 (58.2–61.1)	41.6 (41.3–42.0)	59.3 (59.0–59.7)	99.9 (99.9–99.9)
Maternal characteristics and history plus:						
NT, β-hCG, PAPP-A, UtA-PI	31.3 (29.7–33.0)	45.8 (44.1–47.6)	61.7 (60.0–63.4)	38.9 (38.5–39.4)	56.7 (56.3–57.2)	99.9 (99.9–100.0)
19–24 weeks						
Maternal characteristics and history plus:						
Biometry	37.1 (35.4–38.8)	50.5 (48.7–52.2)	67.7 (66.0–69.3)	32.1 (31.7–32.5)	50.1 (49.7–50.6)	99.6 (99.6–99.7)
Biometry, PAPP-A, UtA-PI	38.3 (32.7–44.0)	53.7 (47.8–59.5)	70.1 (64.6–75.3)	30.1 (28.7–31.5)	45.0 (43.5–46.6)	99.2 (98.9–99.4)
30–34 weeks						
Maternal characteristics and history plus:						
Biometry	50.4 (47.8–53.0)	65.2 (62.7–67.6)	80.8 (78.7–82.8)	19.4 (18.9–19.9)	32.6 (31.9–33.1)	99.6 (99.5–99.7)
Biometry, PlGF, UtA-PI	48.2 (44.1–52.3)	67.0 (63.0–70.7)	84.4 (81.2–87.2)	15.8 (15.0–16.5)	28.2 (27.2–29.1)	99.7 (99.6–99.8)
35–37 weeks						
Maternal characteristics and history plus:						
Biometry	59.8 (54.7–64.8)	72.7 (67.9–77.1)	85.0 (81.1–88.5)	15.0 (14.0–15.9)	28.5 (27.3–29.7)	83.1 (82.1–84.1)
Biometry, PlGF	59.0 (52.8–65.0)	72.8 (67.0–78.1)	86.6 (81.8–90.5)	14.9 (13.7–16.1)	26.0 (24.6–27.5)	89.3 (88.3–90.3)

β-hCG, free β-human chorionic gonadotropin; DR, detection rate; FPR, false-positive rate; NT, nuchal translucency; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

combined screening with maternal factors, fetal biometry, maternal serum PlGF and UtA-PI were 57.0%, 67.0%, 70.9%, 46.9% and 71.4% (Figure 3, Table S13 and Table 3).

35–37-week combined test

At 35–37 weeks, all *Z*-scores of fetal biometric measurements and PlGF MoM were significantly higher and UtA-PI MoM was significantly lower ($P < 0.0001$; Table S6 and S9) in the LGA > 95th group compared to the non-LGA group; sFlt-1 MoM was not significantly different between outcome groups. At 35–37 weeks, multivariable logistic regression analyses demonstrated that in the prediction of LGA > 95th there were significant independent contributions from maternal factors, fetal biometry and $\log_{10}$ MoM PlGF (Table S14), however a diagnosis of GDM in the index pregnancy ($P = 0.100$), maternal serum sFlt-1 ($P = 0.173$) and UtA-PI ($P = 0.231$) did not contribute significantly to this prediction.

Combined screening by maternal factors and fetal biometry at 35–37 weeks predicted 64.2%, 72.7%, 75.9%, 51.4% and 69.2% of LGA > 90th, LGA > 95th, LGA > 97th, LGA > 4000 g and LGA > 4500 g, respectively, at a FPR of 10%. The respective detection rates for combined screening with maternal factors, fetal biometry and maternal serum PlGF were 65.1%, 72.8%, 77.1%, 53.3% and 71.1% (Figure 4, Table S15 and Table 3).

DISCUSSION

Main findings of the study

This screening study for LGA neonates in a large unselected population of pregnant women attending for routine scans has demonstrated that the risk for delivering LGA neonates can be predicted from combined screening with maternal factors and fetal biometry at 19–24, 30–34 and 35–37 weeks' gestation.

The model on maternal factors demonstrated that the risk for delivering LGA neonates is higher in parous women with previous GDM and in women with a medical history of Type 1 diabetes mellitus. The risk is lower in women of Afro-Caribbean and South Asian racial origin than in Caucasian women, in cigarette smokers than in non-smokers, in nulliparous women than in parous women without previous GDM, and in those with a medical history of chronic hypertension. The risk increases with increasing maternal weight and height, and, in parous women, the risk increases with neonatal birth weight in previous pregnancy and decreases with interpregnancy interval.

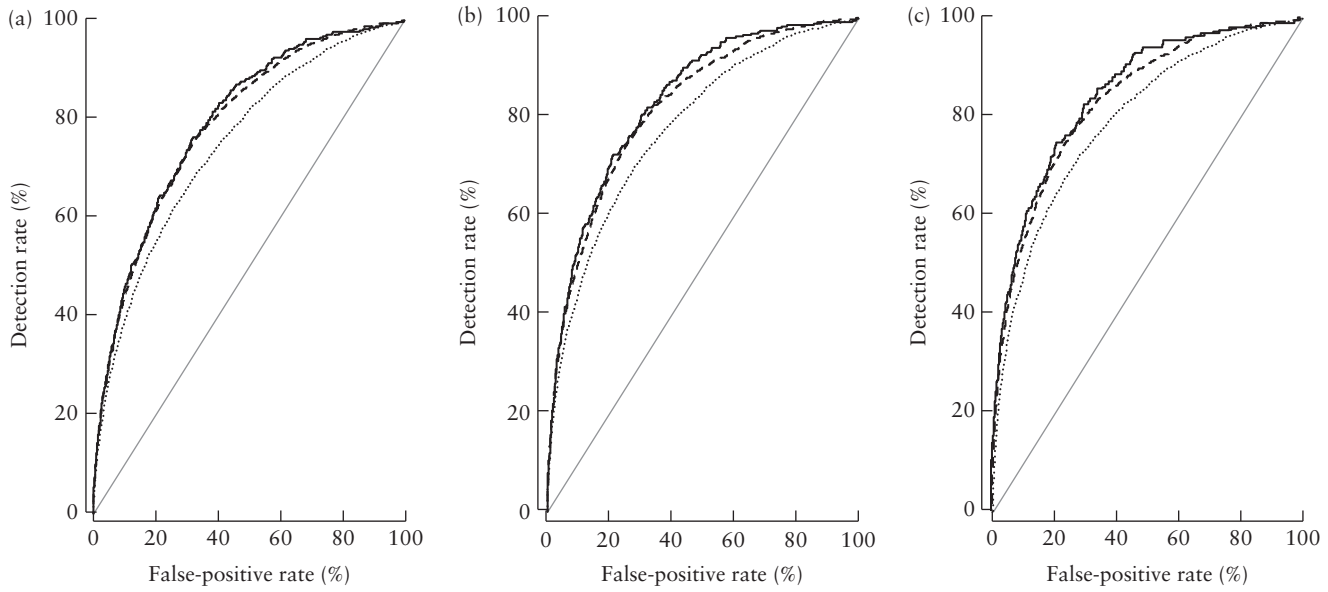

Figure 2 Receiver–operating characteristics curves of maternal factors (·····), maternal factors with fetal biometry (– – – –) and maternal factors with fetal biometry, maternal serum pregnancy-associated plasma protein-A and uterine artery pulsatility index (———), at 19–24 weeks, in the prediction of large-for-gestational-age neonates with birth weight > 90th (a), > 95th (b) and > 97th (c) percentiles.

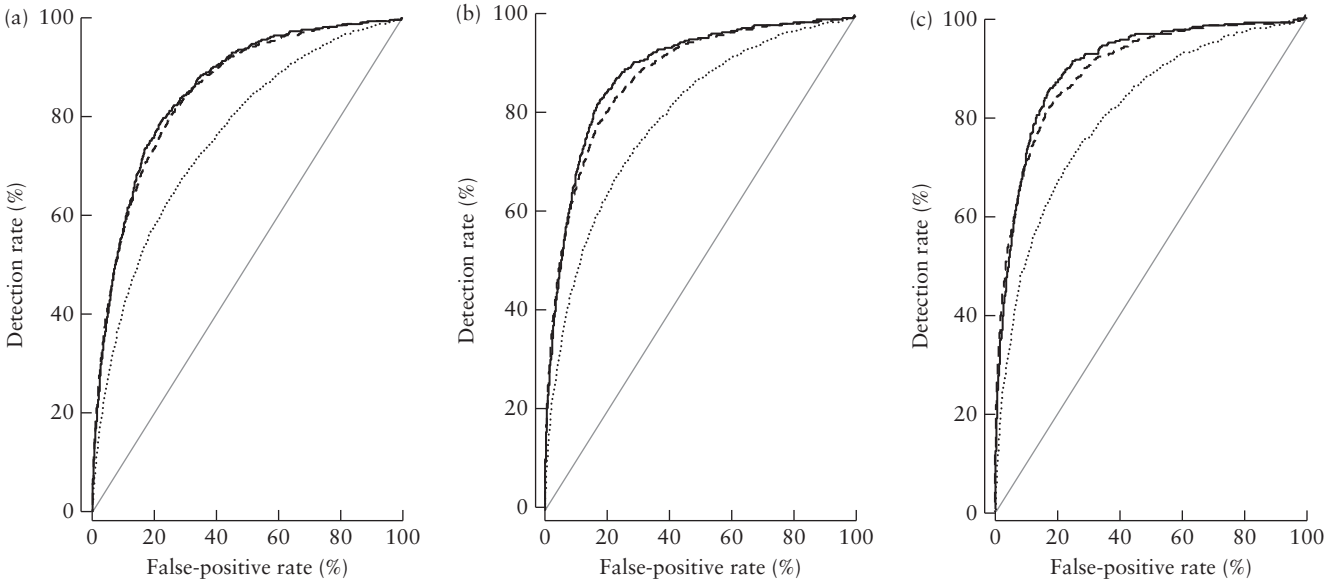

Figure 3 Receiver–operating characteristics curves of maternal factors (·····), maternal factors with fetal biometry (– – – –) and maternal factors with fetal biometry, maternal serum placental growth factor (PlGF) and uterine artery pulsatility index (———), at 30–34 weeks, in the prediction of large-for-gestational-age neonates with birth weight > 90th (a), > 95th (b) and > 97th (c) percentiles.

The findings of this study confirm that, in pregnancies that deliver LGA neonates, fetal biometric measurements at 19–24, 30–34 and 35–37 weeks are increased, and maternal serum metabolites of placental function are increased and UtA-PI is decreased across all trimesters. In addition, fetal NT at 11–13 weeks is increased. However, addition of biomarkers does not improve the performance of screening beyond that obtained by maternal factors and fetal biometry in the second and third trimesters. The performance of the combined test was best at 35–37 weeks, when the detection rate was 73% at a 10% FPR, rather than at 19–24 weeks (51%) or 30–34 weeks (65%).

Comparison with findings from previous studies

The risk factors for LGA incorporated in our new model have been reported in previous studies[3,7,8,28–40]. In our study, continuous variables were treated as such and the risk factors were combined through multivariable logistic analysis that attributes the appropriate importance to each factor and takes into account their possible inter-relations. This approach is an essential first step in the use of a combination of maternal factors with fetal biometry for the continuing development of more effective methods of screening for LGA.

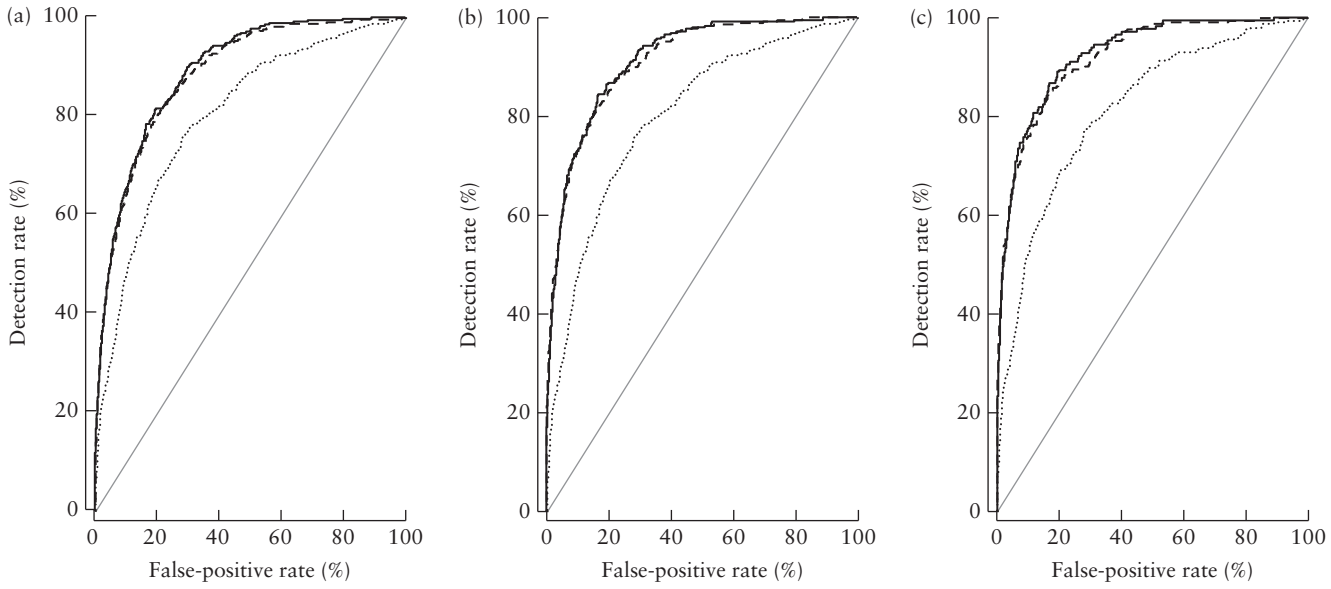

Figure 4 Receiver–operating characteristics curves of maternal factors (·····), maternal factors with fetal biometry (– – – –) and maternal factors with fetal biometry and maternal serum placental growth factor (———), at 35–37 weeks, in the prediction of large-for-gestational-age neonates with birth weight > 90th (a), > 95th (b) and > 97th (c) percentiles.

A systematic review of 20 ultrasound studies on the prediction of birth weight > 4000 g highlighted the great heterogeneity between the studies, in terms of gestational age at investigation which ranged from 28 to ≥ 41 weeks, number of cases examined which ranged from 74 to 1690, prior risk of study populations and fetal measurements recorded; the reported detection rates ranged from 12% to 75% and FPRs ranged from 1% to 32%[41]. Several recent studies have also reported the use of ultrasound-derived estimated fetal weight (EFW) in the third trimester for prediction of delivery of LGA neonates. Kayem *et al.* examined 1689 pregnancies within 8 days of delivery after 37 weeks; the detection rate of birth weight > 4000 g, from EFW derived from the fetal AC, was 54% at a FPR of 5%[42]. Pilalis *et al.* examined 2308 pregnancies and reported that the detection rate of LGA > 95th percentile was 31% at a 10% FPR from a combination of maternal weight, height, fetal CRL and delta NT at 11–13 weeks' gestation and this increased to 52% with the addition of fetal biometry at 30–32 weeks[43]. The same group evaluated screening for LGA > 95th at two different points in the third trimester, with 3690 pregnancies assessed at 30–34 weeks and 2288 at 34–37 weeks; they reported that the detection rate from screening with EFW alone was 53% at 30–34 weeks, at a 10% FPR, and this improved to 63% at 34–37 weeks[44]. In our study of combined screening with maternal factors and fetal biometry, the detection rate of LGA > 95th was 65% at 30–34 weeks and 73% at 35–37 weeks, at a 10% FPR.

Implications for clinical practice

In the proposed new pyramid of pregnancy care[45], first-trimester identification of pregnancies at high risk for subsequent delivery of LGA neonates has the potential to reduce the prevalence of LGA through restriction of maternal weight gain during pregnancy. However, recent randomized studies have reported that, certainly in obese pregnant women, measures such as lifestyle intervention or administration of metformin does not reduce maternal weight gain or the rate of fetal macrosomia[46,47]. The extent to which alternative strategies prove to be beneficial will be the subject of future investigations.

The value of identifying pregnancies with LGA fetuses in the third trimester of pregnancy relates to the potential of reducing macrosomia-related adverse events during labor and delivery. This harm can only be reduced by appropriate intervention. A randomized trial reported that clinically significant shoulder dystocia could be reduced through early term induction of labor in cases of suspected macrosomia[48]. Campbell suggested that pregnancies identified as being LGA at a routine scan at 30–34 weeks' gestation should have a diagnostic scan at 39 weeks and, if EFW is > 4500 g, women should be offered elective Cesarean section[1]. Based on the findings from our study, we believe that the timing of screening for LGA should be at 35–37 weeks, rather than at 30–34 weeks. Counseling women identified as high risk for a LGA fetus will remain problematic until more definitive intervention studies are performed.

Our study provides the basis for identifying high-risk pregnancies that would be the subject of future intervention studies. We found that a combination of maternal factors and fetal biometry at 36 weeks' gestation could identify about 75% of pregnancies with macrosomic fetuses, at a 10% FPR.

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REFERENCES

1. Campbell S. Fetal macrosomia: a problem in need of a policy. *Ultrasound Obstet Gynecol* 2014; **43**: 3–10.
2. Henriksen T. The macrosomic fetus: a challenge in current obstetrics. *Acta Obstet Gynecol Scand* 2008; **87**: 134–145.
3. 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.
4. Bjørstad AR, Irgens-Hansen K, Daltveit AK, Irgens LM. Macrosomia: mode of delivery and pregnancy outcome. *Acta Obstet Gynecol Scand* 2010; **89**: 664–669.
5. King JR, Korst LM, Miller DA, Ouzounian JG. Increased composite maternal and neonatal morbidity associated with ultrasonographically suspected fetal macrosomia. *J Matern Fetal Neonatal Med* 2012; **25**: 1953–1959.
6. Das S, Irigoyen M, Patterson MB, Salvador A, Schutzman DL. Neonatal outcomes of macrosomic births in diabetic and non-diabetic women. *Arch Dis Child* 2009; **96**: F419–22.
7. 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.
8. Stotland NE, Caughey AB, Breed EM, Escobar GJ. Risk factors and obstetric complications associated with macrosomia. *Int J Gynaecol Obstet* 2004; **87**: 220–226.
9. Zhang X, Decker A, Platt RW, Kramer MS. How big is too big? The perinatal consequences of fetal macrosomia. *Am J Obstet Gynecol* 2008; **198**: 517.e1–6.
10. Esakoff TF, Cheng YW, Sparks TN, Caughey AB. The association between birthweight 4000 g or greater and perinatal outcomes in patients with and without gestational diabetes mellitus. *Am J Obstet Gynecol* 2009; **200:** 672.e1–4.
11. Gupta N, Kiran TU, Mulik V, Bethel J, Bhal K. The incidence, risk factors and obstetric outcome in primigravid women sustaining anal sphincter tears. *Acta Obstet Gynecol Scand* 2003; **82**: 736–743.
12. Casey BM, Schaffer JI, Bloom SL, Heartwell SF, McIntire DD, Leveno KJ. Obstetric antecedents for postpartum pelvic floor dysfunction. *Am J Obstet Gynecol* 2005; **192**: 1655–1662.
13. Rogers I, EURO-BLCS Study Group. The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life. *Int J Obes Relat Metab Disord* 2003; **27**: 755–777.
14. Sin DD, Spier S, Svenson LW, Schopflocher DP, Senthilselvan A, Cowie RL, Man SFP. The relationship between birth weight and childhood asthma: a population-based cohort study. *Arch Pediatr Adolesc Med* 2004; **158**: 60–64.
15. Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A. Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. *Am J Epidemiol* 2007; **165**: 849–857.
16. Irion O, Boulvain M. Induction of labour for suspected fetal macrosomia. Irion O, ed. *Cochrane Database Syst Rev* 2000; **2**: CD000938.
17. Rouse DJ, Owen J, Goldenberg RL, Cliver SP. The effectiveness and costs of elective cesarean delivery for fetal macrosomia diagnosed by ultrasound. *JAMA* 1996; **276**: 1480–1486.
18. ACOG. ACOG_Practice_Bulletin_Macrosomia. *Obstet Gynecol* 2000: 1–11.
19. Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH. One-stage screening for pregnancy complications by color doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol* 2000; **96**: 559–564.
20. Snijders RJ, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34–48.
21. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *BJOG* 1975; **82**: 702–710.
22. Poon LCY, Volpe N, Muto B, Syngelaki A, Nicolaides KH. Birthweight with gestation and maternal characteristics in live births and stillbirths. *Fetal Diagn Ther* 2012; **32**: 156–165.
23. Kagan KO, Wright D, Baker A, Sahota D, Nicolaides KH. Screening for trisomy 21 by maternal age, fetal nuchal translucency thickness, free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. *Ultrasound Obstet Gynecol* 2008; **31**: 618–624.
24. Tayyar A, Guerra L, Wright A, Wright D, Nicolaides KH. Uterine artery pulsatility index in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 689–697.
25. Tsiakkas A, Duvdevani N, Wright A, Wright D, Nicolaides KH. Serum soluble fms-like tyrosine kinase-1 in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 584–590.
26. Tsiakkas A, Duvdevani N, Wright A, Wright D, Nicolaides KH. Serum placental growth factor in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 591–598.
27. Wright D, Kagan KO, Molina FS, Gazzoni A, Nicolaides KH. A mixture model of nuchal translucency thickness in screening for chromosomal defects. *Ultrasound Obstet Gynecol* 2008; **31**: 376–383.
28. Poon LCY, Karagiannis G, Stratieva V, Syngelaki A, Nicolaides KH. First-trimester prediction of macrosomia. *Fetal Diagn Ther* 2011; **29**: 139–147.
29. Berkus MD, Conway D, Langer O. The large fetus. *Clin Obstet Gynecol* 1999; **42**: 766–784.
30. Spellacy WN, Miller S, Winegar A, Peterson PQ. Macrosomia--maternal characteristics and infant complications. *Obstet Gynecol* 1985; **66**: 158–161.
31. 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.
32. 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.
33. 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**: 857–662.
34. Ramos GA, Caughey AB. The interrelationship between ethnicity and obesity on obstetric outcomes. *Am J Obstet Gynecol* 2005; **193**: 1089–1093.
35. Mardones-Santander F, Salazar G, Rosso P, Villarroel L. Maternal body composition near term and birth weight. *Obstet Gynecol* 1998; **91**: 873–877.
36. 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.
37. 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.
38. Susa JB, Langer O. Diabetes mellitus in pregnancy. *In Diabetes and fetal growth*; Reece EA, Coustan DR, eds. New York: Churchill Livingstone; 1995. p79–92.
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. Floyd RL, Rimer BK, Giovino GA, Mullen PD, Sullivan SE. A review of smoking in pregnancy: effects on pregnancy outcomes and cessation efforts. *Ann Rev Pub Health* 1993; **14**: 379–411.
41. Chauhan SP, Grobman WA, Gherman RA, Chauhan VB, Chang G, Magann EF, Hendrix NW. Suspicion and treatment of the macrosomic fetus: a review. *Am J Obstet Gynecol* 2005; **193**: 332–346.
42. Kayem G, Grangé G, Bréart G, Goffinet F. Comparison of fundal height measurement and sonographically measured fetal abdominal circumference in the prediction of high and low birth weight at term. *Ultrasound Obstet Gynecol* 2009; **34**: 566–571.
43. Pilalis A, Souka AP, Papastefanou I, Michalitisi V, Panagopoulos P, Chrelias C, Kassanos D. Third trimester ultrasound for the prediction of the large for gestational age fetus in low-risk population and evaluation of contingency strategies. *Prenat Diagn* 2012; **32**: 846–853.
44. Souka AP, Papastefanou I, Pilalis A, Michalitsi V, Panagopoulos P, Kassanos D. Performance of the ultrasound examination in the early and late third trimester for the prediction of birth weight deviations. *Prenat Diagn* 2013; **33**: 1–6.
45. Nicolaides KH. Turning the pyramid of prenatal care. *Fetal Diagn Ther* 2011; **29**: 183–196.
46. Poston L, Bell R, Croker H, Flynn AC, Godfrey KM, Goff L, Hayes L, Khazaezadeh N, Nelson SM, Oteng-Ntim E, Pasupathy D, Patel N, Robson SC, Sandall J, Sanders TA, Sattar N, Seed PT, Wardle J, Whitworth MK, Briley AL; UPBEAT Trial Consortium. Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol* 2015; **3**: 767–777.
47. Chiswick C, Reynolds RM, Denison F, Drake AJ, Forbes S, Newby DE, Walker BR, Quenby S, Wray S, Weeks A, Lashen H, Rodriguez A, Murray G, Whyte S, Norman JE. Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2015; **3**: 778–786.
48. Boulvain M, Senat MV, Perrotin F, Winer N, Beucher G, Subtil D, Bretelle F, Azria E, Hejaiej D, Vendittelli F, Capelle M, Langer B, Matis R, Connan L, Gillard P, Kirkpatrick C, Ceysens G, Faron G, Irion O, Rozenberg P; Groupe de Recherche en Obstétrique et Gynécologie (GROG). Induction of labour versus expectant management for large-for-date fetuses: a randomised controlled trial. *Lancet* 2015; **385**: 1–6.

SUPPORTING INFORMATION ON THE INTERNET

Tables S1–S15 may be found in the online version of this article.

This article has been selected for Journal Club.

A slide presentation, prepared by Dr Aly Youssef, one of UOG's Editors for Trainees, is available online.

Chinese translation by Dr Yang Fang.

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RESUMEN

Objetivo Desarrollar un modelo, basado en las características maternas y la historia médica (factores maternos), con el objetivo de predecir el parto de recién nacidos grandes para la edad gestacional (GEG), valorar el potencial de las biometrías y los biomarcadores del feto en el primer, segundo y tercer trimestre como parámetros que contribuyan a mejorar dicho modelo.

Métodos Este fue un estudio de cribado de 76 300, 54 999, 25 727 y 6181 embarazos únicos entre las semanas de gestación 11–13, 19–24, 30–34 y 35–37, respectivamente. El riesgo *a priori* de neonatos GEG con un peso al nacer > percentil 95 (GEG > p95) se calculó por medio de un análisis de regresión logística multivariable para determinar cuales factores maternos tuvieron una contribución significativa. A continuación se empleó un análisis de regresión para determinar si el cribado mediante una combinación de factores maternos, biometría fetal y una serie de marcadores bioquímicos y biofísicos contribuyó significativamente en la predicción del parto de recién nacidos GEG.

Resultados La probabilidad de GEG > p95 aumentó con el incremento del peso y la altura maternos, y fue menor en mujeres de origen étnico afrocaribeño y de Asia del Sur, en gestantes con hábito tabáquico y en nulíparas. Se encontró un mayor riesgo en mujeres con diabetes *mellitus* tipo 1 preexistente y menor en aquellas con hipertensión crónica. En mujeres no nulíparas, el riesgo aumentó en aquellas en cuyo embarazo anterior se obtuvo recién nacido en Z-score y con historia previa de diabetes gestacional, y disminuyó con el intervalo entre embarazos. El cribado mediante factores maternos entre las semanas 11–13 predijo un 32%, 44% y 60% de GEG > 95, con tasas de falsos positivos (TFP) del 5%, 10% y 20%, respectivamente. Con la incorporación de la biometría fetal al modelo, las tasas de detección mejoraron hasta el 37%, 51% y 68% para las semanas 19–24, el 50%, 65% y 81% para las semanas 30–34 y el 60%, 73% y 85% para las semanas 35–37, con TFP del 5%, 10% y 20%, respectivamente. La incorporación de biomarcadores no mejoró las tasas de detección logradas el cribado mediante una combinación de factores maternos y biometría fetal.

Conclusión El cribado mediante una combinación de factores maternos y biometría fetal puede predecir una alta proporción de embarazos que conllevarán recién nacidos GEG.

目的：根据母体特征和病史（母体因素），开发一个预测分娩大于胎龄（large-for-gestational-age，LGA）新生儿的模型，并研究妊娠早期、妊娠中期和妊娠晚期胎儿生物测量和生物标志物对于改进这一模型的潜在价值。

方法：本研究分别对 76 300 例孕 11~13 周、54 999 例孕 19~24 周、25 727 例孕 30~34 周和 6181 例孕 35~37 周的单胎妊娠进行筛查研究。应用多变量 logistic 回归分析计算出生体重>第 95 百分位数（LGA>95th）时 LGA 的验前风险，确定哪些母体因素发挥重要作用。然后采用回归分析确定结合母体因素、胎儿生物测量以及各种生物物理和生物化学标志物进行筛查，是否对预测分娩 LGA 新生儿发挥重要作用。

结果：LGA>95th 的概率随母体体重和身高增加而增加，在加勒比黑人和南亚女性、吸烟女性和初产妇中较低。妊娠前已患有 1 型糖尿病的女性中风险较高，而慢性高血压女性中风险较低。经产妇中，风险随之前妊娠的出生体重 Z 评分和妊娠期糖尿病既往史而增加，随妊娠间隔时间增加而降低。对孕 11~13 周的母体因素进行筛查，假阳性率（false-positive rates，FPRs）为 5%、10%和 20%时，LGA>95th 预测率分别为 32%、44%和 60%。结合胎儿生物测量后，假阳性率为 5%、10%和 20%时，检出率在孕 19~24 周时提高至 37%、51%和 68%，在孕 30~34 周时提高至 50%、65%和 81%，在孕 35~37 周时提高至 60%、73%和 85%。增加生物标志物并不能提高结合母体因素和胎儿生物测量进行筛查的检出率。

结论：结合母体因素和胎儿生物测量进行筛查能够预测很高比例的分娩 LGA 新生儿的妊娠。