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Prediction of gestational diabetes mellitus by maternal factors and biomarkers at 11 to 13 weeks†

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Objective To develop a model for the prediction of gestational diabetes mellitus (GDM) from maternal characteristics and biochemical markers at 11 to 13 weeks' gestation.

Methods A prospective screening study on early prediction of pregnancy complications ($n = 11,464$), including 297 (2.6%) cases of GDM was used to create the predictive model of GDM based on maternal characteristics. Maternal serum concentrations of adiponectin, follistatin-like-3 (FSTL3) and sex hormone-binding globulin (SHBG) were measured in a case-control study of 80 women who developed GDM and 300 controls.

Results In the screening study, maternal age, body mass index, racial origin, previous history of GDM and macrosomic neonate were significant independent predictors of future GDM. In the GDM group, compared to controls, the median multiple of the normal median adiponectin (0.66; IQR: 0.5–0.9 vs 1.02; IQR: 0.7–1.29) and SHBG (0.81; IQR: 0.6–1.04 vs 1.02; IQR: 0.8–1.2) was lower ($p < 0.05$), but FSTL3 was not significantly different. In screening for GDM by maternal characteristics, the detection rate was 61.6% at a false-positive rate of 20% and the detection increased to 74.1% by the addition of adiponectin and SHBG.

Conclusion First-trimester screening for GDM can be provided by a combination of maternal characteristics and biomarkers. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS: adiponectin; sex hormone-binding globulin; follistatin-like-3; gestational diabetes mellitus

INTRODUCTION

Gestational diabetes mellitus (GDM) is associated with increased risk of maternal and perinatal short-term and long-term complications (Casey *et al*., 1997; Crowther *et al*., 2005; Clausen *et al*., 2008; Feig *et al*., 2008; Metzger *et al*., 2008; Bellamy *et al*., 2009). The frequency of adverse pregnancy outcomes can be reduced by the appropriate treatment of GDM (Crowther *et al*., 2005; Horvath *et al*., 2010). However, there is no internationally accepted method of screening. In the UK, it is recommended that an oral glucose tolerance test (OGTT), which is the diagnostic test for GDM, should be offered to women with any one of the following risk factors: body mass index (BMI) >30 kg/m^2, previous history of GDM or macrosomic baby (>4.5 kg), family history of diabetes or racial origin with a high prevalence of diabetes such as South Asian, African-Caribbean and Middle Eastern (NICE, 2008). The performance of such screening is poor with a detection rate of about 60% at a false-positive rate of 30 to 40% (Scott *et al*., 2002; Waugh *et al*., 2007).

Previous studies investigating the potential value of first-trimester maternal biomarkers for early prediction of GDM reported promising results for adiponectin, follistatin-like-3 (FSTL3) and sex hormone-binding globulin (SHBG) (Thadhani *et al*., 2003, 2010; Williams *et al*., 2004; Worda *et al*., 2004; Spencer *et al*., 2005; Smirnakis *et al*., 2007; Georgiou *et al*., 2008; Lain *et al*., 2008; Paradisi *et al*., 2010).

The aims of this study are (1) to develop a model for the prediction of GDM based on multivariate analysis of factors from maternal history and characteristics; (2) to investigate further the maternal serum concentrations of adiponectin, FSTL3 and SHBG at 11 to 13 weeks in pregnancies that subsequently develop GDM and (3) to estimate the performance of early screening for GDM by a combination of maternal factors and serum biochemistry.

METHODS

Screening study population

The study population for the development of the model for prediction of GDM based on factors from maternal history and characteristics was derived from a prospective screening study on early prediction of pregnancy complications. In women attending for their routine first hospital visit in pregnancy at King's College Hospital, London, at 11^{+0} to 13^{+6} weeks of gestation, we

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record maternal characteristics and medical history and perform an ultrasound scan to (1) confirm gestational age from the measurement of the fetal crown-rump length (CRL), (2) diagnose any major fetal abnormalities and (3) measure fetal nuchal translucency (NT) thickness as part of screening for chromosomal abnormalities. In addition, the maternal serum pregnancy-associated plasma protein-A and free ß-human chorionic gonadotrophin are determined and the results are combined with the fetal NT to calculate the patient-specific risk for trisomy 21 (Snijders *et al*., 1998; Kagan *et al*., 2008). Additional blood is obtained from the women and samples of serum and plasma are stored at −80 °C for subsequent biochemical analysis. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by King's College Hospital Ethics Committee.

The inclusion criteria for this study on screening for GDM were singleton pregnancy delivering a phenotypically normal neonate at or after 30 weeks of gestation. We excluded pregnancies with pre-pregnancy diabetes mellitus type 1 or 2, those ending in termination, miscarriage or delivery before 30 weeks because they may not have had screening and diagnosis of GDM.

Maternal history and characteristics

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), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), medical history including pre-pregnancy diabetes mellitus type 1 or 2, family history of diabetes mellitus (first- or second-degree relative with diabetes mellitus type 1 or 2) and obstetric history including outcome of each pregnancy. The questionnaire was then reviewed by a doctor together with the patient and for the purpose of this study women were classified as parous or nulliparous with no previous pregnancies at or beyond 24 weeks and if parous we recorded whether any of the previous pregnancies were complicated by GDM (yes or no) or the delivery of a macrosomic neonate with birth weight above the 90th centile for gestational age (yes or no) (Poon *et al*., 2010). The maternal weight and height were measured and the BMI was calculated in kg/m^2.

Screening and diagnosis of gestational diabetes mellitus

Screening for GDM in our hospital is based on a two-step approach. In all women a random plasma glucose is measured at 24 to 28 weeks of gestation and if the concentration is more than 6.7 mmol/L an OGTT is carried out within the subsequent 2 weeks. The diagnosis of GDM is made if the fasting plasma glucose level is at least 6 mmol/L or the plasma glucose level 2 h after the oral administration of 75 g glucose is 7.8 mmol/L or more (WHO). In women with normal random blood sugar an OGTT is performed if they have persistent glucosuria, develop polyhydramnios or the fetus becomes macrosomic. Women with the diagnosis of GDM are given dietary and exercise advise and are encouraged to test capillary blood glucose before and 1 h after each meal. If during a period of 1 to 2 weeks the pre-meal or 1 h post-meal blood glucose level is higher than 5.5 and 7 mmol/L, respectively, the women are treated with insulin.

Details of maternal characteristics and the findings of the 11 to 13 weeks assessment were recorded in our 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 database.

Case–control study for biochemical markers

The case–control study involved the measurement of maternal serum concentration of adiponectin, FSTL3 and SHBG at 11 to 13 weeks' gestation in singleton pregnancies that subsequently developed GDM and non-diabetic controls. The cases and controls were drawn from the screening study for pregnancy complications. We searched our database to identify pregnancies that developed GDM with available stored serum. We then selected at random 80 cases of GDM and 300 controls which were matched to the cases for storage time. In all cases and controls, the pregnancies resulted in live birth of phenotypically normal neonates.

None of the samples were previously thawed and refrozen. Maternal serum adiponectin concentration was measured by a quantitative sandwich enzyme-linked immunoassay (ELISA) technique using Quantikine Human Total Adiponectin Immunoassay (DRP300, R&D Systems Europe Ltd, Abingdon, UK). The intra-assay CV varied from 2.5 to 4.7% and the inter-assay CV varied from 6.8 to 6.9%. Maternal serum SHBG was measured by DELFIA® (Dissociation-Enhanced Lanthanide Fluorescent Immunoassay) technique using AutoDELFIA SHBG (product no. B070101) kit. The intra-assay CV ranged from 3.3 to 4.9% and inter-assay CV ranged from 2.3 to 3.0%. The FSTL3 assay was developed for the AutoDELFIA platform for this study using antibodies and antigens from R&D Systems Inc. (MAB1288, AF1288 and 1288-F3; R&D Systems Europe Ltd). The intra-assay CV varied from 0.5 to 2.1% and the inter-assay CV varied from 3.4 to 12.6%.

Statistical analysis

Comparisons between the GDM and non-GDM groups were by χ^2 test or Fisher's exact test for categorical variables and by Mann–Whitney U-test for continuous variables. In the screened population logistic regression analysis with backward stepwise elimination was used to determine which of the factors among the maternal characteristics and obstetric history had a significant contribution in predicting GDM. The patient-specific *a priori* risk for GDM was calculated from the following

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formula: odds/(1 + odds), where odds = e^Y and Y was derived from the logistic regression analysis of maternal characteristics and history.

In the case–control study we used the following steps. First, the distributions of serum adiponectin, FSTL3 and SHBG were made Gaussian after square root (sqrt) transformation. Second, in the unaffected controls multiple regression analysis was used to determine which of the factors among the maternal characteristics and gestation were significant predictors of sqrt adiponectin, FSTL3 and SHBG. The measurements in each case and control were then expressed as a multiple of the normal median (MoM) derived from the regression analysis. Third, Mann–Whitney U-test was used to compare median values of each serum analyte between the outcome groups. Fourth, for the analytes found to be significantly different in cases of GDM, compared to the non-diabetic controls, regression analysis was used to determine the significance of association between the analytes in cases and controls. Fifth, in the GDM group compared to the non-diabetic controls the median adiponectin and SHBG values were significantly reduced and there were no significant associations between the values of the two analytes in either the GDM or the control groups (see Section on Results). Because we measured adiponectin and SHBG only in the case–control study and not the whole population, the means and standard deviations of the Gaussian distributions of sqrt adiponectin and SHBG in the GDM and control groups were used to simulate the values for these markers in the screened population of 11,464 pregnancies. Sixth, likelihood ratios for GDM were calculated from the fitted bivariate Gaussian distributions for each analyte. In each patient in the screened population the *a priori* odds based on maternal history and characteristics were multiplied by the likelihood ratio for sqrt adiponectin and SHBG to derive their *a posteriori* odds. The *a posteriori* risks were used to calculate the detection rates of GDM and false-positive rates and the performance of screening was determined by receiver operating characteristic (ROC) curves analysis. The performance of different methods of screening was compared by the areas under the ROC curves (AUROC) (Zweig and Campbell, 1993).

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

RESULTS

Screening study

We prospectively examined 12,283 singleton pregnancies between March 2006 and August 2009. We excluded 819 (6.7%) because they had pre-pregnancy diabetes mellitus, the pregnancies ended in termination, miscarriage or delivery before 30 weeks, there was no pregnancy outcome or they resulted in the birth of neonates with major defects. In the 11,464 included cases there were 297 (2.6%) that developed GDM and 11,167 that were unaffected by diabetes. The maternal and pregnancy characteristics of the GDM and non-diabetic pregnancies are compared in Table 1. In the GDM group women were older, they had a higher BMI, a higher proportion was of African and South Asian racial origin, had a first-degree relative with diabetes, developed GDM or delivered a macrosomic neonate in a previous pregnancy.

Logistic regression analysis demonstrated that in the prediction of GDM there were significant contributions from maternal age, BMI, racial origin, previous history of GDM and delivery of macrosomic neonates (Table 2).

In the screened population there were 107 with a history of GDM in a previous pregnancy and 63 (58.8%) of these developed GDM in the current pregnancy. In order to investigate the effect of maternal characteristics in the group without previous GDM, we performed a separate logistic regression analysis (Table 2).

Case–control study

The maternal and pregnancy characteristics of the GDM and non-diabetic controls are compared in Table 3. In the GDM group women were older, they had a higher BMI, a higher proportion was of South Asian racial origin, had a first-degree relative with diabetes, developed GDM or delivered a macrosomic neonate in a previous pregnancy.

In the non-diabetic controls multiple regression analysis demonstrated that serum adiponectin, FSTL3 and SHBG were affected by significant contributions from maternal characteristics:

Sqrt adiponectin expected = $130.19 + 0.74 \times$ maternal age in years + (-18.24 if the racial origin was African, -31.89 if South Asian, 0 if Caucasian, East Asian or Mixed) $- 0.53 \times$ maternal weight in kg $-$ 10.38 if cigarette smoker; $R^2 = 0.223$, $p < 0.0001$.

Sqrt SHBG expected $= 14.85 - 0.04 \times$ maternal weight in kg $+ 0.08 \times$ CRL in mm; $R^2 = 0.060$, $p < 0.0001$.

Sqrt FSTL3 expected $= 3.50 - 0.01 \times$ maternal weight in kg $- 0.16$ if African racial origin; $R^2 = 0.068$, $p < 0.0001$.

In the pregnancies that subsequently developed GDM, compared to the non-diabetic controls, the median adiponectin MoM and SHBG MoM were lower but the median FSTL3 MoM was not significantly different (Table 4). In the group of GDM there were no significant differences between those with and without a previous history of GDM in adiponectin ($p = 0.470$), FSTL3 ($p = 0.962$) or SHBG ($p = 0.156$).

In both the GDM and non-diabetic groups, there was no significant association between sqrt adiponectin MoM and sqrt SHBG MoM ($p = 0.054$ and 0.133, respectively).

Estimated performance of early screening for gestational diabetes mellitus

In the simulated screened population, the *a posteriori* odds for GDM were derived by multiplying the *a priori* odds by the likelihood ratio of adiponectin and SHBG.

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Table 1—Maternal and pregnancy characteristics in the screening population

Characteristics	Non-diabetic controls ($N = 11,167$)	Gestational diabetes ($N = 297$)
Maternal age in years, median (IQR)	31.4 (26.7–35.2)	33.2 (29.3–37.2)*
Body mass index in kg/m^2, median (IQR)	24.2 (21.8–27.8)	29.4 (25.0–34.2)*
Crown-rump length in mm, median (IQR)	63.4 (58.2–68.9)	62.9 (57.9–68.8)
Gestation at sampling in days, median (IQR)	89 (86–92)	89 (86–92)
Gestation at delivery in weeks, median (IQR)	40.2 (39.2–41.0)	38.9 (38.3–39.6)*
Birth weight in kg, median (IQR)	3.4 (3.1–3.7)	3.4 (3.0–3.8)
Racial origin		
Caucasian, *n* (%)	6033 (54.0)	122 (41.1)
African, *n* (%)	3970 (35.6)	130 (43.8)*
South Asian, *n* (%)	501 (4.5)	27 (9.1)*
East Asian, *n* (%)	248 (2.2)	10 (3.4)
Mixed, *n* (%)	415 (3.7)	8 (2.7)
Parity		
Nulliparous, *n* (%)	5478 (49.1)	100 (33.7)
Parous—no previous gestational diabetes, *n* (%)	5645 (50.6)	134 (45.1)
Parous—previous gestational diabetes, *n* (%)	44 (0.4)	63 (21.2)*
Parous—previous large for gestation, *n* (%)	559 (5.0)	53 (17.8)*
Family history of diabetes		
No family history of diabetes	8108 (72.6)	189 (63.6)
First-degree relative, *n* (%)	1559 (14.0)	71 (23.9)*
Second-degree relative, *n* (%)	1500 (13.4)	37 (12.5)
Cigarette smoker, *n* (%)	863 (7.7)	20 (6.7)
Conception		
Spontaneous, *n* (%)	10,873 (97.4)	285 (96.0)
Ovulation drugs, *n* (%)	294 (2.6)	12 (4.0)

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

Table 2—Logistic regression analysis for the prediction of gestational diabetes mellitus by factors in the maternal history and characteristics

				Multivariate analysis					
	Univariate analysis			All pregnancies			No previous GDM		
Variables	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Maternal age (per year)	1.07	1.05–1.09	<0.0001	1.06	1.03–1.08	<0.0001	1.06	1.04–1.09	<0.0001
Body mass index (per kg/m^2)	1.12	1.11–1.14	<0.0001	1.12	1.10–1.14	<0.0001	1.12	1.10–1.14	<0.0001
Racial origin									
Caucasian (reference)	1.00								
African	1.62	1.26–2.08	<0.0001						
South Asian	2.67	1.74–4.08	<0.0001	2.73	1.73–4.30	<0.0001	2.44	1.46–4.08	0.001
East Asian	1.99	1.03–3.85	0.040	2.43	1.20–4.93	0.014	2.63	1.27–5.48	0.009
Mixed	0.95	0.46–1.96	0.897						
Family history of diabetes									
No family history (reference)	1.00								
First-degree relative	1.95	1.48–2.58	<0.0001						
Second-degree relative	1.06	0.74–1.51	0.756						
Parity									
Nulliparous (reference)	1.00								
Parous with previous GDM	78.44	50.88–120.92	<0.0001	41.37	26.82–63.83	<0.0001			
Parous with no previous GDM	1.30	1.00–1.69	0.049				0.72	0.53–0.96	0.025
Parous with previous LGA	5.19	3.68–7.33	<0.0001	1.97	1.36–2.84	<0.0001	2.71	1.82–4.05	<0.0001
Cigarette smoking	0.86	0.55–1.36	0.526						
Conception									
Spontaneous (reference)	1.00								
Use of ovulation induction drugs	1.56	0.86–2.81	0.141						

The *a posteriori* risk was calculated using the following formula: $\beta/(1+\beta)$, where β is *a posteriori* odds. The AUROC curve and detection rates of GDM in screening by maternal factors only and by a combination of maternal factors with adiponectin and SHBG are given in Table 5 and Figure 1. There was significant improvement in the AUROC for maternal factors by the addition of adiponectin ($p = 0.001$) and both adiponectin and

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Table 3—Maternal and pregnancy characteristics in the case–control study

Characteristics	Non-diabetic controls ($N = 300$)	Gestational diabetes ($N = 80$)
Maternal age in years, median (IQR)	32.2 (26.9–35.6)	33.8 (31.5–37.2)*
Body mass index in kg/m^2, median (IQR)	23.1 (21.3–26.3)	28.4 (23.3–33.0)*
Crown-rump length in mm, median (IQR)	64.0 (58.7–69.6)	62.3 (58.0–68.7)
Gestation at sampling in days, median (IQR)	89 (87–92)	88 (86–92)
Gestation at delivery in weeks, median (IQR)	40.4 (39.5–41.1)	39.0 (38.5–39.5)*
Birth weight in kg, median (IQR)	3.4 (3.2–3.7)	3.3 (3.0–3.5)*
Racial origin		
Caucasian, *n* (%)	189 (63.0)	44 (55.0)
African, *n* (%)	86 (28.7)	20 (25.0)
South Asian, *n* (%)	10 (3.3)	10 (12.5)*
East Asian, *n* (%)	6 (2.0)	5 (6.2)
Mixed, *n* (%)	9 (3.0)	1 (1.3)
Parity		
Nulliparous, *n* (%)	148 (49.3)	30 (37.5)
Parous—no previous gestational diabetes, *n* (%)	150 (50.0)	34 (42.5)
Parous—previous gestational diabetes, *n* (%)	2 (0.7)	16 (20.0)*
Parous—previous large for gestation, *n* (%)	17 (5.7)	13 (16.3)*
Family history of diabetes		
No family history of diabetes, *n* (%)	219 (73.0)	48 (60.0)
First-degree relative, *n* (%)	40 (13.3)	20 (25.0)*
Second-degree relative, *n* (%)	41 (13.7)	12 (15.0)
Cigarette smoker, *n* (%)	28 (9.3)	5 (6.3)
Conception		
Spontaneous, *n* (%)	296 (98.7)	79 (98.7)
Ovulation drugs, *n* (%)	4 (1.3)	1 (1.3)

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

SHBG ($p < 0.0001$). At a false-positive rate of 20% the estimated detection of GDM improved from 61.6% for maternal factors to 74.1% for maternal factors with adiponectin and SHBG.

In 63 (21.2%) of the 297 cases of GDM and in 44 (0.4%) of the 11,167 unaffected pregnancies the women had a previous history of GDM. The estimated detection of GDM by maternal factors in the women with no previous history of GDM was 52.6%, at a false-positive rate of 20%, and this was improved to 66.2% by the addition of serum adiponectin and SHBG (Table 5). In a two-stage policy, whereby all women with previous GDM are classified as screen positive and screening by maternal factors and serum adiponectin and SHBG is carried out only in those with no previous history of GDM, the estimated detection rate of GDM would be 74.1% (220 of 297, including all 63 from first-stage screening and 66.2% of the 234 or 157 from second-stage screening) at a false-positive rate of 20.4%.

Table 4—Median and interquartile range of maternal circulating adiponectin, follistatin-like-3 and sex hormone-binding globulin in the case–control study

	Unaffected controls ($N = 300$)	Gestational diabetes ($N = 80$)
Adiponectin (median, IQR)		
ng/mL	12,035 (8595–17,085)	7591 (4552–10,870)
MoM	1.02 (0.70–1.29)	0.66 (0.50–0.92)*
Follistatin-like-3 (median, IQR)		
ng/mL	9.00 (7.14–10.72)	8.31 (6.77–10.35)
MoM	0.97 (0.82–1.19)	0.99 (0.76–1.14)
Sex hormone-binding globulin (median, IQR)		
nmol/L	295.9 (233.0–370.3)	224.5 (166.2–283.8)
MoM	1.02 (0.80–1.24)	0.81 (0.60–1.04)*

MoM, multiple of the unaffected median.
Comparisons between groups by Mann–Whitney U-test: * $p < 0.05$.

DISCUSSION

The findings of this study on early screening for GDM demonstrate that (1) well-recognized maternal risk factors can be combined into a model in which each factor is attributed its appropriate weight and (2) the performance of screening is improved by combining maternal characteristics with biochemical testing.

The study confirms that risk factors for the development of GDM include increased maternal age and BMI, African and South Asian racial origin, family history of diabetes and previous pregnancies complicated by GDM and delivery of macrosomic neonates (Waugh *et al*., 2007). The performance of screening by a regression model based on maternal factors, with an estimated detection rate of about 60% for a false-positive rate of 20%, is superior to that achieved by using each maternal factor as an independent screening test (NICE, 2008). Our results are similar to those reported in a recent study which also used regression analysis to develop a prediction model and reported that the AUROC was 0.77 (Van Leeuwen *et al*., 2010). Ultimately, such models will require prospective validation studies.

Low levels of adiponectin, an adipocyte-derived polypeptide, and SHBG, a liver-derived glycoprotein,

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Table 5—Performance of screening for gestational diabetes mellitus by maternal factors, adiponectin, sex hormone-binding globulin and by their combinations

Screening test	AUROC (95% CI)	Detection rate for fixed FPR		
		5%	10%	20%
All pregnancies				
Maternal factors	0.788 (0.759–0.817)	40.4	52.9	61.6
Maternal factors plus				
Adiponectin	0.831 (0.806–0.856)	45.1	56.2	68.7
SHBG	0.808 (0.778–0.837)	45.1	54.2	69.7
Adiponectin and SHBG	0.842 (0.817–0.867)	49.8	58.6	74.1
No previous gestational diabetes				
Maternal factors	0.738 (0.705–0.711)	26.5	40.6	52.6
Maternal factors plus				
Adiponectin	0.791 (0.762–0.820)	30.8	44.0	62.4
SHBG	0.764 (0.731–0.798)	30.3	44.9	60.3
Adiponectin and SHBG	0.806 (0.776–0.835)	37.2	50.4	66.2
Previous gestational diabetes				
Maternal factors	0.819 (0.780–0.858)	54.0	60.1	68.1
Maternal factors plus				
Adiponectin	0.860 (0.828–0.893)	55.8	63.8	72.4
SHBG	0.832 (0.794–0.870)	52.1	62.6	69.9
Adiponectin and SHBG	0.865 (0.833–0.898)	57.7	65.0	77.9

AUROC, area under receive operating characteristic curve.

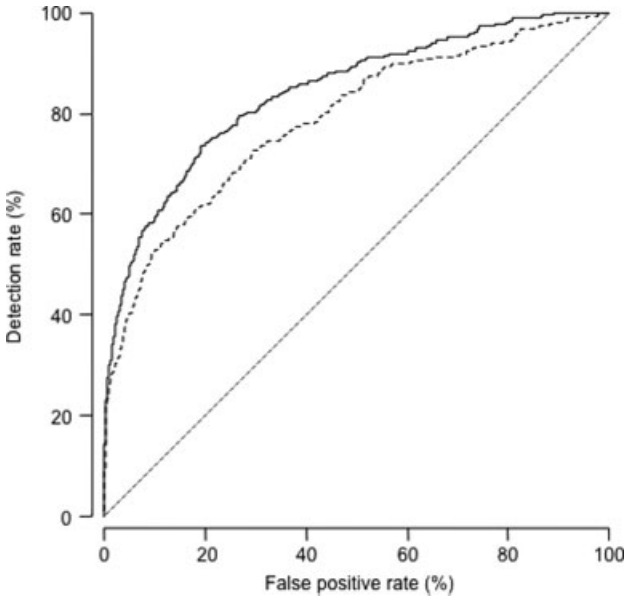

Figure 1—Receiver operating characteristics curves of maternal factors only (·····) and by a combination of maternal factors and maternal serum adiponectin and sex hormone-binding globulin (———) in the prediction of gestational diabetes mellitus

have been reported prior to the development and in overt GDM and type 2 diabetes (Bartha *et al*., 2000; Weyer *et al*., 2001; Thadhani *et al*., 2003; Tsai *et al*., 2004; Williams *et al*., 2004; Worda *et al*., 2004; Retnakaran *et al*., 2005, 2007; Mazaki-Tovi *et al*., 2009; Paradisi *et al*., 2010).

Our finding that in the GDM group maternal serum adiponectin and SHBG levels at 11 to 13 weeks were reduced by about 30 and 20%, respectively, are consistent with the results of previous smaller studies (Thadhani *et al*., 2003; Williams *et al*., 2004; Spencer *et al*., 2005; Smirnakis *et al*., 2007; Georgiou *et al*., 2008; Lain *et al*., 2008; Paradisi *et al*., 2010). In our GDM group serum FSTL3, which may be involved in up-regulation of hepatic gluconeogenesis (Mukherjee *et al*., 2007), was not significantly different than in the non-diabetic controls. In contrast, a recent study of 37 cases and 127 controls at 11 to 13 weeks reported that in the GDM group the levels were reduced by 65% (Thadhani *et al*., 2010).

This study has shown that screening for GDM can be provided by a combination of maternal characteristics and maternal serum adiponectin and SHBG at 11 to 13 weeks. Because the risk of recurrence of GDM, both in this and in previous studies is very high (Kim *et al*., 2007), any screening policy would automatically classify such women as screen positive with a marginal increase in the false-positive rate. In nulliparous women and in those without a previous history of GDM screening by a combination of maternal factors and serum adiponectin and SHBG could identify about 65% of pregnancies that subsequently develop GDM, at a false-positive rate of 20%. Such two-stage screening policy could identify about 75% of affected pregnancies at 11 to 13 weeks' gestation.

The extent to which the performance of early screening for GDM can be improved further by additional biomarkers is currently under investigation. Similarly, the extent to which early identification of the high-risk group and early diagnosis of the condition by adjusting the traditional criteria of the OGTT (Plasencia *et al*., 2011) can lead to a reduction in the maternal and perinatal complications associated with GDM remains to be determined.

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