First-Trimester Prediction of Gestational Diabetes Mellitus: Examining the Potential of Combining Maternal Characteristics and Laboratory Measures

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OBJECTIVE—Predictors of gestational diabetes mellitus (GDM) have been widely studied, but few studies have considered multiple measures. Our objective was to integrate several potential GDM predictors with consideration to both simple and novel measures and to determine the extent to which GDM can be predicted in the first trimester.

RESEARCH DESIGN AND METHODS—We identified first-trimester maternal samples from 124 women who developed GDM and 248 control subjects who did not. We gathered data on age, BMI, parity, race, smoking, prior GDM, family history of diabetes, and blood pressure. Using retrieved samples, we measured routine (lipids, high-sensitivity C-reactive protein, and γ-glutamyltransferase) and novel (adiponectin, E-selectin, and tissue plasminogen activator [t-PA]) parameters. We determined independent predictors from stepwise regression analyses, calculated areas under the receiver-operating characteristic curves (AUC-ROC), and integrated discrimination improvement (IDI) for relevant models.

RESULTS—Compared with control subjects, women who subsequently developed GDM were older, had higher BMIs, were more likely to be of Asian origin, had a history of GDM or family history of type 2 diabetes, and had higher systolic blood pressure ($P < 0.05$ for all). With regard biochemical measures, stepwise analyses identified only elevated t-PA and low HDL cholesterol levels as significant ($P \leq 0.015$) independent predictors of GDM beyond simple non–laboratory-based maternal measures. Their inclusion improved the AUC-ROC from 0.824 to 0.861 and IDI by 0.052 (0.017–0.115).

CONCLUSIONS—GDM can be usefully estimated from a mix of simple questions with potential for further improvement by specific blood measures (lipids and t-PA). ***Diabetes*** **59:3017–3022, 2010**

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There is growing interest in our ability to predict which women will develop gestational diabetes mellitus (GDM), given that there is now emerging evidence that lifestyle changes cannot only lessen diabetes risk in nonpregnant individuals but also risks in women with GDM. Currently, the traditional method of GDM screening is based on maternal history, which provides a detection rate of ~60% for a 40% false-positive rate (National Institute for Health and Clinical Excellence, available at http://www.nice.org.uk/CG63). In contrast to the wealth of work for type 2 diabetes, as recently reviewed (1), the literature on early first-trimester biomarkers predictive of GDM are less mature and considerably further from clinical utility. Moreover, most relevant studies on this topic (2–4) generally included *1*) <50 incident cases with various numbers of control subjects, *2*) tended to focus on one or two biomarkers in isolation rather than capture several potential markers, and *3*) generally did not examine predictive ability using metrics such the receiver-operating characteristic curve (ROC) analyses or integrated discrimination improvement (IDI) analyses.

We sought to advance the field by examining the predictive ability of routinely booking maternal demographic and clinical variables and, importantly, a range of commonly available biochemical tests in most laboratories (lipids, high-sensitivity C-reactive protein [CRP], and γ-glutamyltransferase [GGT]) and key nonroutine tests derived by organs relevant to diabetes (adipose tissue, liver, and endothelium). Among the fat-derived markers, adiponectin is strongly predictive of type 2 diabetes, as documented by a recent meta-analysis (5). Similarly, recent meta-analyses report hepatic-derived CRP (6) and GGT (7) to be associated with risk for type 2 diabetes, although CRP's association with type 2 diabetes may not be independent of central obesity. Finally, we have shown tissue plasminogen activator (t-PA) to be a strong independent predictor of diabetes, independent even of insulin resistance (8), whereas E-selectin is the strongest adhesion molecule predictive of diabetes (9). Overall, therefore, we captured key measures reflecting perturbances in a range of different pathways (lipids, inflammation, liver fat, adipocytes, and vascular function) pertinent to the pathogenesis of diabetes.

RESEARCH DESIGN AND METHODS

We performed a nested case-control study using first-trimester samples that were stored as part of our large prospective observational ongoing study aimed at identifying first-trimester predictors of adverse pregnancy outcomes. The study involved women attending for their routine hospital visit at King's

College Hospital. In this visit, which is held at 11 + 0 to 13 + 6 weeks' gestation, all women have an ultrasound scan to confirm gestational age, diagnose any major fetal abnormalities, and measure fetal nuchal translucency thickness, which together with maternal free β-chorionic gonadotrophin and pregnancy-associated plasma protein A, is used for screening for chromosomal abnormalities. Patients were asked to complete a questionnaire on maternal age, address, and postcode to assess area-based socioeconomic status, racial group, cigarette smoking during pregnancy, method of conception, parity, and obstetric and family history of diabetes. The maternal weight and height were measured, and BMI was calculated as weight in kilograms divided by the square of height in meters. Peripheral maternal blood pressure was measured using an ambulatory blood pressure monitor (3BTO-A2; Microlife Medical, Taipei, Taiwan), which has been validated in pregnancy. Maternal blood was taken and stored at −80°C for future biochemical analyses.

All women underwent routine second-trimester screening for GDM (24–28 weeks' gestation) according to the two-step risk factor screening procedure (http://www.nice.org.uk/CG63). A 75-g load, 2-h oral glucose tolerance test (OGTT) was performed based on maternal risk factors as defined by the NICE (BMI >30 kg/m^2, previous GDM, first-degree relative with diabetes, previous large-for-gestational-age infant) or in those women with no risk factors if an initial random plasma glucose was ≥6.7 mmol/l. Gestational diabetes was defined by one abnormal plasma glucose value following the OGTT, with normal values of <7 and <7.8 mmol/l for fasting and 2-h postprandial values, respectively, based on World Health Organization criteria. If women with normal random blood glucose subsequently developed apparent risk factors such as polyhydramnios, a large-for-gestational-age fetus, or persistent glucosuria, then an OGTT was performed (requiring, in some cases, a second OGTT). The values of the OGTT and A1C levels, whenever available, were obtained. Furthermore, details including gestational age at delivery, mode of delivery, birth weight, and sex of the neonate have also been retrieved. Women with preexisting diabetes and twin pregnancies were excluded. All women had phenotypically normal neonates. All women had given written informed ethical consent and the project had been approved by the local research ethics committee.

We had aimed to identify stored samples (all <3 years old) from at least 100 women with subsequent GDM, verified with an OGTT, and 200 women who did not develop GDM. This would provide 80% power at an α of 0.05 to detect a standardized difference of 0.3 for any variable or 96% power at an α of 0.01 to detect a standardized difference of 0.5. For each woman who developed GDM, two control subjects were selected who were matched according to the date of the ultrasound scan and consequent storage time of the samples.

Biochemical assays. Lipids (cholesterol, LDL cholesterol, HDL cholesterol, nonfasting triglycerides, CRP, and GGT) were measured by routine automated methods in an accredited laboratory. The CRP method is sensitive to a value of 0.2 mg/l, and all methods have coefficients of variation of <4%. Baseline adiponectin, E-selectin, and t-PA were measured by enzyme-linked immunosorbent assay (R&D Systems, Abingdon, U.K.) on previously unthawed serum samples stored at −80°C. The methods had interassay coefficients of variation <7%. Samples were processed by technicians blinded to the identity of samples.

Statistics. Categorical variables are summarized as numbers and percentages and compared between control mothers and mothers with GDM using Fisher exact tests. Continuous variables are summarized as means and SDs or as median and interquartile ranges and compared between control mothers and mothers with GDM using *t* tests or Wilcoxon tests, as appropriate. To assess the role of each variable in predicting GDM, logistic regression models were fitted adjusting for maternal age, BMI, gestational age at sampling, smoking, racial group, parity, conception status, and previous GDM. HDL cholesterol, triglycerides, and CRP were log transformed as this enhanced model fit. Forward stepwise, backward, and bootstrap variable selection (10) procedures were used to identify the most important predictors. As resulted from logistic regressions, effect estimates were reported along with 95% CIs and *P* values. The predictive abilities of the different models were illustrated using ROC curves and IDI analyses as described (11). CIs for IDI were obtained through bootstrap based on 1,000 samples. The same analyses were repeated in the subgroup of mothers who had not had previous GDM. All analyses have been carried out in R, version 2.9.1 (12). *P* values were not adjusted for multiple testing and were therefore considered descriptive.

RESULTS

Baseline characteristics and simple adjustments. We identified 124 women who developed GDM and 248 control subjects. Their characteristics are provided in Table 1. In univariate analyses, women who developed GDM were older, had greater BMI, and more had prior GDM and family history of type 2 diabetes. They also had higher systolic blood pressure, but there were no relevant differences in parity, smoking history, or method of conception.

As regards biochemical measures, women destined to develop GDM had higher total cholesterol, LDL cholesterol, triglycerides, CRP, and t-PA but lower levels of HDL cholesterol and adiponectin. GGT levels demonstrated a tendency to be higher in women destined to develop GDM, and there was no relevant difference in E-selectin. Adjustment for potential confounders resulted in loss of significance for several of the above measures, most notably systolic blood pressure, and the results were similar whether we examined the entire group or looked at the large subgroup of women without a history of GDM.

Stepwise variable selection in all mothers and mothers without prior GDM. Given that many of the risk factors have known strong interrelationships (e.g., triglycerides, HDL cholesterol, adiponectin, and t-PA, etc.), we examined for independent predictors using a forward stepwise variable-selection approach (Table 2). In the entire cohort, we noted that of the measures forced into the model, gestational age at sampling, BMI, Asian racial group, parity, and prior GDM were associated with GDM, whereas of the parameters shown to be significant in univariate analyses but not forced into model, only family history of diabetes, lower HDL cholesterol, and higher t-PA remained independently predictive (Table 2). The results were near identical when analysis was repeated in the women without prior GDM (Table 2). The models obtained through backward selection were identical.

Predictive ability of simple and extended prediction models. We determined the predictive ability of simple measures routinely available at booking visit (namely maternal age, gestational age at sampling, BMI, race, family history of diabetes, and prior GDM) in the entire cohort. This demonstrated an AUC-ROC of 0.824, which increased significantly to 0.861 with the addition of HDL cholesterol and t-PA (Fig. 1*A*). Upon repeating the same analyses but removing all women with prior GDM, the AUC-ROCs were 0.751 and 0.806, respectively (Fig. 1*B*).

As an additional prediction test, we examined for IDI in the models, a test that is not based on a priori risk classes and is therefore applicable in this setting. The results for IDI are similar to those found for the AUC: adding HDL cholesterol to the basic risk factor model improves discrimination compared with the basic model (IDI = 0.031, 95% bootstrap CI [1,000 samples] 0.000–0.092), adding t-PA to the basic model improves discrimination slightly more than does HDL cholesterol (0.033 [0.006–0.082]), whereas using both variables leads to the biggest improvement (0.052 [0.017–0.115]) over the basic model. Adding t-PA to the basic model plus HDL cholesterol yields an IDI of 0.021 (0.002–0.062), adding HDL cholesterol to the basic model plus t-PA yields an IDI of 0.019 (0.000–0.066). So each variable improves discrimination when added to the basic model, and discrimination further improves if they are both used.

Bootstrap variable selection. Applying bootstrap variable selection (with the adjustment variables forced into the model), the variables with the highest selection probabilities are family history of diabetes (90.1%), t-PA (59.8%), adiponectin (61.3%), and HDL cholesterol (50.5%). In a joint model using all those variables, adiponectin is no longer significant (see the supplementary Table in the online

TABLE 1
Characteristics of mothers with GDM versus control mothers

	Missing values	Control mothers (n = 248)	Women who developed GDM (n = 124)	P value (univariate)	P value (adjusted)*	P value (adjusted)†
Maternal age (years)	0/0	32.6 ± 5.2	34.3 ± 5.0	0.002‡	0.430	0.420
Maternal BMI at booking (kg/m^2)	0/0	25.4 ± 5.2	29.2 ± 7.9	<0.001§	<0.001	<0.001
Parity						
Nullip	0/0	89 (35.9)	45 (36.3)	1.000‖	0.003	0.003
Parous		159 (64.1)	79 (63.7)			
Ethnicity						
White		148 (59.7)	73 (58.9)			
Black	0/0	62 (25.0)	34 (27.4)	0.769‖	0.325	0.440
Asian		29 (11.7)	11 (8.9)			
Other		9 (3.6)	6 (4.8)			
Previous GDM						
No		158 (63.7)	44 (35.5)			—
Yes	0/0	1 (0.4)	35 (28.2)	<0.001‖	<0.001	
Nulliparous		89 (35.9)	45 (36.3)			
Family history of diabetes						
No	0/0	218 (87.9)	76 (61.3)	<0.001‖	<0.001	<0.001
Yes		30 (12.1)	48 (38.7)			
Smoker						
No	0/0	230 (92.7)	115 (92.7)	1.000‖	0.605	0.593
Yes		18 (7.3)	9 (7.3)			
Gestational age at booking (days)	0/0	87.4 ± 3.2	87.3 ± 3.6	0.737‡	0.864	0.967
Systolic blood pressure (mmHg)	58/27	111.7 ± 16.6	118.4 ± 14.1	0.001§	0.281	0.269
Diastolic blood pressure (mmHg)	58/27	71.4 ± 8.9	72.9 ± 8.4	0.163‡	0.585	0.688
Mode of delivery						
Vaginal		190 (77.2)	80 (65.0)			
Elective caesarean section	2/1	36 (14.6)	25 (20.3)	0.037‖	0.438	0.503
Emergency caesarean section		19 (7.7)	18 (14.6)			
Ventouse		1 (0.4)	0 (0.0)			
Sex						
Female	0/0	118 (47.8)	62 (50.0)	0.741‖	0.862	0.985
Male		129 (52.2)	62 (50.0)			
Birth weight (g)	0/0	3,392.8 ± 540.3	3,343.2 ± 495.0	0.378‡	0.896	0.911
Gestation at OGTT (weeks)	0	—	27.7 ± 4.7			
OGTT (fasting, 2-h glucose)	0, 6	—	5.3 ± 1.7; 9.1 ± 1.6			
OGTT (A1C) (%)	14	—	5.8 ± 0.8			
Total cholesterol (mmol/l)	0/0	4.59 ± 0.85	4.88 ± 0.90	0.003‡	0.040	0.038
HDL cholesterol (mmol/l)*	0/0	1.68 ± 0.36	1.55 ± 0.38	0.002‡	0.003	0.001
LDL cholesterol (mmol/l)	0/0	2.29 ± 0.71	2.59 ± 0.78	<0.001‡	0.003	0.003
Triglycerides (mmol/l)*	0/0	1.23 (0.95–1.62)	1.49 (1.14–2.05)	<0.001§	0.017	0.012
Adiponectin (μg/ml)	0/0	9.88 ± 5.57	7.38 ± 4.19	<0.001§	0.027	0.040
E-selectin (ng/ml)	0/0	31.3 (23.2–40.4)	31.3 (24.7–44.2)	0.308§	0.867	0.827
GGT (U/l)	0/0	11.0 (9.0–16.0)	12.0 (9.8–17.0)	0.063§	0.632	0.566
CRP (mg/l)*	0/0	3.21 (1.62–6.97)	5.77 (2.7–11.6)	<0.001§	0.030	0.024
t-PA	27/16	5.32 (4.23–6.58)	6.41 (5.19–8.27)	0.001§	0.001	<0.001

Data are means ± SD, n (%), or median (interquartile range). Log transformed for regression analyses. *Adjusted for maternal age, BMI, gestational age at sampling, smoking, ethnicity, parity, conception status, and previous GDM. †Women without previous GDM (nulliparous or previous pregnancies without GDM) adjusted for maternal age, BMI, gestational age at sampling, smoking, ethnicity, parity, and conception status. ‡t test; §Wilcoxon test; ‖Fisher exact test.

appendix, available at http://diabetes.diabetesjournals.org/cgi/content/full/db10-0688/DC1). In women without previous GDM, the results are very similar (selection probabilities for family history of diabetes 81.8%, for t-PA 70.3%, for adiponectin 55.8%, and for HDL cholesterol 54.0%). Again, adiponectin is not significant in a joint model of all those variables.

DISCUSSION

This study, conducted in a mixed ethnic population in a U.K. teaching hospital, highlights some novel and potentially clinically important aspects of routine and nonroutine tests to predict GDM. Most importantly, our results suggest that very good prediction of GDM, using a panel of simple maternal demographic and clinical characteristics, is possible, with achieved AUC-ROC values not dissimilar to those noted for type 2 diabetes in the general population where AUC-ROCs typically around 0.75–0.85 are reported (1). Our work also extends the recent study by Van Leeuwen et al. (13), in which a few maternal characteristics yielded an AUC-ROC of 0.77 for GDM, although in this study only 22 cases were recorded from 995 women screened. Furthermore, we show that although several novel biochemical parameters may be associated with

TABLE 2
Regression models obtained from variable selection (forward stepwise selection) using variables that were significant in Table 1, with adjustment variables forced into the model

All mothers	Effect	95% CI	*P*
Variables forced in			
Intercept	−2.180	(−6.042 to 1.683)	0.267
Age	0.017	(−0.056 to 0.090)	0.648
BMI	0.127	(0.072–0.181)	<0.001
Gestational age at sampling	−0.085	(−0.163 to −0.006)	0.034
Smoking	−0.165	(−1.695 to 1.365)	0.832
Ethnicity			
Black	−0.146	(−0.956 to 0.664)	0.722
Asian	−1.847	(−3.310 to −0.385)	0.013
Other	1.256	(−0.409 to 2.920)	0.138
Parity (parous)	−1.367	(−2.148 to −0.585)	0.001
Conception (spontaneous)	−0.459	(−1.908 to 0.990)	0.533
Previous GDM	4.477	(2.221–6.733)	<0.001
Variables selected			
Family history of diabetes	1.196	(0.382–2.011)	0.004
HDL cholesterol*	−1.959	(−3.546 to −0.372)	0.015
t-PA	0.195	(0.042–0.349)	0.012
Mothers without prior GDM			
Variables forced in			
Intercept	−2.383	(−6.345 to 1.579)	0.236
Age	0.017	(−0.057 to 0.091)	0.650
BMI	0.128	(0.072–0.184)	<0.001
Gestational age at sampling	−0.079	(−0.160 to 0.002)	0.055
Smoking	−0.148	(−1.697 to 1.402)	0.851
Ethnicity			
Black	−0.161	(−0.990 to 0.668)	0.701
Asian	−1.675	(−3.129 to −0.222)	0.023
Other	1.306	(−0.364 to 2.976)	0.124
Parity (parous)	−1.385	(−2.176 to −0.594)	0.001
Conception (spontaneous)	−0.496	(−1.961 to 0.969)	0.505
Variables selected			
Family history of diabetes	1.160	(0.326–1.994)	0.006
HDL cholesterol	−2.196	(−3.821 to −0.572)	0.008
t-PA	0.219	(0.063 to 0.374)	0.006

Conducted in all mothers and separately in mothers without prior GDM. *Log transformed.

higher risk for GDM, low HDL cholesterol and high t-PA antigen (but not blood pressure, CRP, GGT, or adiponectin) remain independently predictive in multivariate models and add predictive information beyond a simple panel of predictors. Finally, useful prediction of GDM in women without prior GDM also appears possible using simple biochemical variables added to the readily attainable maternal information. Collectively, our observations should encourage others to test and validate similar simple GDM prediction models in the same way risk prediction algorithms for type 2 diabetes have been proposed for clinical use (14).

The observation of an association of t-PA antigen with incident GDM appears novel and concurs with work, most recently from our group, of a strong association of t-PA with risk for type 2 diabetes (8). t-PA is considered to reflect endothelial activation, but its circulating levels likely also reflect hepatic fat content (1), with reductions in t-PA in association with weight loss (1,15) and metformin independent of glycemia or weight changes (16). It should also be noted that t-PA appears to have a remarkable strong correlation to insulin resistance in women with and without polycystic ovarian syndrome (17). Thus, using t-PA to predict GDM is in line with its known associations to liver fat and insulin resistance and known responses to mechanisms (lifestyle, metformin) that reduce diabetes risk.

Our finding that low HDL cholesterol predicts incident GDM, and type 2 diabetes in general, is also of interest but not surprising considering the inverse association between HDL cholesterol and triglycerides; a high-triglyceride and low–HDL cholesterol pattern is apparent in women with GDM (18). The clinical utility of this marker is further enhanced by virtue of not being altered in nonfasting samples (unlike triglyceride) and also the fact that HDL cholesterol is routinely available in most hospitals.

It should be noted that although risk factors such as blood pressure, CRP, and GGT may be higher, and adiponectin lower in women destined to develop GDM, their associations with GDM risk appear not to be independent when set against other potential predictors, which, we have argued, yield overlapping information in type 2 diabetes (1). Likewise, others have reported that adiponectin may not be independently associated with GDM (19), and our CRP results are consistent with recent data (6) regarding the limited independent predictive value of CRP for incident type 2 diabetes.

The potential clinical significance of our findings relates to the increasing importance attributed to maternal dysglycemia enhancing the risk for related pregnancy compli-

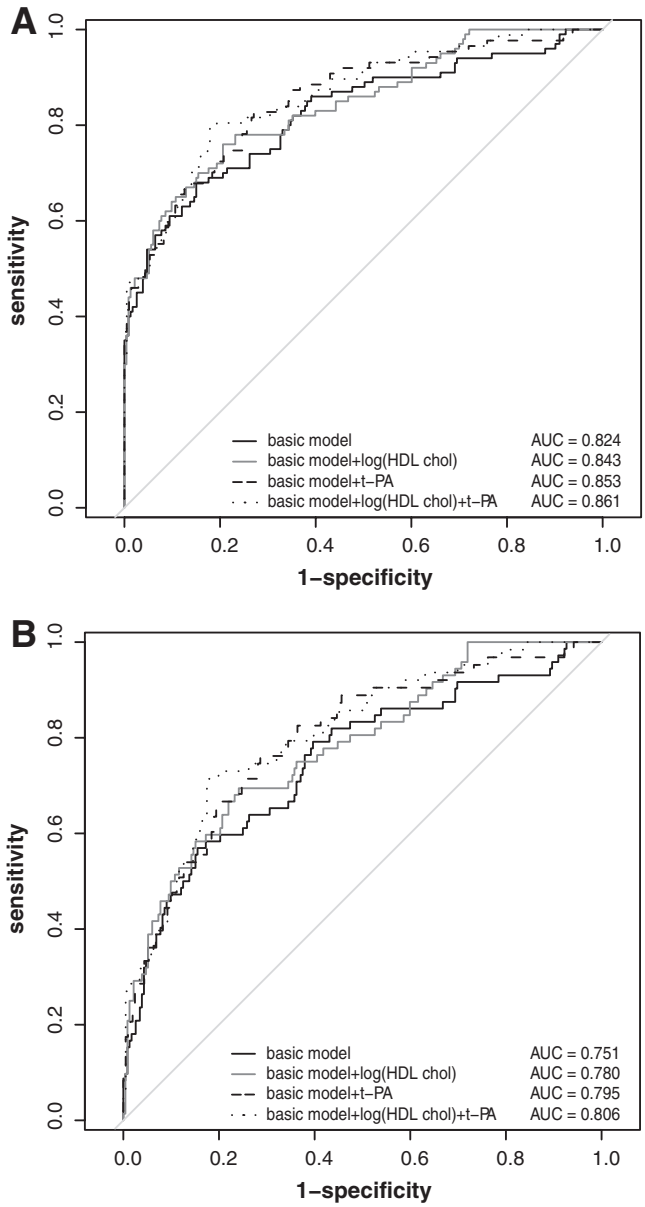

FIG. 1. *A*: ROC curves and summaries for all mothers using a basic model (including age, gestational age at sampling, BMI, ethnicity, family history of diabetes, and prior GDM) and with addition of independent predictors (HDL cholesterol and t-PA). AUC, area under ROC curve. *B*: ROC curves and summaries for women with no prior GDM using a basic model (including age, gestational age at sampling, BMI, ethnicity, and family history of diabetes) and with addition of independent predictors (HDL cholesterol and t-PA).

cations and in programming offspring adiposity (via fetal hyperinsulinaemia) (20). Rising levels of obesity and recent proposed changes to GDM diagnostic criteria (including reducing fasting blood glucose levels to 5.1 mmol/l) mean that the incidence of GDM may rise substantially (21). The possibility, therefore, of first-trimester identification of women at greatest risk of GDM, with subsequent implementation of possible lifestyle or medical interventions at this stage, requires further study (22). Of course, ongoing studies will help determine whether such interventions lead to measurable clinical benefits, but, nevertheless, the possibility of early screening is advanced by our data.

Our work has a number of strengths. We measured a range of clinical and novel predictors of GDM simultaneously rather than one or two novel measures in isolation. As a result, our data give a better overall reflection of predictive abilities, or lack thereof, for specific factors of relevance. The size of our study was relatively large, set against other such studies in the literature, and sufficiently powered to detect associations. Finally, we were very careful in statistical analyses and considered relevant multivariate and stepwise models for consistency of findings, as well as two relevant prediction metrics. We acknowledge a number of limitations. We did not have fasting samples at baseline, but, of course, fasting is not mandated for booking clinical visits in pregnancy. Diagnosis of GDM was based on current National Institute for Health and Clinical Excellence–based criteria but with a lower random glucose cut off but did not use the recently proposed new criteria (21). As a result, many control subjects did not have an OGTT, but this omission would potentially bias results toward the null and not the other way. Furthermore, becuase all factors identified in our analyses relate to glucose elevations in a generally continuous fashion, our data are likely applicable to any future changes to criteria. Moreover, the mean fasting blood glucose in subsequent GDM cases was 5.3 mmol/l, which is above the suggested new fasting blood glucose cut off of 5.1 mmol/l, so our results appear broadly applicable to the new criteria. Finally, we acknowledge the lack of detailed validation of our models in other cohorts, but our aim was not to define the best model (nor to currently consider cost-effectiveness issues) but rather to be hypothesis generating and to prompt others to advance our findings toward possible clinical utility.

In conclusion, we have shown that risk for GDM can be usefully estimated in the first trimester of pregnancy from a mix of simple maternal demographic and clinical characteristics with potential for further improvement by simple and novel biochemical markers. Our results suggest further development, and potential clinical application of risk algorithms for GDM in a range of populations, is possible. Such work should therefore be prioritized, especially at a time of rising obesity levels and changing diagnostic criteria for GDM, factors which in combination will substantially increase the number of women with this condition.

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M.S., S.M.N., N.S., and K.N. conceived and designed the study. S.M.N. and N.S. gained local funding to support biomarker measurements. C.M.M. conducted statistical analysis. N.S. and M.S. cowrote the first draft. All authors contributed to article revision.

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