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Development of a Screening Tool for Predicting Adverse Outcomes of Gestational Diabetes Mellitus

A Retrospective Cohort Study

Jee Soo Park, BS, Deok Won Kim, PhD, Ja-Young Kwon, MD, PhD, Yong Won Park, MD, PhD, Young Han Kim, MD, PhD, and Hee Young Cho, MD

Abstract: Gestational diabetes mellitus (GDM) is a common disease in pregnancy causing maternal and fetal complications. To prevent these adverse outcomes, optimal screening and diagnostic criteria must be adequate, timely, and efficient. This study suggests a novel approach that is practical, efficient, and patient- and clinician-friendly in predicting adverse outcomes of GDM. The authors conducted a retrospective cohort study via medical record review of patients admitted between March 2001 and April 2013 at the Severance Hospital, Seoul, South Korea. Patients diagnosed by a conventional 2-step method were evaluated according to the presence of adverse outcomes (neonatal hypoglycemia, hyperbilirubinemia, and hyperinsulinemia; admission to the neonatal intensive care unit; large for gestational age; gestational insulin therapy; and gestational hypertension). Of 802 women who had an abnormal 50-g, 1-hour glucose challenge test, 306 were diagnosed with GDM and 496 did not have GDM (false-positive group). In the GDM group, 218 women (71.2%) had adverse outcomes. In contrast, 240 women (48.4%) in the false-positive group had adverse outcomes. Women with adverse outcomes had a significantly higher body mass index (BMI) at entry ($P = 0.03$) and fasting blood glucose (FBG) ($P = 0.03$). Our logistic regression model derived from 2 variables, BMI at entry and FBG, predicted GDM adverse outcome with an area under the curve of 0.642, accuracy of 61.3%, sensitivity of 57.2%, and specificity of 66.9% compared with the conventional 2-step method with an area under the curve of 0.610, accuracy of 59.1%, sensitivity of 47.6%, and specificity of 74.4%. Our model performed better in predicting GDM adverse outcomes than the conventional 2-step method using only BMI at entry and FBG. Moreover, our model represents a practical, inexpensive, efficient, reproducible, easy, and patient- and clinician-friendly approach.

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From the Department of Medicine (JSP); Department of Medical Engineering (DWK); Graduate Program in Biomedical Engineering (DWK); and Department of Obstetrics and Gynecology, Institute of Women's Medical Life Science, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea (YHK, JK, YWP, HYC).
Correspondence: Hee Young Cho, MD, Department of Obstetrics and Gynecology, Institute of Women's Medical Life Science, Yonsei University College of Medicine, Yonsei University Health System, 134 Shinchon-dong Seodaemun-gu, Seoul 120-752, South Korea (e-mail: hycho@yuhs.ac).
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Abbreviations: ACOG = American Congress of Obstetricians and Gynecologists, AUC = area under the curve, BMI = body mass index, FBG = fasting blood glucose, GCT = glucose challenge test, GDM = gestational diabetes mellitus, GTT = oral glucose tolerance test, HAPO = Hyperglycemia and Adverse Pregnancy Outcomes.

INTRODUCTION

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset during pregnancy, is a common disease affecting approximately 6% to 7% of pregnant women.[1,2] Pregnancies complicated by GDM have maternal and fetal implications, including increased preeclampsia, rate of operative delivery, and subsequent diabetes mellitus as maternal complications.[3,4] Fetal risks include macrosomia, shoulder dystocia, other birth traumas, neonatal hypoglycemia, and long-term sequelae such as obesity and impaired intellectual achievement.[5–7] To prevent these adverse outcomes, optimal screening and diagnostic criteria must be adequate, timely, and efficient.

Most clinicians have used the 2-step method that was introduced in 1964 by O'Sullivan and Mahan[8] for GDM screening and diagnosis. The 2-step method remains the recommendation of the American Congress of Obstetricians and Gynecologists (ACOG).[1] A 1-step method, introduced by the Hyperglycemia and Adverse Pregnancy Outcomes Study in 2008,[9] however, has become an alternative option for GDM screening and diagnosis. The 1-step method allows earlier GDM diagnosis and treatment, thereby decreasing the risks associated with the disease.[10] Despite an association with adverse outcomes, optimal screening and diagnostic criteria for GDM, including both the 1- and 2-step methods, remain controversial.[11,12] Furthermore, both approaches, although validated by extensive research and endorsed by experts, are extremely demanding. The oral glucose tolerance test (GTT), whether it is 75 or 100 g, is a costly and cumbersome test, both for patients and clinicians. We identified several risk factors associated with adverse outcomes, and using those risk factors, we developed a screening tool for predicting adverse outcomes of GDM. Because the GDM diagnostic tests are imperfect, our model suggests an alternative approach, which is more practical, efficient, and patient- and clinician-friendly.

MATERIALS AND METHODS

This is a retrospective cohort study conducted via medical record review of patients admitted between March 2001 and April 2013 at the Severance Hospital, Seoul, South Korea. The Institutional Review Board of the Yonsei University Health

System approved the protocol of this study (project no: 4–2014–1031). No consent was given because the data were anonymized before analysis. Eligible patients were diagnosed with GDM via the 2-step method during a current pregnancy. Exclusion criteria were preexisting type 1 or type 2 diabetes and diagnosis with GDM at <24 weeks' gestation. Multiple gestations, anomalous fetuses, and patients with chronic hypertension were also excluded. In our institution, we have used the 2-step method following the ACOG recommendation. Gestational diabetes mellitus was defined as 2 or more of the 4 values (fasting, 1 hour, 2 hours, or 3 hours) being abnormal on the 100-g, 3-hour GTT in a patient with an abnormal 50-g, 1-hour glucose challenge test (GCT), for which fasting is not required. Abnormal values for the 100-g, 3-hour GTT were defined as fasting blood glucose (FBG) ≥95, 1-hour blood glucose ≥180, 2-hour blood glucose ≥155, and 3-hour blood glucose ≥140 mg/dL. An abnormal value for the 50-g, 1-hour GCT was blood glucose ≥140 mg/dL.

Adverse outcomes included neonatal hypoglycemia, hyperbilirubinemia, and hyperinsulinemia; admission to the neonatal intensive care unit; large for gestational age, gestational insulin therapy; and preeclampsia or gestational hypertension. Women having atleast 1 of those adverse outcomes were considered as having adverse outcomes. Hypoglycemia was defined as blood glucose <40 mg/dL by using the heel stick within 2 hours of birth and before the first nonbreast-feeding, and hyperbilirubinemia was defined as a bilirubin level >5 mg/dL. Hyperinsulinemia was defined as an insulin level >10.7 μU/mL. Large for gestational age was defined as birth weight above the 90th percentile compared with gestational age based on sex-specific and race-specific norms. Preeclampsia was diagnosed according to the criteria of the ACOG Practice Bulletin: new onset of blood pressure ≥140/90 mm Hg on 2 separate readings taken 6 hours apart after 20 gestational weeks and proteinuria ≥300 mg/24 hours. Gestational hypertension was defined by criteria 1 of preeclampsia but without proteinuria.

Data are reported as the mean (SD) for continuous variables. For univariate analysis, the *t* test was used to compare continuous variables. For multivariate analysis, we used multivariate models of logistic regression that included all risk factors that were significantly associated in the univariate analysis. We developed a model using multiple logistic regression including body mass index (BMI), calculated as weight (kg)/height squared (m^2), and FBG. We evaluated diagnostic abilities including not only accuracy, sensitivity, and specificity but also area under the curve (AUC). To compare the performance of our model with the 2-step method, we selected as a cutoff value, the point on the receiver operating characteristic curve closest to the upper left corner. This method maximized the Youden index, giving equal weight to sensitivity and specificity.[13] SPSS software version 20.0 (SPSS Inc., Chicago, IL) was used for statistical analyses, all reported *P* values were 2-tailed, and a *P* value <0.05 was considered statistically significant.

RESULTS

Between March 2001 and April 2013, among 3434 women who came to the hospital, 802 women had an abnormal 50-g, 1-hour GCT, of whom 306 were diagnosed with GDM and 496 were found to not have GDM (the false-positive group; Fig. 1). In the GDM group, 218 women (71.2%) had an adverse outcome. In contrast, 240 women (48.4%) in the false-positive group had an adverse outcome (Table 1). In the false-positive group, women with adverse outcomes had significantly higher BMI at entry and FBG in both univariate and multivariate analyses (Table 2). In the GDM group, women with adverse outcomes had significantly higher glucose levels after GCT and GTT only in the univariate analysis (Table 3).

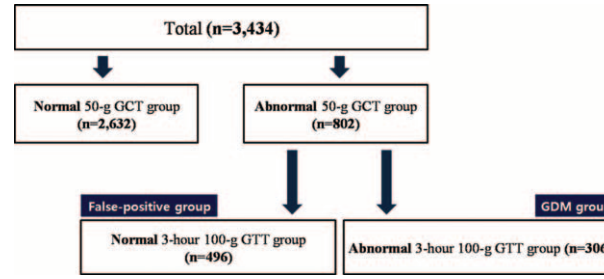

FIGURE 1. Flow chart for diagnosing gestational diabetes in this study population. GCT = glucose challenge test, GDM = gestagestational diabetes, GTT = glucose tolerance test.

Table 4 describes our logistic regression model derived from 2 variables, BMI at entry and FBG, which were significantly different in women in the false-positive group with adverse outcomes. Our model was well calibrated (Hosmer–Lemeshow goodness-of-fit test, $P = 0.27$). The conventional 2-step method predicted GDM adverse outcomes with an AUC of 0.610, accuracy of 59.1%, sensitivity of 47.6%, and specificity of 74.4%. In contrast, our model predicted GDM adverse outcomes with an AUC of 0.642, accuracy of 61.3%, sensitivity of 57.2%, and specificity of 66.9% (Table 5). Figure 2 shows the receiver operating characteristic curves of the conventional 2-step method and our logistic regression model for predicting GDM adverse outcomes.

DISCUSSION

Our logistic regression model performed better in predicting GDM adverse outcomes than the conventional 2-step method using only BMI at entry and FBG. Our model is cost-effective, patient-friendly, and convenient because these 2 variables are simple to measure and require only 1 venipuncture. The GTT in the conventional 2-step method requires 4 venipunctures and a wait period of 3 hours. With our model, women do not have to wait for 3 hours at the hospital. Moreover, our model compensates for the drawbacks of the 2-step method and corresponds to the strengths of the 1-step method. The reasoning behind the shift from the 2 step to the 1 step is the ability of the 1-step method to allow earlier GDM diagnosis and

TABLE 1. Number of Patients With or Without Adverse Outcomes

	False-Positive Group	GDM group	Total
Without adverse outcomes	256 (51.6%)	88 (28.8%)	344
With adverse outcomes	240 (48.4%)	218 (71.2%)	458
Total	496	306	802

GDM = gestational diabetes mellitus.

TABLE 2. False-Positive Group With or Without Adverse Outcomes

	False-Positive Group			
	Without Adverse Outcomes (n = 256)	**With Adverse Outcomes (n = 240)**	P^*	$P^\dagger$
Age (y)	32.9 (3.8)	33.1(3.8)	0.66	
Height (cm)	161.0 (4.9)	161.6 (4.9)	0.14	
BMI at entry (kg/m^2)	21.3 (3.1)	22.1 (3.9)	0.01	0.03
Parity	0.6 (0.7)	0.6 (0.7)	0.23	
Glucose level after 50-g GCT (mg/dL)	151.5 (11.6)	150.5 (10.0)	0.28	
FBG (mg/dL)	78.7 (8.0)	81.0 (11.6)	0.01	0.03
Glucose level after 1 hour of 100-g, 3-hour GTT (mg/dL)	143.0 (25.8)	146.7 (27.5)	0.13	
Glucose level after 2 hours of 100-g, 3-hour GTT (mg/dL)	125.3 (20.8)	127.2 (23.5)	0.33	
Glucose level after 3 hours of 100-g 3-hour GTT (mg/dL)	104.7 (20.9)	103.8 (23.0)	0.65	

Data are shown as mean (SD) for continuous variables.
BMI = body mass index, FBG = fasting blood glucose, GCT = glucose challenge test, GDM = gestational diabetes mellitus, GTT = glucose tolerance test.
* *P* value calculated using the *t* test.
† *P* value calculated using logistic regression for multivariate analysis.

treatment, which results in decreased risk associated with the disease, and its ease of administration, convenience for patients and clinicians, and its diagnostic accuracy.[10] Use of the 1-step method began after release of the Hyperglycemia and Adverse Pregnancy Outcomes Study findings in 2008,[9] and is recommended in the 2010 recommendations of the International Association of Diabetes and Pregnancy Study Group[14] and by the American Diabetes Association in 2011.[15] Our model is more convenient than the 1-step method because it avoids the 1- and 2-hour postload measures and there is no need to wait at the hospital. Moreover, because there is no GCT step, GDM diagnosis and treatment can be as fast as the 1-step method.

Higher BMI at entry and FBG were selected as important risk factors for adverse outcomes. There have been various studies indicating a significant association between higher BMI and GDM.[16–19] Torloni et al[20] performed a systematic review of the literature and a meta-analysis and found out that the maternal prepregnancy BMI is directly associated with the risk of developing GDM. Insulin resistance seems to play a central role among changes in maternal metabolism caused by obesity. There is a report that pregnancy further exacerbated defects of insulin receptors and postreceptors associated with obesity.[21] In addition to insulin resistance, inflammation also might be related to the mechanism of obesity in relation to GDM. Although the pathogenesis of GDM is not clearly understood, several studies found higher levels of serum C-reactive protein, interleukin-6, and ferritin in GDM, suggesting that GDM is associated with systemic inflammation.[22–24] Obesity is usually accompanied by inflammation because of the secretion of proinflammatory cytokines by adipocytes.[25] Thus, women with higher BMI have abundant adipocytes that produce excessive proinflammatory cytokines and might lead to the development

TABLE 3. Gestational Diabetes Mellitus Group With or Without Adverse Outcomes

	GDM Group			
	Without Adverse Outcomes (n = 88)	**With Adverse Outcomes (n = 218)**	P^*	$P^\dagger$
Age (y)	33.5 (3.5)	33.7 (4.0)	0.65	
Height (cm)	159.9 (5.4)	160.6 (5.5)	0.32	
BMI at entry (kg/m^2)	22.6 (4.2)	23.7 (4.5)	0.06	
Parity	0.5 (0.7)	0.7 (0.8)	0.12	
Glucose level after 50-g GCT (mg/dL)	165.9 (18.9)	176.8 (33.9)	<0.001	0.15
FBG (mg/dL)	91.6 (25.0)	100.9 (28.0)	0.01	0.35
Glucose level after 1 hour of 100-g 3-hour GTT (mg/dL)	191.1 (25.8)	199.5 (29.6)	0.02	0.67
Glucose level after 2 hours of 100-g 3-hour GTT (mg/dL)	172.1 (25.1)	182.3 (34.7)	0.01	0.96
Glucose level after 3 hours of 100-g 3-hour GTT (mg/dL)	134.4 (28.6)	146.5 (33.2)	0.01	0.06

Data are shown as mean (SD) for continuous variables.
BMI = body mass index, FBG = fasting blood glucose, GCT = glucose challenge test, GDM = gestational diabetes mellitus, GTT = glucose tolerance test.
* *P* value calculated using the *t* test.
† *P* value calculated using logistic regression for multivariate analysis.

TABLE 4. Odds Ratios for Predicting Gestational Diabetes Mellitus Adverse Outcomes Using the Multiple Logistic Regression

Variables	β-Coefficient	Odds ratio (95% CI)	*P*
BMI at entry (kg/m^2)	0.055	1.057 (1.014–1.100)	0.01
FBG (mg/dL)	0.025	1.025 (1.015–1.036)	<0.001

BMI = body mass index, CI = confidence interval, FBG = fasting blood glucose, GDM = gestational diabetes mellitus.

TABLE 5. Comparison of the Performance of the Conventional 2-Step Method and Logistic Regression in Predicting Gestational Diabetes Mellitus Adverse Outcomes

	Conventional 2-Step Method	Logistic Regression
AUC	0.610	0.642
Accuracy	59.1%	61.3%
Sensitivity	47.6%	57.2%
Specificity	74.4%	66.9%

AUC = area under the curve.

of GDM. Owing to the probable pathogenesis of obesity in association with GDM as mentioned earlier, BMI at entry was selected as a significant factor for predicting GDM adverse outcomes.

Another significant factor for predicting GDM adverse outcomes was elevated FBG, which indicates insulin resistance and impaired insulin secretion.[26] An elevated FBG suggests an underlying pathology of gestational diabetes and does not change throughout gestation, which offers another advantage in its use.[26,27] During the years, FBG has been widely used as a screening test for GDM, because of its advantages of being less expensive, reproducible, and universally easily administered.[28]

Most studies have focused on investigating the optimal factors and its values in predicting GDM.[26–28] The main strength of our study is its focus on investigating performance for predicting GDM adverse outcomes and suggesting a more efficient and effective prediction model. There, however, are several limitations. First, because our institution does not perform the 1-step method, we could not compare the performance of that method with our model. Second, our model might have been fit to the study population; therefore, future studies in other populations are needed to verify this model.

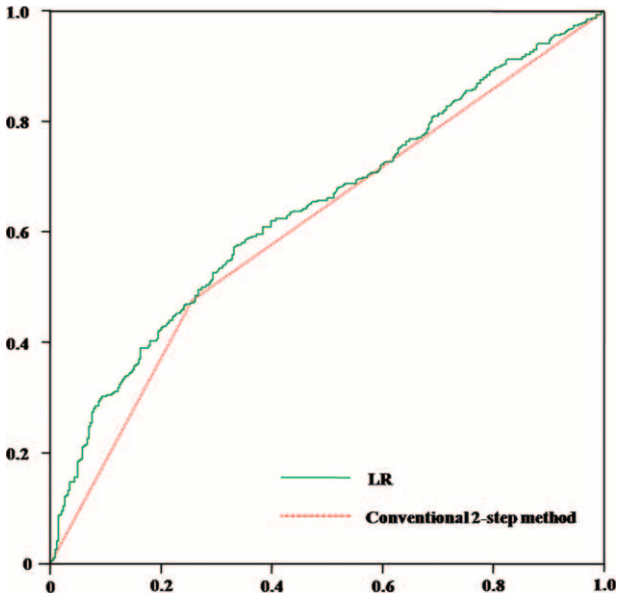

FIGURE 2. Receiver operating characteristic curves of logistic regression and conventional 2-step method for predicting gestational diabetes mellitus adverse outcomes. GDM = gestational diabetes mellitus, LR = logistic regression, ROC = receiver operating characteristics.

CONCLUSIONS

Our logistic regression model performed better than the conventional 2-step method in predicting GDM adverse outcomes. Furthermore, using only BMI at entry and FBG in our model, we attained a practical, inexpensive, efficient, more reproducible, easier, and patient- and clinician-friendly approach. Further studies should be targeted to evaluating our model in other very high-risk populations, including overweight, obese, African–American, and Hispanic women.

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