Quantitative Risk Estimation for Large for Gestational Age Using the Area Under the 100-g Oral Glucose Tolerance Test Curve

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We devised a complementary quantitative method for gestational diabetes (GDM) that uses the area under the curve (AUC) of the results of the oral glucose tolerance test (OGTT), and evaluated its efficacy in predicting neonates that would be large for gestational age (LGA). The study subjects were 648 pregnant women. The AUC–OGTT (concentration $\times$ time) was calculated from the 100-g OGTT results. The incidence of LGA according to each range of the AUC–OGTT was estimated and odds ratios were analyzed using multiple logistic regression analysis.

The incidence of LGA increased with the AUC–OGTT value and was 0% for AUC < 300, 7.8% for 300–400, 14.9% for 400–500, 20.8% for 500–600, and 45.5% for ≥ 600 . The odds ratio of LGA increased by approximately two-fold with an increase of 100 in the AUC–OGTT. The results indicated that the AUC–OGTT can be used to quantify the risk of LGA in GDM. The AUC–OGTT could complement a diagnosis of GDM using conventional diagnostic criteria. *J. Clin. Lab. Anal.* 23:231–236, 2009. © 2009 Wiley-Liss, Inc.

Key words: area under the curve; oral glucose tolerance test; large for gestational age; gestational diabetes; risk quantification

INTRODUCTION

Gestational diabetes (GDM) is a carbohydrate intolerance that has its onset during pregnancy and can vary in severity (1,2). The definition applies irrespective of whether insulin is used for the treatment or the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated the pregnancy (2). The prevalence of GDM in the United States is 1–14% according to the diagnostic method and ethnicity (3–5), and is increasing gradually (1). Excessive fetal growth remains an important perinatal concern in GDM (1). The risk of large for gestational age (LGA) can be great when GDM is not recognized or is treated casually (1). The diagnosis of GDM is important because intensive management is associated with a decrease in mortality and morbidity in infants (1,6–8).

GDM is generally diagnosed using an oral glucose tolerance test (OGTT), although there are no internationally standardized criteria for screening and

diagnosing GDM (9,10). In Europe and Japan, the 75-g OGTT, which is recommended by the World Health Organization (WHO), is most commonly used (11), whereas in the United States, a 100-g OGTT is used for diagnosing GDM (9,12). The National Diabetes Data Group (NDDG) (13) and the Carpenter and

Abbreviations: GDM, Gestational diabetes; OGTT, Oral glucose tolerance test; WHO, World Health Organization; NDDG, National Diabetes Data Group; LGA, Large for gestational age; AUC, Area under the curve; AUC–OGTT, Area under the curve for the results of the 100-g OGTT; AUC–OGTT/100, AUC–OGTT divided by 100; C/S, Cesarean section.

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Coustan (14) criteria, which are applied frequently for diagnosis based on a 100-g OGTT, are qualitative diagnostic criteria that diagnose GDM when two or more of the four measured values exceed the criteria.

We devised a complementary quantitative diagnostic method for GDM that uses the area under the curve (AUC) plotting the results of the 100-g OGTT (AUC-OGTT), and examined whether the AUC-OGTT can be used to quantify the risk for LGA in GDM.

MATERIALS AND METHODS

A retrospective study examined 4,766 women at 24–28 weeks of pregnancy who had undergone a screening test for GDM as recommended by the American College of Obstetricians and Gynecologists (15) at Asan Medical Center between January 2004 and December 2006. A 50-g OGTT was performed after the administration of 50-g of glucose, regardless of whether the patient had been fasting. The venous plasma glucose concentration was measured after 1 hr. Based on the screening tests, 991 patients (20.8%) with glucose levels exceeding 140 mg/dL were judged as positive, and a 100-g OGTT was performed in 778 of these women; the others refused or failed to drink all the glucose. An additional 130 patients were excluded from the final analysis (52 were pregnant with twins and 78 delivered elsewhere). Consequently, 648 patients who delivered a single baby at our hospital were included in this study (Fig. 1). The 100-g OGTT was performed by measuring the plasma glucose level after 12 hr of fasting and 1, 2, and 3 hr after the administration of 100 g of glucose. The nature of the carbohydrate load was explained to all the subjects before the 50- and 100 g OGTT, and all agreed. The glucose levels were measured using the glucose oxidase method (TBA-200 FR, Toshiba, Tokyo, Japan). The percent coefficient of variation of the glucose oxidase method was 1.4–1.5%. The study protocol was

approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea.

The AUC was calculated from the results of the 100-g OGTT using the trapezoidal method, as follows. A graph was plotted with time (hr) as the horizontal axis and glucose level (mg/dL) as the vertical axis, and the area under the line connecting the four measured values was calculated by multiplying time by glucose level (mg/dL hr; Fig. 2). To view the relationship between the AUC-OGTT and the incidence of LGA, we classified the AUC-OGTT into five ranges by 100. We chose <300 as the baseline range for convenience, because the AUC-OGTT is 315 when all four measured values are 105, which is the cutoff value of the fasting glucose. For the multiple regression analysis, we divided the AUC by 100 to make another convenient variable (AUC-OGTT/100) and used these values for statistical analysis.

The mother's age, height, body weight before and after pregnancy, gestational age at delivery, use of glucose-lowering agents or insulin, and the gender and birth weight of the neonate were reviewed from electronic medical records. LGA was defined as a neonate with a birth weight exceeding the 90th percentile for gestational age, using the standard Korean neonatal birth weights as the criteria (16).

To estimate the relationship between the AUC-OGTT and incidence of LGA, we estimated the incidence of LGA according to each range of AUC-OGTT and performed multiple logistic regression analysis including maternal age, gestational age, pregestational body mass index (BMI), and AUC-OGTT as variables. For comparison, our subjects were also analyzed using the conventional NDDG criteria to estimate the incidence of LGA based on different numbers of abnormal results. Multiple logistic regression analysis was performed to estimate the utility of the NDDG criteria for predicting LGA. The statistical analyses were performed with SPSS

Fig. 1. Schematic flow diagram of this study showing the number of subjects included and excluded at each step.

Fig. 2. Calculation of the area under the 100-g OGTT curve (AUC-OGTT). $AUC-OGTT = (a + 2b + 2c + d)/2$ (mg/dL · h). **a–d:** the plasma glucose concentrations for fasting, and 1, 2, and 3 hr after glucose loading, respectively.

TABLE 1. General Characteristics of the Patients Enrolled in the Study and Their Pregnancy Outcomes ($n = 648$)

Characteristic	Value
Maternal age (yr, mean $\pm$ SD)	32.9 $\pm$ 3.7
Height (m, mean $\pm$ SD)	1.6 $\pm$ 0.05
Prepregnancy weight (kg, mean $\pm$ SD)	56.8 $\pm$ 9.5
Prepregnancy BMI (kg/m ² , mean $\pm$ SD)	22.2 $\pm$ 3.6
Gestational age at delivery (wk, mean $\pm$ SD)	38.5 $\pm$ 1.5
Gestational diabetes by NDDG criteria (%)	70 (10.8)
Mean birth weight (g, mean $\pm$ SD)	3223.7 $\pm$ 455.5
Neonate gender (male:female)	1.1:1
Cases of LGA, number (%)	78 (12.1)

BMI, body mass index; NDDG, National Diabetes Data Group; LGA, large for gestational age.

version 13.0 (SPSS, Chicago, IL) and Microsoft Office Excel 2003 (Microsoft, Redmond, WA). The level of statistical significance was $P < 0.05$.

RESULTS

The average age of the women was 32.9 ± 3.7 years, and their weight before pregnancy averaged 56.8 ± 9.5 kg. There were 71 (11.0%) patients with GDM according to the NDDG criteria. Of these, only 15 patients were treated for GDM with a glucose-lowering agent or insulin. The birth weight of the neonates averaged $3,223.7 \pm 455.5$ g, and the gender

TABLE 2. Rates of LGA According to Each Range of AUC-OGTT values ($n = 648$)

	No. of cases	Cases of LGA	Rate of LGA (%)
AUC-OGTT < 300	10	0	0.0
$300 \leq AUC-OGTT < 400$	308	24	7.8
$400 \leq AUC-OGTT < 500$	295	44	14.9
$500 \leq AUC-OGTT < 600$	24	5	20.8
$600 \leq AUC-OGTT$	11	5	45.5
Total	648	78	12.0

LGA, large for gestational age; AUC-OGTT, area under the 100-g OGTT curve; CI, confidence interval.

TABLE 3. Variables Tested in the Multiple Logistic Regression Analysis With LGA ($n = 648$)

Variables	OR	95% CI	P
AUC-OGTT/100*	1.99	1.36–2.92	< 0.001
Maternal age	1.09	1.02–1.16	0.009
Pregestational BMI	1.07	1.00–1.14	0.047
Gestational age	1.06	0.89–1.26	0.509

LGA, large for gestational age; AUC-OGTT, area under the 100-g OGTT curve; OR, odds ratio; CI, confidence interval; BMI, body mass index.

*For the multiple regression analysis, we divided the AUC by 100 to make another convenient variable.

ratio was 1.1:1 (male:female) for the 648 patients enrolled in the study. The incidence of LGA was 12.1% (Table 1). The gender ratio was 2.1:1 in the LGA group and 1:1 in the non-LGA group ($P = 0.01$).

The incidence of LGA according to the ranges of AUC-OGTT values was 0% for $AUC < 300$, 7.8% for 300–400, 14.9% for 400–500, 20.8% for 500–600, and 45.5% for ≥ 600 ; the incidence of LGA increased with the AUC-OGTT (Table 2). The odds ratio of LGA increased by approximately two-fold, for an increase in AUC-OGTT/100 in the multiple logistic regression analysis including confounding variables such as maternal age, pregestational BMI, and gestational age (OR = 1.99; 95% CI: 1.36–2.92, $P < 0.001$; Table 3). Partial correlation analysis adjusted by maternal age, pregestational BMI, and gestational age showed a positive relationship between AUC-OGTT and birth weight (partial correlation coefficient = 0.136, $P = 0.001$).

For comparison, based on the NDDG diagnostic criteria, the incidence of LGA in our subjects increased gradually with each added abnormal result, although there was no difference between the incidence of LGA for one abnormal result, which was interpreted as a normal pregnancy, and two abnormal results, which was

interpreted as GDM; the incidence was 9.4% for no abnormal results, 15.0% for one abnormal result, 14.3% for two abnormal results, 29.2% for three abnormal results, and 50.0% for four abnormal results. Moreover, the multiple logistic regression analysis did not identify any significant difference (Table 4).

DISCUSSION

In this study, the incidence of LGA increased with the range of the AUC-OGTT and the odds ratio of LGA increased by approximately two-fold with an increase of 100 in the AUC-OGTT. The AUC-OGTT was valuable for estimating the quantitative risk of LGA in GDM. By contrast, based on the NDDG criteria, although the incidence of LGA increased gradually with the number of abnormal 100-g OGTT results, there was no difference between one abnormal result, which was interpreted as a normal pregnancy, and two abnormal results, which was interpreted as GDM, and the multiple logistic regression analysis was not statistically significant.

There are few reports on the association between the number of abnormal values for a 100-g OGTT and complications of GDM in semi-quantitative approaches using conventional diagnostic criteria. Nasrat et al. (17) reported that the incidence of macrosomia increased with the number of abnormal values after performing a 100-g OGTT on 660 patients, but for a 100-g OGTT, the incidence of macrosomia was higher in cases with one abnormal value than in cases with two abnormal values, which is similar to our results. In a cohort study of 1,400 patients, Berkus and Langer (18) reported that the incidence of LGA was 13% in patients with normal 100-g OGTT results and 24, 27, 23, and 23% in patients with one to four abnormal values, respectively. This suggests that the incidence of LGA does not increase with the number of abnormal OGTT results, although the presence of abnormal results was highly correlated with LGA compared to patients with no abnormal values. There is a limit to estimating the risk for gestational diabetic complications using semi-quantitative methods based on the number of abnormal values for a 100-g OGTT and a quantitative method is required.

Sermer et al. (19,20) analyzed the 100-g OGTT quantitatively in a prospective cohort study of 3,637 patients and reported that the incidence of macrosomia increased significantly with the fasting blood glucose level and the levels 1 and 2 hr after glucose administration. They reported a two-fold increase in the risk of macrosomia associated with a 1 mmol/L increase in the fasting glucose level. In our analysis, the risk of LGA also increased with the glucose levels measured at 1, 2, and 3 hr (data not shown). Therefore, the AUC-OGTT, which is a quantity unifying the four values measured in

TABLE 4. The Incidence of LGA According to the Number of Abnormal Values Using the NDDG Criteria, the Variables Examined in the Multiple Logistic Regression Analysis, and the Rate of Treatment (n = 648)

Variables	No. of cases	Cases of LGA	Rate of LGA (%)	OR	95% CI	P	AUC-OGTT (mean ± SD)	No. treated (%)
No. of abnormal results using the NDDG criteria	0	44	9.4	1.00		0.068	380.4 ± 38.7	0
	1	16	15.0	1.31	0.69–2.50	0.406	436.2 ± 27.5	0
	2	5	14.3	1.26	0.45–3.50	0.662	475.1 ± 24.7	4 (11.4%)
	3	7	29.2	2.70	1.01–7.23	0.049	530.9 ± 54.6	3 (12.5%)
	4	6	50.0	5.29	1.44–19.53	0.012	616.9 ± 63.0	8 (66.7%)
Maternal age				1.10	1.03–1.18	0.004		
Pregestational BMI				1.07	1.00–1.14	0.048		
Gestational age				1.05	0.88–1.25	0.598		

LGA, large for gestational age; AUC-OGTT, area under the 100-g OGTT curve; NDDG, National Diabetes Data Group; OR, odds ratio; CI, confidence interval.

the 100-g OGTT, was more effective for estimating the risk for LGA. The AUC–OGTT is a continuous value, which gives laboratories the advantage of adjusting the diagnostic values. The AUC–OGTT can be used to elucidate the risk of LGA in women already diagnosed with GDM using conventional diagnostic criteria.

We determined the threshold of the AUC–OGTT method based on the incidence of LGA as a criterion, calculated the diagnostic accuracy of the AUC–OGTT method, and compared it with that of the NDDG criteria. The area under the receiver operating characteristic curve of the AUC–OGTT method was 0.668 (Supplemental Figure). The AUC–OGTT method, with a threshold value of 465, showed good diagnostic agreement with the NDDG criteria (96.5% agreement, κ index = 0.82) and had excellent diagnostic accuracy with higher sensitivity, positive predictive value, negative predictive value, and positive likelihood ratio than the NDDG criteria, with a similar specificity (Supplemental Table). Because the likelihood of intrauterine fetal death is not detectably higher than in the general population with appropriate therapy (1), it is not appropriate to use the “fetal death rate” as a clinical endpoint. We use the incidence of LGA as the criterion for statistical analysis because it is relatively objective and quantitative. A larger prospective study should be performed to decide the appropriate threshold value for clinical application of the AUC–OGTT method.

Of our participants, 71 patients were diagnosed with GDM using the NDDG criteria used in our institution, but only 15 of these patients were treated with a glucose-lowering agent or insulin. Patients with more abnormal values obtained using the NDDG criteria had a higher rate of LGA despite the higher proportion of treated subjects (Table 4). However, we could not collect sufficient information on other forms of management, such as diet and exercise. Therefore, we could not clarify the potential confounding effects of the management of GDM, which constitutes a study limitation. In addition to LGA, well-known complications of GDM include an increased cesarean section (C/S) rate, neonatal metabolic problems, preeclampsia, shoulder dystocia, and perinatal mortality. During the study period, no perinatal mortality or shoulder dystocia was reported. Among the participants, 41.8% (271/648) were delivered by C/S, with 49.8% (135/271) of these following a previous C/S delivery, and only 34.3% (93/271) due to difficulty in labor. This makes an analysis of the relationship between the C/S rate and AUC–OGTT meaningless. We also could not collect enough data on preeclampsia or neonatal metabolic problems.

In conclusion, the incidence of LGA increased with the range of the AUC–OGTT and the odds ratio of

LGA increased approximately two-fold with an increase of 100 in the AUC–OGTT, demonstrating that the AUC–OGTT can estimate the quantitative risk of LGA in GDM. The AUC–OGTT can be calculated easily using measured OGTT values without additional cost and it is a continuous value, allowing laboratories the advantage of adjusting the diagnostic values. Although we do not present compelling data here, the AUC–OGTT can be used to further elucidate the risk of LGA for women already diagnosed with GDM using conventional diagnostic criteria.

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