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Progression to Gestational Diabetes Mellitus in Pregnant Women with One Abnormal Value in Repeated Oral Glucose Tolerance Tests

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Background: Women with one abnormal value (OAV) in a 100 g oral glucose tolerance test (OGTT) during pregnancy are reported to have an increased risk of adverse pregnancy outcomes. However, there is limited data about whether women with OAV will progress to gestational diabetes mellitus (GDM) when the OGTT is repeated.

Methods: To identify clinical and metabolic predictors for GDM in women with OAV, we conducted a retrospective study and identified women with OAV in the OGTT done at 24 to 30 weeks gestational age (GA) and repeated the second OGTT between 32 and 34 weeks of GA.

Results: Among 137 women with OAV in the initial OGTT, 58 (42.3%) had normal, 40 (29.2%) had OAV and 39 (28.5%) had GDM in the second OGTT. Maternal age, prepregnancy body mass index, weight gain from prepregnancy to the second OGTT, GA at the time of the OGTT, and parity were similar among normal, OAV, and GDM groups. Plasma glucose levels in screening tests were different (151.8±15.7, 155.8±14.6, 162.5±20.3 mg/dL, $P<0.05$), but fasting, 1-, 2-, and 3-hour glucose levels in the initial OGTT were not. Compared to women with screen negative, women with untreated OAV had a higher frequency of macrosomia.

Conclusion: We demonstrated that women with OAV in the initial OGTT significantly progressed to GDM in the second OGTT. Clinical parameters predicting progression to GDM were not found. Repeating the OGTT in women with OAV in the initial test may be helpful to detect GDM progression.

Keywords: Diabetes, gestational; Glucose tolerance test; Pregnancy outcome

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with the first recognition during pregnancy, regardless of whether the condition started before pregnancy or not [1]. Because of the recent obesity epidemic and the increase in type 2 diabetes mellitus in general, there has been an increase in undiagnosed type 2 diabetes mellitus in

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women of childbearing age [2]. Therefore, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommends that women diagnosed with diabetes, according to the diagnostic criteria in the first trimester, should be classified as having overt diabetes [3]. It has been reported that approximately 6% to 9% of pregnancies are complicated by GDM [4], and it is well-known that women with GDM have an increased risk of preeclampsia, Caesarean delivery, and preterm delivery [5]. GDM also increases the risk of perinatal morbidities including macrosomia, large for gestational age (LGA), neonatal hypoglycemia, neonatal hyperbilirubinemia, and respiratory distress syndrome [6]. Tight control of blood sugar during pregnancy and labor significantly reduces these risks [7].

However, there is no consensus for the universal diagnostic tests and threshold values for GDM diagnosis. Currently, GDM is diagnosed by either a one-step or two-step approach [8]. The prevalence of GDM significantly changes according to the criteria used to diagnose it. Different diagnostic criteria may lead to different numbers of pregnant women identified as at risk and to different pregnancy outcomes.

A recent systematic review showed that women with one abnormal value (OAV) in a 100 g oral glucose tolerance test (OGTT) had a significantly increased risk of adverse pregnancy outcomes, which is comparable to women with GDM [9]. The American College of Obstetricians and Gynecologists (ACOG) mentioned that OAV, as opposed to two abnormal values, might be used for the diagnosis of GDM [6]. Kim et al. [10] reported that Korean women with a 1 hour OAV in a 100 g OGTT showed increased adverse pregnancy outcomes compared with women with normal OGTT, or 2 or 3 hours OAV.

Even though GDM is detected using different diagnostic criteria, we may still need another approach to identify patients with GDM who need appropriate treatment. Considering the low reproducibility of OGTTs [11,12] and the increase of insulin resistance during pregnancy, some women with OAV may progress to having GDM when re-tested.

In this study, we first evaluated the incidence of GDM when the OGTT was re-tested in pregnant women with OAV in the initial OGTT. Second, we evaluated potential clinical and metabolic predictors for GDM development in women with OAV.

METHODS

This study is a retrospective observational study. This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (B-1808/486-105). Informed consent was waived by the IRB. We collected patient data from Cheil General Hospital & Women's Healthcare Center. Since 1991, pregnant women have been screened for GDM at 24 to 28 weeks, as recommended by the Third International Workshop-Conference on Gestational Diabetes Mellitus [13]. If the plasma glucose levels measured 1 hour after the 50 g oral glucose challenge tests (GCT) in pregnant women were greater than or equal to 130 mg/dL, they were scheduled for a 100 g OGTT before 30 weeks. Women who had OAV in the first OGTT were recommended for re-testing at 32 to 34 weeks. From January 1996 to June 1997 we identified 149 women with OAV in the first OGTT. However, nine women performed the first OGTT after 30 weeks, and three women refused to do the second OGTT. Thus, 137 women were enrolled in this study.

All pregnant women scheduled for an OGTT were instructed to consume a normal diet containing at least 150 g of carbohydrates per day for 3 days, and to perform usual physical activities. They were encouraged to sit quietly throughout the test, and they were not allowed to eat, drink, and smoke. Glucose tolerance tests were done between 8:00 AM to 9:00 AM, after overnight fasts of at least 8 hours, but no more than 14 hours. After fasting, blood samples were obtained, and the women were instructed to drink a 100 g glucose solution within 5 minutes. Blood samples were drawn 1, 2, and 3 hours after glucose intake. Plasma glucose levels were measured with a YSI 2300-STAT glucose analyzer (Yellow Springs Instrument Co., Yellow Springs, OH, USA). Plasma insulin concentrations were measured using a Human Specific Radioimmunoassay Kit (Linco Research Inc., St. Louis, MO, USA). The intra-assay variance of insulin was 4.5%, and the inter-assay variance of insulin was 8.9%.

Based on the results of the second OGTT (32 to 34 weeks), we classified pregnant women who had OAV in the first OGTT into three groups: normal, OAV, and GDM. The women were considered to have OAV if one glucose value was greater than or equal to the following values: fasting, 105 mg/dL; 1 hour, 190 mg/dL; 2 hours, 165 mg/dL; and 3 hours, 145 mg/dL. A GDM diagnosis was made if two or more glucose levels met or exceeded the cutoff values [13]. Insulin secretion was assessed using the insulinogenic index at 60 minutes (IGI60) and the oral dispositional index (ODI). Insulin sensitivity was evaluated using the Matsuda insulin sensitivity index (ISI). IGI60 was calculated as follows: [insulin (60 minutes)−insulin (0

minute)]/[glucose (60 minutes)−glucose (0 minute)] [14]. The Matsuda ISI was calculated as follows: 10,000/√(fasting glucose×fasting insulin×mean glucose×mean insulin) [15]. The ODI was calculated as follows: IGI60×ISI of Matsuda [16].

Neonatal and pregnancy outcomes were evaluated using the following parameters: gestational age (GA) at delivery, birth weight, Apgar score, and other perinatal complications. LGA was defined as a birth weight greater than or equal to the 90th percentile for that GA [17]. Macrosomia was defined as a newborn weighing more than 4,000 g at birth.

The women who developed GDM, as determined by the results of the second OGTT, were managed with medical nutritional therapy and exercise [5]. If maternal hyperglycemia persisted after diet and exercise therapy, insulin therapy was added. However, we did not provide any medical advice or treatment to women with the result of normal and OAV in the second OGTT.

We analyzed clinical characteristics, results of the first OGTT, and pregnancy outcomes using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were analyzed with the analysis of variance (ANO-

VA) test (normally distributed data) and the Kruskal-Wallis test (non-normally distributed data). Normally distributed data were expressed as mean±SD, and Turkey's method was used for *post hoc* analysis. Non-normally distributed data were expressed as median and a 95% confidence interval, and a Mann-Whitney test was used for *post hoc* analysis. Categorical data were compared using the chi-square test and expressed in percentages. To compare the pregnancy outcomes of the three groups (normal, OAV, and GDM) with those of the screen-negative group, which was characterized in our previous article [18], we used a two-sample *t*-test (R program version 3.4.0). *P* values less than 0.05% were considered significant.

RESULTS

Among 137 pregnant women with OAV in the first OGTT, 39 women (28.5%) progressed to being diagnosed with GDM in the second OGTT, done between 32 to 34 weeks. Still 29.2% of the women maintained their OAV status, and the rest (42.3%) recovered and exhibited a normal glucose tolerance status.

Clinical characteristics of the three groups, classified by the

Table 1. Clinical characteristics of study subjects according to the results of the second oral glucose tolerance test

Characteristic	Second OGTT				Screen negative ($n=2,120$)	P value[b]		
	Normal	OAV	GDM	P value[a]		Normal	OAV	GDM
Number	58 (42.3)	40 (29.2)	39 (28.5)					
At screening test								
Age, yr	30.3±3.9	31.1±3.8	30.0±3.8	0.464	28.8±3.3	<0.001	<0.001	0.024
Height, cm	157.4±5.9	156.9±4.4	157.5±4.4	0.830	159.9±4.1	<0.001	<0.001	<0.001
Prepregnancy weight, kg	54.8±8.5	56.0±8.3	54.7±8.7	0.763	51.4±6.4	<0.001	<0.001	0.001
Prepregnancy BMI, kg/m²	22.1±3.0	22.8±3.3	22.1±3.4	0.539	20.1±2.3	<0.001	<0.001	<0.001
Obesity (BMI ≥25 kg/m²)	11 (19)	10 (25)	7 (17.9)	0.691	75 (3.5)	<0.001	<0.001	<0.001
Family history of DM	15 (25.9)	12 (30.0)	17 (43.6)	0.176	229 (14.1)	0.001	<0.001	<0.001
Parity	0.38±0.5	0.38±0.7	0.23±0.4	0.388	0.36±0.53	0.777	0.815	0.135
At first OGTT								
Gestational age, wk	27.0±1.8	26.5±2.3	26.3±1.8	0.173				
Weight, kg	62.9±9.1	63.9±8.6	62.3±10.2	0.744				
At second OGTT								
Gestational age, wk	32.3±1.1	31.8±1.4	32.1±1.5	0.246				
Weight, kg	64.9±9.2	66.1±8.5	65.1±10.1	0.800				
Weight gain, kg	10.1±3.3	10.2±3.6	10.3±4.3	0.952				

Values are presented as number (%) or mean±standard deviation.
OGTT, oral glucose tolerance test; OAV, one abnormal value; GDM, gestational diabetes mellitus; BMI, body mass index; DM, diabetes mellitus.
[a]P for comparison among the three groups, [b]P for comparison between Screen negative group and each three group.

Table 2. Metabolic characteristics of study subjects according to the results of the second oral glucose tolerance test

Characteristic	Second OGTT			P value[a]	P value[b]	P value[c]	P value[d]
	Normal (n=58)	OAV (n=40)	GDM (n=39)				
Screening test							
Glucose, mg/dL	151.8±15.7	155.8±14.6	162.5±20.3	0.010	0.484	0.007	0.179
First OGTT							
Glucose, mg/dL							
0 hr	83.1±8.1	84.2±9.8	85.2±10.5	0.607	0.818	0.594	0.936
1 hr	172.4±23.2	175.1±18.4	177.4±24.1	0.546	0.825	0.522	0.889
2 hr	154.3±20.1	148.3±24.8	151.3±21.1	0.397	0.366	0.784	0.805
3 hr	132.4±22.9	137.1±21.7	133.2±22.4	0.578	0.566	0.982	0.727
Insulin, μU/mL							
0 hr	9.4 (8.3–10.3)	10.0 (9.5–13.1)	8.6 (8.2–10.8)	0.245	0.159	0.834	0.125
1 hr	43.0 (45.4–66.5)	51.0 (47.6–99.5)	36.0 (38.4–60.0)	0.142	0.257	0.373	0.040
2 hr	54.0 (53.1–72.0)	54.0 (49.2–101.4)	38.0 (41.4–65.5)	0.115	0.825	0.082	0.044
3 hr	50.0 (47.1–69.6)	50.0 (52.7–89.3)	39.0 (38.7–68.7)	0.144	0.337	0.246	0.144
IGI60	0.38 (0.42–0.60)	0.45 (0.40–0.90)	0.34 (0.33–0.57)	0.189	0.349	0.190	0.104
Matsuda ISI	4.95 (4.84–6.95)	4.18 (3.90–5.57)	5.53 (4.88–6.41)	0.224	0.269	0.485	0.081
ODI	2.13 (2.03–2.53)	2.04 (1.80–2.58)	1.80 (1.65–2.40)	0.230	0.563	0.099	0.247

Values are presented as mean±standard deviation or median (95% confidence interval). In normally distributed data, Tukey's method was used for *post hoc* analysis. In non-normally distributed data, Mann-Whitney test was used for *post hoc* analysis.

OGTT, oral glucose tolerance test; OAV, one abnormal value; GDM, gestational diabetes mellitus; IGI60, insulinogenic index at 60 minutes; ISI, insulin sensitivity index; ODI, oral dispositional index.

[a]P for analysis of variance (ANOVA) in normally distributed data, P for Kruskal-Wallis in non-normally distributed data, [b]Normal vs. OAV, [c]Normal vs. GDM, [d]OAV vs. GDM.

results of the second OGTT, were not statistically different at the time of the screening test, and the first and second OGTT. As shown in Table 1, maternal age, height, weight, prepregnancy body mass index (BMI), and parity were very similar among the three groups. The frequencies of obese women, as defined by a BMI greater than or equal to 25 kg/m², were 19% in the normal, 25% in the OAV, and 17.9% in the GDM group. Differences in obesity among the three groups were not significant. The frequencies of the first-degree family history of diabetes mellitus were 43.6% in the GDM group, 30% in the OAV group, and 25.9% in the normal group, but these differences were not statistically significant. Compared with the screen-negative group, each of the three groups had significantly higher frequencies of obesity and family history of diabetes. The maternal age, weight, and prepregnancy BMI of the three groups were also significantly higher than those of the screen-negative group. GA and maternal weight at the time of the first and second OGTTs were similar among the three groups. There was also no difference in weight gain from prepregnancy

up until the time of the second OGTT.

Table 2 denotes plasma glucose concentrations of the GCT and the first OGTT in the three groups, classified by the result of the second OGTT. Plasma glucose concentrations of the GCT were highest in the GDM, intermediate in the OAV, and lowest in the normal group. Fasting, 1, 2, and 3 hours glucose concentrations of the first OGTT were not significantly different among the three groups. However, the mean glucose levels at fasting and at 1 hour increased for each group in order from normal to OAV and GDM group.

We also compared the insulin response measured in the first OGTT among the three groups. Mean insulin concentrations 1 hour after glucose intake were highest in the OAV, intermediate in the normal, and lowest in the GDM group, but they were not statistically different. Insulin concentrations 1 and 2 hours after glucose intake in the GDM group were significantly lower compared with those in the OAV group. The IGI60 and Matsuda ISI levels were not different among the three groups. The ODI, a composite index of insulin secretion for insulin re-

Table 3. Pregnancy outcomes in study subjects according to the results of the second oral glucose tolerance test

Variable	Second OGTT			P value[a]	Screen negative (n=2,120)	P value[b]		
	Normal (n=58)	OAV (n=40)	GDM (n=39)			Normal	OAV	GDM
GA at delivery, wk	39.0±1.7	39.6±1.5	39.0±1.5	0.154	39.5±1.5	0.012	0.676	0.039
Apgar score (1 min)	8.11±1.2	8.21±0.7	8.25±1.5	0.860	8.5±1.0	0.003	0.068	0.126
Apgar score (5 min)	9.25±0.9	9.28±0.7	9.41±0.8	0.687	9.7±0.7	<0.001	<0.001	0.011
Low Apgar score (1 min)[c]	1 (1.9)	0	1 (3.1)	0.570				
Low Apgar score (5 min)[c]	1 (1.9)	0	0	0.509				
Birth weight, g	3,402±554	3,494±406	3,420±450	0.657	3,301±450	0.093	<0.001	0.102
LGA	16 (27.6)	12 (30.0)	10 (25.6)	0.900	287 (13.5)	0.002	0.003	<0.001
Macrosomia[d]	5 (9.4)	5 (12.8)	3 (8.6)	0.808	106 (5.0)	0.148	0.028	0.338
Preterm delivery (<37 wk)	7 (12.7)	2 (5.1)	3 (8.3)	0.445	71 (3.3)	<0.001	0.542	0.103
Preeclampsia or PIH	2 (3.6)	0	1 (2.8)	0.500	9 (0.4)	<0.001	-	0.039
Total C-section[e]	32 (58.2)	21 (53.8)	21 (58.3)	0.898	642 (30.3)	<0.001	0.002	<0.001
Primary C-section	19 (34.5)	13 (33.3)	15 (41.7)	0.715				

Values are presented as mean±standard deviation or number (%).
OGTT, oral glucose tolerance test; OAV, one abnormal value; GDM, gestational diabetes mellitus; GA, gestational age; LGA, large for gestational age; PIH, pregnancy induced hypertension.
[a]P for comparison among the three groups: normal, OAV, GDM classified by the results of second OGTT, [b]P for comparison between Screen negative group and each three group, [c]Low Apgar score, defined as Apgar score <7, [d]Macrosomia, defined as birth weight >4,000 g, [e]Total C-section, the composite of primary and repeat Caesarian section.

sistance, was also not different among the three groups.

Finally, we compared pregnancy outcomes among the three groups, and we also compared these outcomes with those of the screen-negative group (Table 3). There were no differences in GA at delivery, Apgar scores, and birth weight among the three groups. The frequencies of LGA, macrosomia, preterm delivery, and other adverse pregnancy outcomes, such as primary Caesarean section and preeclampsia, or pregnancy-induced hypertension, were comparable among the three groups. When we compared the pregnancy outcomes of the three groups with those of the screen-negative group, the mean GA at delivery was earlier in the normal and GDM groups, but similar in the OAV group. Mean birth weight of the OAV group was higher than that of the screen-negative group. The mean Apgar score at 5 minutes from birth of the three groups was significantly lower than that of the screen-negative group. LGA frequencies in the normal, OAV, and GDM groups were about two times higher than those in the screen-negative group. Macrosomia frequency was 12.8% in the OAV group, which was significantly higher than in the screen-negative group. The frequency of preterm delivery in the normal group was higher than that in the screen-negative group, and the frequencies of total Caesarian section in each of the three groups were about two times higher than those in the screen-negative group.

DISCUSSION

Of the 137 women who had OAV in the OGTT performed between 24 to 30 weeks, 28.5% had developed GDM as detected by a second OGTT performed between 32 to 34 weeks. The GDM group showed higher glucose levels in the GCT compared with the normal group. The GDM group also had significantly decreased insulin levels at the 1 and 2 hours of first OGTT compared to the levels in the OAV group. These results suggest that β-cell dysfunction might be associated with the development of GDM in women with OAV. Previous studies demonstrated that women who had limited β-cell capacity for compensating increased insulin resistance during pregnancy were likely to develop GDM [19,20]. In addition, we also found that Korean women with previous GDM, who showed normal glucose tolerance after delivery, had lower β-cell secretory capacity compared with women without GDM [21].

However, there was no difference in the IGI60 and ODI levels among the three groups in this study. Although there is some controversy about the insulinogenic index at 30 minutes (IGI30) as a valid test method [14,22,23], IGI30 and ODI are

widely used for clinical assessment of β-cell function. One study showed that IGI60 from the OGTT might be used as a surrogate for IGI30 [24], but further studies are needed to validate IGI60 as an assessment method for the β-cell function.

Currently, GDM is diagnosed with either a one-step or two-step approach [8]. The two-step approach is based on a screening test using a 50 g GCT followed by a 3-hour, 100 g OGTT. GDM is diagnosed when at least two abnormal glucose values are detected in the 3-hour OGTT. In 2010, the IADPSG recommended the use of a one-step 75 g OGTT to diagnose GDM. The diagnostic threshold for GDM was based on glucose levels which increased the risk for adverse pregnancy outcome 1.75 times, as determined in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [3]. However, the one-step approach was expected to increase the incidence of GDM about three times (from 5%–6% to 15%–20%) [25]. In 2013, the National Institutes of Health (NIH) recommended the use of the two-step approach, since clinical data supporting the benefits and cost effectiveness of the one-step strategy were lacking [26]. The two-step approach has different cutoffs for the 3-hour OGTT. The diagnostic thresholds suggested by Carpenter and Coustan are lower than those suggested by the National Diabetes Data Group (NDDG), which results in an increase of GDM incidences by 50% compared with the former threshold [27]. As different diagnostic criteria predict different degrees of maternal and fetal risk, experts are still debating about the appropriate diagnostic thresholds.

The ACOG has supported the two-step approach, but it recently mentioned that one elevated glucose value in the 100 g OGTT might be sufficient to diagnose GDM [6]. There are several previous studies about the significance of OAV, and some studies reported that women with OAV had a higher risk of adverse maternal and neonatal outcomes compared with women with normal OGTT [9,10,28]. However, if we followed the ACOG suggestion, the incidences of GDM would significantly increase, and some pregnant women may not actually need intensive GDM treatment.

Pregnancy is characterized by increased insulin resistance caused by placental hormones, such as progesterone, cortisol, placental lactogen, prolactin, and growth hormone [29]. Considering that insulin resistance continuously increases from the second trimester to late pregnancy, performing a second OGTT on women with OAV in the first OGTT may help to detect women with GDM who need intensive treatment. However, in this study, we could not find out clinical predictors for progressing GDM in women with OAV, which makes repeating the OGTT more necessary to diagnose GDM.

In this study, macrosomia frequency was significantly higher in the OAV group compared with the screen-negative group. However, all three groups showed increased frequencies of LGA and total Caesarian section, and lower Apgar score at 5 minutes after birth compared with the screen-negative group. There is no consensus as to whether women with OAV should be managed similarly to women with GDM or not. Berkus and Langer [30] and Langer et al. [31] compared perinatal outcomes of normal OGTT group, OAV group, and GDM group that received treatment. The OAV group showed a high incidence of large infants (macrosomia and LGA) and neonatal complications compared with the normal group and the GDM group with treatment [30,31]. Another study showed different results. Forest et al. [32] compared the perinatal outcomes between four groups: normal, OAV women with treatment, OAV women without treatment, and the GDM group. There was no statistical difference in the perinatal outcomes among OAV women with treatment, OAV women without treatment, and women with a normal OGTT [32]. In our study, women with treated GDM diagnosed in the second OGTT had lower incidences of macrosomia compared with OAV group who had untreated. This result supports the premise that women with OAV may benefit from repeating the OGTT, which can diagnose cases of GDM in women who need treatment to reduce maternal and perinatal complications.

This study has several limitations. First, it is a retrospective study, and the pregnancy outcomes of the screen-negative group were obtained from our previous study. Even though the data of pregnancy outcomes were obtained from the same hospital, there was a 3-year time difference between testing the women with OAV and the screen-negative group. Second, the number of women with OAV may not have been enough to compare pregnancy outcomes in a statistically significant manner.

In conclusion, this study showed that a significant proportion of women with OAV in the OGTT, done prior to 30 weeks of GA, developed GDM as diagnosed by a second OGTT, done between 32 to 34 weeks. Thus, repeating the OGTT can be helpful to determine GDM in women with OAV.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: M.Y.K., S.H.K., H.C.J.
Acquisition, analysis, or interpretation of data: S.K., M.H.K., J.S.H., S.H.K., S.H.C., S.L.
Drafting the work or revising: S.K., M.Y.K., S.H.K., K.S.P., H.C.J.
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