Subsequent Pregnancy After Gestational Diabetes Mellitus

Frequency and risk factors for recurrence in Korean women

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OBJECTIVE — The purpose of this study was to determine the frequency of recurrent gestational diabetes mellitus (GDM) and to find risk factors that can predict the recurrence of GDM in Korean women with previous GDM.

RESEARCH DESIGN AND METHODS — We evaluated women who had GDM in an index pregnancy (1993–2001) and a subsequent pregnancy by 2003. An oral glucose tolerance test (OGTT) was performed during the index pregnancy and 2 months postpartum. The recurrence rate of GDM was assessed among 111 women who had a subsequent pregnancy. Multivariate logistic regression analysis was used to identify independent predictors of recurrent GDM.

RESULTS — The frequency of recurrent GDM in subsequent pregnancies was 45.0% (95% CI 35.6–54.4%). Women with impaired fasting glucose and/or impaired glucose tolerance 2 months postpartum were at increased risk for recurrent GDM (relative risk 2.31, 95% CI 1.24–4.30). Higher BMI before the subsequent pregnancy ($P = 0.024$), higher fasting glucose concentration ($P = 0.007$) 2 months postpartum, and lower 1-h insulin concentration ($P = 0.004$) of the diagnostic OGTT in the index pregnancy were independent risk factors for recurrence of GDM in subsequent pregnancies.

CONCLUSIONS — GDM recurred in nearly half of subsequent pregnancies in Korean women. Fasting glucose 2 months postpartum might be a clinically valuable predictor of recurrent GDM risk.

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Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable severity with onset or first recognition during pregnancy (1). GDM is associated with adverse outcomes of pregnancy such as preeclampsia, cesarean delivery, macrosomia, and birth trauma (1,2). Furthermore, women with GDM and their offspring are at increased risk for the development of diabetes later in life (3–5). Recently, a randomized clinical trial demonstrated that treatment of maternal hyperglycemia significantly reduced perinatal morbidity in GDM (6). If we could identify risk factors for recurrent GDM, we might possibly prevent its recurrence. It may also be possible to reduce perinatal morbidity by early diagnosis and optimal treatment of recurrent GDM during the subsequent pregnancy.

The reported frequency of recurrent GDM varies widely, from 30 to 84%, depending on the ethnicity of the subjects and the diagnostic criteria used (7). Although one study reported the recurrence rate of GDM in Asian women (8), the sample size was small and widely used diagnostic criteria for GDM were not applied.

Risk factors associated with recurrence of GDM have also varied among reported studies (7,9). In general, greater maternal age, obesity, degree of hyperglycemia in the index pregnancy, increased weight gain, and short interval between pregnancies were suggested to be associated with recurrent GDM (7–11). However, biochemical parameters, such as glucose and insulin levels during pregnancy and/or early postpartum, have not often been evaluated as risk factors for recurrence of GDM. It is recommended that women with GDM have a glucose tolerance test to reevaluate glycemic status at the first postpartum visit (12). We hypothesized that the early postpartum glucose concentration might provide important information for predicting risk of recurrence of GDM. In this study we evaluated the recurrence rate of GDM in Korean women and risk factors for its recurrence, including a postpartum oral glucose tolerance test (OGTT).

RESEARCH DESIGN AND METHODS

We conducted a retrospective study among subjects with the first diagnosis of GDM at Cheil General Hospital, Seoul, Korea, between July 1993 and March 2001. A total of 792 women with the first diagnosis of GDM were identified during the study period. Among them, 120 women had a subsequent pregnancy by March 2003. The average duration of surveillance for subsequent pregnancy was 5.3 ± 2.3 years.

Our protocol for screening and diagnosis of GDM has been described in previous publications (13,14). Briefly, all pregnant women who had not been identified as having glucose intolerance before 24 weeks were screened for GDM between 24 and 28 weeks' gestation using the 50-g 1-h glucose challenge test. A plasma glucose concentration of ≥130

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mg/dl was considered a positive result and was followed by a diagnostic OGTT. The diagnosis of GDM was made according to the criteria of the Third International Workshop-Conference on Gestational Diabetes Mellitus (1). The threshold values were fasting ≥105 mg/dl, 1 h ≥190 mg/dl, 2 h ≥165 mg/dl, and 3 h ≥145 mg/dl.

After delivery, women with GDM were scheduled for a 75-g OGTT 2 months postpartum. They were asked to consume at least 150 g carbohydrate/day for 3 days and fast for ≥10 h before the OGTT. Postpartum OGTT results were interpreted to American Diabetes Association criteria (15). Women with diabetes at the postpartum evaluation were excluded from this analysis. At the time of postpartum testing, women with GDM were counseled regarding risks of recurrence of GDM and type 2 diabetes in the future.

At the screening test for both the index and subsequent pregnancies, the following information was recorded prospectively for each patient: age, height, prepregnancy weight from patient's recall, present weight, obstetric history including gestational age and parity, and family history of diabetes in the first-degree relatives. Maternal weight and pregnancy outcome were also recorded at the time of delivery. The interval of time between two pregnancies was also calculated.

Plasma glucose concentration was measured with a glucose oxidase method using a YSI 2300 STAT (YSI, Yellow Springs, Ohio). The concentration of insulin was measured using a human-specific radioimmunoassay kit (Linco Research, St. Charles, MO). The intra-assay and interassay coefficients of variation for insulin measurements were 4.5 and 8.8%, respectively. Insulin resistance was estimated by homeostasis model assessment (HOMA-IR) according to the method described by Matthews et al. (16).

Differences between the recurrent GDM group and non-GDM group were analyzed by Student's *t* test and χ^2 test. The insulin concentration was log-transformed to correct for nonnormal distributions. Kruskal-Wallis and Fisher's exact tests were also used to analyze nonnormally distributed and dichotomous variables (e.g., family history of diabetes and parity). Potential risk factors, selected by clinical and/or statistical significance, were examined using multivariate logistic regression analysis to identify independent risk factors for recurrence of GDM. The receiver operating characteristics (ROC) curve was plotted to determine the cutoff value of postpartum fasting glucose level that could best predict the recurrence of GDM. Data are presented as means ± SD and percentage for normally distributed data and otherwise as median (range). $P < 0.05$ was considered to be significant. Statistical analyses were performed using SPSS 12.0 for Windows software (SPSS, Chicago, IL).

Table 1—*Demographic characteristics of women with NGT and recurrent GDM during a subsequent pregnancy*

	NGT	Recurrent GDM	*P* value
Index pregnancy			
Age (years)	28.9 ± 3.4	29.7 ± 3.2	0.20
Prepregnancy weight (kg)	52.9 ± 7.5	57.5 ± 11.5	0.02
Prepregnancy BMI (kg/m^2)	21.1 ± 2.7	23.0 ± 3.9	<0.01
Weight at delivery (kg)	64.7 ± 8.2	69.9 ± 11.3	<0.01
Family history of diabetes (%)	32.8	44.0	0.24
Baby weight (g)	3192 ± 449	3387 ± 494	0.04
Body weight change during pregnancy (kg)	12.0 ± 4.0	12.3 ± 5.5	0.81
Gestational age at diagnosis of GDM (weeks)	29.1 ± 2.9	28.2 ± 3.4	0.11
Insulin treatment (%)	4.9	32.0	<0.01
Subsequent pregnancy			
Age (years)	31.3 ± 3.4	32.4 ± 3.3	0.09
Body weight change between pregnancies (kg)	1.7 ± 3.9	1.2 ± 3.7	0.52
Prepregnancy weight (kg)	54.1 ± 7.6	59.1 ± 10.6	<0.01
Prepregnancy BMI (kg/m^2)	21.5 ± 2.7	23.8 ± 3.7	<0.01
Parity	1.1 ± 0.3	1.1 ± 0.4	0.58
Interval from index to subsequent pregnancy (months)	29.8 ± 13.8	32.8 ± 18.3	0.34

Data are means ± SD unless otherwise indicated.

RESULTS

Recurrent GDM

Between July 1993 and March 2001, we identified 792 women with the first diagnosis of GDM. Of them, 102 (12.9%) had tubal ligation immediately after delivery. Of the remaining 690 subjects who were followed up until March 2003, 120 (17.4%) were found to have a subsequent pregnancy.

Five women with diabetes at the 2 months postpartum test were excluded from the analysis. An additional four women did not have an OGTT during the subsequent pregnancy and were also excluded from the analysis. Results from 111 women were analyzed, and 50 (45.0%, 95% CI 35.6–54.4%) women had recurrent GDM at a subsequent pregnancy. Of these 111 women, 86 had received a 75-g OGTT 2 months after the index pregnancy. Among the 86 subjects, 31 (36.0%) had abnormal glucose tolerance (one had isolated impaired fasting glucose [IFG], 24 had isolated impaired glucose tolerance [IGT], and 6 had IFG and IGT), and 55 women had normal glucose tolerance (NGT). In the abnormal glucose tolerance group, 21 (67.7%) women had recurrence of GDM, whereas only 20 (36.4%) of the NGT group had recurrent GDM. The relative risk (RR) of recurrent GDM in the subgroup with abnormal postpartum glucose tolerance was 2.31 (95% CI 1.24–4.30) compared with that for the NGT group.

Demographic factors related to recurrence of GDM

Demographic characteristics of women who had recurrent GDM and those without GDM during a subsequent pregnancy are shown in Table 1. Those with recurrent GDM had higher prepregnancy BMI and body weight, both at index and at the subsequent pregnancy, and weighed more at the time of delivery than the non-GDM group. Birth weight of infants was also greater in the recurrent GDM group. The proportion of subjects receiving insu-

Table 2—*Comparison of metabolic variables between normal pregnancy and recurrent GDM group*

	Normal	Recurrent GDM	*P* value
Index pregnancy (100-g OGTT)			
Glucose (mg/dl)			
Fasting	84.4 ± 17.4	94.6 ± 24.5	0.02
1 h	190.8 ± 20.0	202.7 ± 35.0	0.03
2 h	174.5 ± 17.1	188.9 ± 38.5	0.02
3 h	147.0 ± 19.1	149.4 ± 49.6	0.70
Insulin (pmol/l)*			
Fasting	60 (13–180)	76 (19–222)	<0.01
1 h	390 (66–1,340)	288 (56–1,399)	<0.01
2 h	480 (49–1,616)	455 (96–1,669)	0.42
3 h	408 (75–1,680)	317 (126–1,548)	0.04
HOMA-IR*	2.20 (0.43–6.16)	3.18 (0.58–20.65)	<0.01
2 months postpartum after index pregnancy (75-g OGTT)			
Glucose (mg/dl)			
Fasting	88.8 ± 7.9	97.9 ± 11.9	<0.01
1 h	155.2 ± 35.6	182.1 ± 37.5	<0.01
2 h	122.2 ± 24.5	134.9 ± 28.5	0.05
Insulin (pmol/l)*			
Fasting	41 (10–126)	48 (13–132)	0.09
1 h	234 (54–1,266)	264 (102–846)	0.71
2 h	189 (31–870)	186 (102–600)	0.47
HOMA-IR*	1.38 (0.36–5.19)	2.04 (0.55–5.25)	<0.01
Abnormal glucose tolerance (%)	22.7 ± 6.4	54.1 ± 8.3	<0.01

Glucose data are means ± SD, and insulin and HOMA-IR data are given as median (range). *Frequency of abnormal glucose tolerance values are means ± SEM. These variables were log-transformed before analyses.

lin treatment was significantly higher in the recurrent GDM group. The average interval between the two pregnancies was not different.

OGTT and recurrence of GDM. The recurrent GDM group had significantly higher fasting and 1-h and 2-h OGTT glucose concentrations during the index pregnancy compared with the non-GDM group (Table 2). Fasting insulin concentration and HOMA-IR were also significantly higher in the recurrent GDM group. However, the recurrent GDM group had significantly lower 1- and 3-h OGTT insulin concentration.

In the 2 months postpartum 75-g OGTT, the recurrent GDM group had significantly higher fasting and 1-h glucose concentrations than the non-GDM group. Fasting, 1-h, and 2-h insulin concentrations did not differ in the two groups. HOMA-IR was again increased in the recurrent GDM group.

Independent risk factors of recurrent GDM. Multiple logistic regression analysis was performed to test for independent risk factors for GDM recurrence. We included variables that were clinically important and significantly different between the two groups in a single logistic model (Table 3). The prepregnancy BMI of subsequent pregnancy, the 1-h insulin level of OGTT in the index pregnancy, and the fasting glucose concentration of the 2 months postpartum OGTT were independent predictors of recurrent GDM.

To further examine the association between these risk factors and recurrence of GDM, we stratified the study subjects into quartiles based on the 1-h insulin concentration of the OGTT in the index pregnancy and the fasting plasma glucose concentration of the postpartum OGTT. As shown in Table 4, the recurrence of GDM was higher as fasting glucose concentration increased and 1-h insulin concentration decreased. Those with a 1-h insulin concentration <220 pmol/l had a 1.9-fold greater risk of recurrent GDM than those with insulin concentration ≥540 pmol/l. Women with a fasting plasma glucose concentration ≥100 mg/dl at the 2 months postpartum OGTT had a 4.8-fold higher risk of having recurrent GDM compared with those with fasting plasma glucose <85 mg/dl. The ROC curve was drawn between fasting plasma glucose concentration and the recurrence of GDM. The cutoff value of 93 mg/dl ensured the best sensitivity and specificity of 65.1 and 70.5%, respectively (area under the ROC curve 0.73, 95% CI 0.62–0.83).

CONCLUSIONS — This hospital-based cohort study demonstrated that the frequency of recurrent GDM in subsequent pregnancies was 45.0% in Korean women. Independent risk factors for recurrent GDM were higher BMI before the subsequent pregnancy, the 1-h insulin concentration of the OGTT in the index pregnancy, and the fasting glucose concentration 2 months postpartum. One of the key features of this study was that we examined whether recurrence of GDM was associated with indexes of insulin resistance and β-cell function (OGTT insulin concentration) along with index pregnancy and postpartum OGTT glucose concentrations. Many risk factors of previous reports, such as early diagnosis of GDM, the need for insulin treatment, and macrosomia, are probably surrogates of β-cell dysfunction and/or severity of glucose intolerance. Another advantage of our study is that the subjects have been followed up for a long period with the average interval of time between index and subsequent pregnancies being ~30.5 months. The longer the period of surveillance, the larger the number of women with a subsequent pregnancy. This might be one of the reasons why it is difficult to compare reports of rates of GDM recurrence. The risk factors for recurrence might also be different with a relatively short versus a relatively long interpregnancy interval.

We attempted to provide comprehensive information about the reproductive history of our GDM cohort. From the 792 index GDM women, we documented that 102 (12.9%) had undergone tubal ligation. The parity of the 690 women after index GDM was 1.24. The total fertility rate of Korean women during the study period (1993–2003) was 1.47 (17). Based on national demographics, we estimated that there might be 159 (690 × 0.23) additional pregnancies during the follow-up period of >5 years. The number that we identified was somewhat less than that. We do not know if there were pregnancies at other hospitals that we did not capture.

Several researchers have applied the same diagnostic criteria used in this study. The frequency of recurrent GDM in our study (45.0%) was similar to that (35.6%) in the report of MacNeill et al. (9), which was obtained from 651 Cana-

Table 3—*Independent risk factors for recurrence of GDM according to multivariate logistic regression analysis*

	Unstandardized coefficients		
	β	SEM	*P* value
Age at subsequent pregnancy	0.098	0.106	0.355
Prepregnancy BMI of subsequent pregnancy	0.277	0.123	0.024
Parity	−0.364	1.185	0.759
Insulin treatment during index pregnancy	1.248	1.176	0.288
Interval between the two pregnancies	−0.001	0.021	0.952
1 h log insulin of OGTT at index pregnancy*	−4.096	1.410	0.004
Fasting plasma glucose at 2 months postpartum	0.098	0.037	0.007

Variables included: age at subsequent pregnancy, prepregnancy BMI of subsequent pregnancy, parity, usage of insulin during index pregnancy, interval between the two pregnancies, fasting and 2-h glucose levels and fasting and 1-h insulin levels of the diagnostic OGTT of index pregnancy, and fasting and 2-h glucose levels at 2 months postpartum. *This variable was log-transformed before analysis.

dians. The study population was predominantly white, and the underlying incidence of GDM was estimated to be ~2%, which was similar to that in a Korean population (14). In contrast, in the reports of Spong et al. (10) and Major et al. (9), whose populations were composed mainly of Hispanics, the recurrence rates of GDM were about 68% in both studies. One of the possible explanations for differences in GDM recurrence rate is that the underlying incidence of GDM in Hispanics was as high as 5% (18). Higher incidence of GDM might reflect increased susceptibility of having GDM and its recurrence in a certain population. We speculated that these differences in ethnicity and underlying incidence of GDM could influence the recurrence rate of GDM in a given population.

Fasting, 1-h, and 2-h glucose concentrations of the OGTT in the index pregnancy were significantly higher in the recurrent GDM group. This finding was in agreement with results of previous studies showing that higher glucose concentrations for an OGTT were associated with increased risk of recurrent GDM. Gaudier et al. (19) reported that women with recurrent GDM had higher 1- and 2-h glucose concentrations. Spong et al. (10) also reported that fasting and 2-h OGTT glucose concentrations were higher in the recurrent GDM group. Therefore, it would be acceptable to state that the severity of hyperglycemia during the index pregnancy is related to recurrent GDM risk.

It is interesting that the 1-h insulin concentration was significantly lower in the recurrent GDM group than that in the non-GDM group. Although the fasting insulin concentration was higher in the recurrent GDM group, the increment of insulin concentration at 1 h was significantly lower (275 ± 250 vs. 400 ± 270 pmol/l). Furthermore, a lower 1-h insulin level was an independent risk factor for recurrence of GDM. This finding implies that the insulin secretion reservoir might be decreased in the recurrent GDM group. There were similar reports stating that β-cell function is decreased in patients with GDM (20,21), but we did not evaluate the disposition index, which measures pancreatic compensation for insulin resistance. However, our result suggests that patients with poor β-cell compensation for insulin resistance at pregnancy are more prone to have recurrence of GDM in a subsequent pregnancy.

It is worth noting that factors identified as independent predictors of recurrent GDM are the same as those that predict the progression to diabetes after GDM. Several studies have shown that impaired β-cell function during the index pregnancy and early postpartum OGTT values were factors that predicted future development of type 2 diabetes in women with GDM (22,23). These findings suggest that a common pathophysiological basis underlies the two diseases. Furthermore, impaired β-cell function and early metabolic derangement seem to have a crucial effect on future glucose metabolism.

It is recommended that maternal glycemic status be evaluated at least 2 months after delivery (15). Among 111 patients with index pregnancy GDM, 86 (77.4%) patients had a 75-g OGTT at 2 months postpartum. Although 22.6% of the women did not have a postpartum OGTT, excluding those patients did not result in differences in clinical characteristics and frequency of recurrent GDM (data not shown). Analysis of the 75-g OGTT at 2 months postpartum after the index pregnancy showed that 34.1% of patients had abnormal glucose tolerance. Women showing abnormal glucose tolerance had as much as 2.3 times increased risk of having recurrent GDM. Furthermore, elevated fasting glucose concentration at 2 months postpartum was an independent risk factor for recurrence of GDM. When we set the cutoff value of fasting glucose concentration at 93 mg/dl, it had acceptable sensitivity and specificity to predict recurrence of GDM. Examination of results of the 75-g OGTT, especially the fasting glucose level at 2

Table 4—*RR for recurrent GDM according to quartiles of independent predictors*

Variable	Recurrence of GDM (%)	RR (95% CI)
1 h insulin of OGTT at index pregnancy (pmol/l)		
<220	18 (72.0)	1.90 (1.12–3.21)
220–339	12 (42.9)	1.13 (0.60–2.13)
340–519	9 (31.0)	0.82 (0.40–1.67)
≥520	11 (37.9)	1
Fasting plasma glucose at 2 months postpartum (mg/dl)*		
<85	6 (27.3)	1
85–93	9 (37.5)	1.24 (0.72–2.15)
94–99	11 (50.0)	1.58 (0.89–2.82)
≥100	19 (86.4)	4.81 (1.67–13.92)

Data are *n* (%) or RR (95% CI). RR was calculated using 86 recurrent cases of GDM according to quartiles of 1-h insulin level of diagnostic OGTT at the index pregnancy and fasting glucose level at 2 months postpartum. *The number of subjects analyzed for fasting glucose was 90, as there were four additional subjects whose fasting glucose level was measured.

months postpartum, could aid in identifying women who are at high risk for GDM recurrence. These subjects should be more intensively monitored for the recurrence, and efforts should be made to improve the metabolic risk factors before they have a subsequent pregnancy.

In summary, GDM recurs in nearly half of subsequent pregnancies among the Korean population. A decreased 1-h insulin concentration for the OGTT in the index pregnancy, higher BMI before subsequent pregnancy, and fasting hyperglycemia at 2 months postpartum were independent risk factors for the recurrence of GDM. Early postpartum examination of maternal glycemic status could help to assess the risk of GDM at subsequent pregnancy.

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