Risk factors for postpartum diabetes mellitus in Japanese patients with gestational diabetes mellitus

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ABSTRACT

Purpose: The objective of this study was to assess the risk factors for postpartum development of impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and diabetes mellitus (DM) in Japanese women with a history of gestational diabetes mellitus (GDM).

Methods: We conducted this retrospective cohort study at St. Luke's International Hospital between January 2011 and February 2019. The results of the 75-g oral glucose tolerance test (OGTT) performed at 3 months after delivery were taken as the primary outcome measure, while the secondary outcome measure was insulin sensitivity (HOMA-IR) measured at 3 months after delivery.

Results: In a total of 293 patients, postpartum OGTT results revealed normal glucose tolerance in 229 patients (78.2%), and IGT, IFG, or both, in 61 patients (20.8%); DM was detected in 3 patients (1.0%). Significant risk factors for the detection of IGT, IFG or DM on the postpartum OGTT were the severity of GDM ($p = 0.037$) and use of insulin therapy during pregnancy ($p = 0.039$). The HOMA-IR value was positively correlated with pregestational BMI ($p < 0.001$).

Conclusion: In the Japanese population, the significant risk factors for postpartum development of IGT, IFG or DM were the severity of GDM and use of insulin therapy during pregnancy.

KEYWORDS

Gestational diabetes mellitus, postpartum diabetes mellitus, impaired glucose tolerance, impaired fasting glucose, insulin sensitivity.

Introduction

Gestational diabetes mellitus (GDM) refers to onset or first recognition of abnormal glucose tolerance during pregnancy [1]. Although it was initially believed that GDM is problematic only during pregnancy [2], it was then found that women with GDM are at a higher risk of developing of type 2 diabetes mellitus (T2DM) after delivery [3]. Given the increasing prevalence of GDM across different ethnic groups [4], it has become important to understand the risk factors for future development of glucose intolerance, so as to prevent it from occurring. The risk factors for the development of impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and diabetes mellitus (DM) after delivery have been investigated in many previous studies [5-9]. However, the risk factors reported in these studies vary among different races, and depending on aspects of the study design, such as sample size, observation period, and whether multiparous women were included as study subjects. Although non-white race/ethnicity is known as one of the strongest risk factors [10], most previous studies were undertaken in non-Asian countries. Therefore, in this study, we evaluated the risk factors for early *postpartum* development of IGT/IFG and DM in Japanese women with a history of GDM.

Materials and methods

We conducted this retrospective cohort study at St. Luke's International Hospital. All women over 20 years old who had been diagnosed as having GDM and who delivered single babies at their first childbirth between January 2011 and February 2019 were included in the study. In the case of women who delivered more than one baby during the research period, we used the data from their first delivery. We excluded those with a known history of stillbirth, miscarriage and/or abortion, and those who had previously been diagnosed as having steroid-induced diabetes during and/or prior to the first pregnancy. In addition, patients with pre-existing diabetes and patients with overt diabetes during pregnancy were also excluded. The results of the 75-g oral glucose tolerance test (OGTT) performed at 3 months after delivery constituted the primary outcome measure, while the secondary outcome measure was insulin sensitivity (HOMA-IR) measured at 3 months after delivery.

This study was conducted with the approval of the St Luke's International Hospital Ethics Committee Institutional Review Board (IRB). Even though the IRB did not require the consent form to be signed by each patient, as this was a retrospective study, we nevertheless excluded patients who did not wish to

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provide consent for any research in which their anonymized data would be used.

Screening and diagnosis

GDM was diagnosed by a two-step approach. The first step was a blood glucose screening in the first trimester and a 50-g 1-h glucose challenge test performed between 24 and 27 weeks of gestation. Plasma glucose was measured 1 h after a 50-g oral glucose load, and the cut-off value to define a positive screen was 140 mg/dL. Screening-positive patients then underwent a 75-g OGTT in the second step. GDM was diagnosed when one or more of the following criteria were met: fasting blood glucose ≥92 mg/dL, 1-h blood glucose ≥180 mg/dL, 2-h blood glucose ≥153 mg/dL. With regard to the severity of GDM, patients in our study who met one of the aforementioned blood glucose criteria were classified as having mild GDM, those meeting two of the criteria as having moderate GDM, and those meeting all three criteria as having severe GDM.

Data collection

We collected the demographic data of the patients, including age, height, pre-pregnancy weight, gestational weight gain, family history of DM, pregnancy and delivery history, gestational weeks at diagnosis of GDM, sex and birth weight of the infant, and history of use of insulin therapy. All data were extracted from medical records.

Outcome

The OGTT was performed from 8 to 12 weeks after delivery, as recommended by the American Diabetes Association. On the basis of the fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG) levels recorded on the OGTT performed after delivery, the women were diagnosed as having normal glucose tolerance (NGT) (FPG <110 mg/dL, 2hPG <140mg/dL), IGT (2hPG between 140 and 199 mg/dL, and FPG < 126 mg/dL), IFG (FPG between 110 and 125 mg/dL), or DM (FPG ≥126 mg/dL, 2hPG ≥200 mg/dL). We compared the risk factors between the Normal group, consisting of patients with NGT, and the Abnormal group, consisting of patients identified as having IGT, IFG or DM. The HOMA-IR value was calculated as FPG (mg/dL) x fasting plasma insulin (mU/L)/405. The cut-off value of HOMA-IR for the diagnosis of insulin resistance was 1.6.

Statistical analysis

The characteristics of the women identified through the *postpartum* OGTT as having NGT were compared with those of the women identified as having IGT, IFG or DM, using Student's t test for continuous variables and Fisher's exact test for categorical variables. The mean adjusted blood glucose levels at each time point in the OGTT performed during pregnancy were compared between the Normal group and Abnormal group by multiple regression analysis, with adjustments for the following covariates: age, pre-pregnancy body mass index (BMI), gestational weight gain, weeks of gestation at the time of the OGTT, history of use of insulin therapy during pregnancy, family history of DM, infant's sex and birth weight. Associations of the results of the post-delivery 75-g OGTT with clinical characteristics were analysed by multiple logistic regression analysis. All statistical analyses were performed using the JMP software (version 14; SAS Institute, Cary, NC, USA). $p < 0.05$ was considered as indicative of statistical significance.

Results

A total of 293 patients with a mean age of 36.7 ± 4.9 years and a mean BMI measured before pregnancy of 21.7 ± 3.4 kg/m^2 were included in this study. Of these, 66 patients (22.5%) were diagnosed as having GDM before 24 weeks of gestation, 114 (38.9%) were diagnosed as having moderate or severe GDM, and 64 (21.8%) received insulin therapy during pregnancy (Table 1).

Table 1 Patients' characteristics.

Variables	Total (n=293)	Normal postpartum OGTT (n=229)	Abnormal postpartum OGTT (n=64)	*p*-value
Age, mean, y (SD)	36.7 (4.9)	36.4 (4.9)	37.7 (4.6)	0.053
Body mass index, mean, kg/m^2 (SD)	21.7 (3.4)	21.8 (3.5)	21.7 (3.2)	0.987
Gestational weight gain, kg (SD)	7.5 (4.1)	7.7 (4.1)	6.8 (3.9)	0.107
Diagnosed as having GDM before 24 weeks' gestation, n (%)	66 (22.5)	52 (22.7)	14 (21.9)	1.000
Diagnosed as having moderate or severe GDM, n (%)	114 (38.9)	80 (34.9)	34 (53.1)	0.0094
Use of insulin therapy during pregnancy, n (%)	64 (21.8)	42 (18.3)	22 (34.4)	0.0097
Positive family history of DM, n (%)	96 (34.9)	74 (34.6)	22 (36.1)	0.879
Male infants, n (%)	153 (52.2)	122 (53.3)	31 (48.4)	0.572
Infant's birth weight, mean, g (SD)	2987 (433)	2996 (442)	2941 (407)	0.371
Blood glucose level on OGTT during pregnancy				
Fasting blood glucose, mean, mg/dl (SD)	84.2 (9.3)	84.4 (9.3)	83.3 (9.4)	0.437
60-min glucose, mean, mg/dl (SD)	175.7 (26.3)	173.0 (26.8)	185.2 (22.2)	0.0009
120-min glucose, mean, mg/dl (SD)	160.6 (25.5)	157.8 (25.3)	170.6 (24.1)	0.0004

The *postpartum* OGTT identified 229 patients (78.2%) as having NGT (Normal group), 61 (20.8%) as having IGT, IFG, or both, and 3 (1.0%) as having DM (Abnormal group). There were no significant differences between the Normal group and the Abnormal group in the fasting blood glucose levels measured on the OGTT performed during pregnancy (Table 1). In addition, the Abnormal group had a significantly higher percentage of women with moderate or severe GDM (p = 0.0094), and a significantly higher percentage of women who received insulin therapy during pregnancy (p = 0.0097) as compared to the Normal group (Table 1). The multiple linear regression analysis identified a diagnosis of moderate or severe GDM (p = 0.037), and use of insulin therapy during pregnancy (p = 0.039) as significant risk factors for being classified as having IGT, IFG or DM on the basis of the *postpartum* OGTT (Table 2). Fasting blood insulin levels, which were used to calculate the HOMA-IR (mean ± SD), were measured during the *postpartum* OGTT in 148 patients. Of these, the HOMA-IR was normal (≤1.6) in 120 and abnormal (>1.6) in 28 patients. Multiple linear regression analysis was carried out to compare factors between the normal HOMA-IR group and the abnormal HOMA-IR group, and it revealed that the HOMA-IR value was significantly positively correlated with BMI measured before pregnancy (p < 0.001) (Table 3).

Discussion

This study identified use of insulin therapy during pregnancy and the severity of GDM as the risk factors for being classified as having IGT, IFG or DM on OGTT performed in the early *postpartum* phase. Lending support to our data, previous studies have identified insulin therapy during pregnancy as one of the most important risk factors for the development of DM in the early *postpartum* period [5-8].

Insulin therapy during pregnancy is associated with a higher risk of development of DM after delivery, as it seems to be related to the mechanism of development of GDM. During pregnancy, insulin sensitivity decreases, mainly due to placental peptides, such as human placental lactogen, oestrogen and progesterone [11, 12]. It is suggested that insulin sensitivity decreases as pregnancy progresses, reaching its nadir in the third trimester [13]. In health, the decrease in insulin sensitivity during pregnancy is compensated for by hyperfunction and hypertrophy of the pancreatic beta-cells and consequent increase in insulin secretion, with resultant maintenance of normal levels of blood glucose during pregnancy [11, 14-17]. However, women with GDM have impaired pancreatic beta-cell function and cannot produce sufficient amounts of insulin to compensate for the in-

Table 2 Risk factors for having IGT, IFG and DM as shown by postpartum OGTT (n=293).

Variables	Odds ratio (95%CI)	*p*-value
Age, mean, y (SD)	1.052 (0.989-1.120)	0.106
Body mass index, mean, kg/m² (SD)	0.980 (0.893-1.077)	0.678
Gestational weight gain, kg (SD)	0.964 (0.887-1.046)	0.379
Diagnosed as having GDM before 24 weeks gestation, n (%)	0.686 (0.320-1.474)	0.335
Diagnosed as having moderate or severe GDM, n (%)	1.925 (1.042-3.556)	0.037
Use of insulin therapy during pregnancy, n (%)	2.046 (1.037-4.037)	0.039
Positive family history of DM, n (%)	0.835(0.434-1.584)	0.580
Male infants, n (%)	0.790 (0.432-1.446)	0.446
Birth weights of infants, mean, g (SD)	1.000 (0.999-1.001)	0.756

Table 3 Risk factors for having abnormal HOMA-IR (>1.6) as shown by postpartum OGTT (n=148).

Variables	Odds ratio (95%CI)	*p*-value
Age, mean, y (SD)	1.075 (0.951-1.215)	0.245
Body mass index, mean, kg/m² (SD)	1.544 (1.282-1.861)	<0.001
Gestational weight gain, kg (SD)	0.965 (0.836-1.115)	0.631
Diagnosed as having GDM before 24 weeks of gestation	2.244 (0.699-7.206)	0.175
Diagnosed as having moderate or severe GDM	0.551 (0.168-1.812)	0.327
Use of insulin therapy during pregnancy	1.385 (0.431-4.456)	0.585
Positive family history of diabetes mellitus, n (%)	0.967 (0.303-3.087)	0.955
Male infants, n (%)	0.916 (0.295-2.847)	0.880
Birth weights of infants, mean, g (SD)	1.000 (0.999-1.001)	0.849

sulin resistance [11, 18, 19]. Our results imply that GDM patients who need insulin therapy during pregnancy may have more severely impaired beta-cell function and more severe insulin resistance compared to those who do not need and that these features persist even after delivery, and may increase the risk of future development of DM [10].

On the basis of the above-mentioned mechanism, insulin resistance is deeply related to the risk of future development of DM in women with GDM. HOMA-IR is known to be a useful parameter for measuring insulin resistance. In our study, HOMA-IR was significantly positively correlated with pre-pregnancy BMI.

Numerous mechanisms have been proposed to explain the increased insulin resistance during pregnancy [11], and increased maternal adiposity is one of them [17]. It is also reported that obesity and the insulin resistance which persists after the pregnancy can exacerbate pancreatic beta-cell dysfunction in the long term [17]. Women with GDM who had a higher pre-pregnancy BMI seem to have increased insulin resistance after delivery, and by implication, sustained insulin resistance after delivery may lead to future DM.

With regard to the severity of GDM, some previous studies have suggested that the FPG, 1-h plasma glucose, and 2hPG levels recorded on OGTT performed during pregnancy are significantly related to the development of abnormal glucose tolerance after delivery, consistent with our results [5, 7, 20]. Our finding that women with moderate or severe GDM were more likely to develop abnormal glucose intolerance after delivery as compared to women with mild GDM is novel, in that the severity of GDM has never been specifically discussed in previous studies in the Japanese population.

Regarding other risk factors, the findings of our study were also inconsistent with previous reports, and the variations in the results could be attributed to differences, between the studies, in the ethnicities considered, the sample sizes, and the inclusion/exclusion of multiparous women.

It should be noted that this study was carried out at a single medical facility, and may, therefore, carry systemic bias, as decision-making regarding treatment by the attending physician may differ from hospital to hospital. However, the criteria for diagnosing GDM are universal and our hospital sees a large number of women with GDM, as it is one of the major hospitals providing care for pregnant women with various pregnancy-related problems. In addition, our study was retrospective in nature, and we did not investigate the long-term risk of abnormal glucose intolerance in the women with GDM. Therefore, to verify our results, a prospective study is warranted to investigate the long-term risk of DM in women with GDM.

Conclusion

In the Japanese population, the significant risk factors for *postpartum* development of IGT, IFG or DM were the severity of GDM and use of insulin therapy during pregnancy. It may be possible to prevent *postpartum* IGT, IFG and DM by controlling body weight before pregnancy and blood glucose during pregnancy.

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