Risk factors during the early postpartum period for type 2 diabetes mellitus in women with gestational diabetes

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Abstract. For women with gestational diabetes mellitus (GDM), the evaluation of glucose tolerance (GT) in the early postpartum period is universally recommended. Nevertheless, few studies have evaluated the risk factors for T2DM on the basis of GT data obtained during the early postpartum period. We aimed to identify the risk factors for type 2 diabetes mellitus (T2DM) by evaluating GT in the first 12 weeks postpartum (12wPP) in women with GDM and to categorize the risk using a combination of the principal risk factors. This retrospective multicenter observational study included 399 East Asian women with GDM who underwent a 75-g oral glucose tolerance test (OGTT) within 12wPP, which was repeated annually or biennially and used to identify the postpartum development of T2DM. Forty-three women (10.8%) developed T2DM during a median follow-up period of 789 ± 477 days. The independent risk factors for T2DM were pre-pregnancy obesity (BMI ≥25 kg/m²), early postpartum impairment in glucose tolerance (IGT), and an early postpartum glycated hemoglobin (HbA1c) ≥5.7%. The odds ratios (95% confidence intervals) for T2DM were 3.2 (1.3–7.8) in women with either early postpartum IGT or pre-pregnancy obesity, 9.2 (3.0–28.3) in those with early postpartum IGT, pre-pregnancy obesity, and HbA1c <5.7%, and 51.4 (16.1–163.9) in those with early postpartum IGT, pre-pregnancy obesity, and HbA1c ≥5.7%, compared with those without obesity or IGT. T2DM risk in East Asian women with GDM should be stratified according to pre-pregnancy obesity and early postpartum IGT, and these patients should be followed up and receive appropriate care for their risk category.

Key words: Gestational diabetes mellitus, Type 2 diabetes mellitus, Early postpartum period, Oral glucose tolerance test, Prediction

GESTATIONAL DIABETES MELLITUS (GDM) is characterized by mild carbohydrate intolerance that commences or is first recognized during pregnancy [1]. GDM is associated with various adverse maternal and perinatal outcomes [2]. Although shortly after delivery, the glucose tolerance of most women diagnosed with GDM is restored to normal [3], a meta-analysis of 20 studies showed that the lifetime risk of developing T2DM in women with GDM diagnosed using the previous diagnostic criteria is 7.4-fold higher than that of women with normal glucose tolerance (NGT) during pregnancy [4]. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) follow-up study showed that...
women with GDM diagnosed using the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria [5] still have a 5.4-fold higher risk of developing T2DM a median 11.4 years after their pregnancy than those who did not have GDM [6].

A few studies have shown that there is a high risk of the postpartum progression of abnormalities in glucose metabolism, including T2DM, in women diagnosed with GDM using the IADPSG criteria [7-9].

A meta-analysis performed by Rayanagoudar and colleagues of the risk of developing T2DM in women with GDM found that this was higher for women who used insulin, had a high body mass index (BMI), had a family history of DM, were of non-white ethnicity, were older mothers, were diagnosed early with GDM, had a high fasting plasma glucose (FPG), 1-h glucose, or 2-h glucose concentration when diagnosed with GDM, or had a high concentration of glycated hemoglobin (HbA1c) [10]. However, importantly, all 39 studies included in the meta-analysis used non- IADPSG criteria to diagnose GDM.

In most studies of the risk of developing T2DM in women with GDM, glucose tolerance was assessed at the time of GDM diagnosis. However, the use of a 75-g oral glucose tolerance test (OGTT) [11-13], fasting plasma glucose measurement [14], or HbA1c measurement [14] is recommended worldwide for the re-evaluation of glucose tolerance within 12 weeks of delivery in women with GDM. Nevertheless, glucose tolerance has rarely been assessed in the early postpartum period when determining the risk of subsequent T2DM in published studies, and those that did report these data were performed a quarter-century ago [15, 16]. Recently, the Women’s Preventive Services Initiative recommended that studies should be performed to determine the predictors of subsequent T2DM in women after childbirth, particularly for those with initially negative or borderline screening test results [17]. Indeed, the OGTT data at the diagnosis of GDM may not always be available at the time of early postpartum reevaluation with OGTT.

In this study, we aimed to identify the risk factors for T2DM in East Asian women with GDM diagnosed using the IADPSG criteria, on the basis of glucose tolerance data obtained within 12 weeks of delivery, not on the results of OGTT at the diagnosis of GDM, and to categorize the risk using a combination of the principal risk factors.

Materials and Methods

Study population

In this retrospective multi-center observational study, we collected GDM registration data from three perinatal centers in Japan: the National Center for Child Health and Development in Tokyo (Tokyo), Osaka Women’s and Children’s Hospital in Izumi City (Osaka), and the National Hospital Organization Nagasaki Medical Center in Omura City (Nagasaki). Women with a singleton pregnancy and GDM who delivered between 1995 and 2011 were included, and most participants were Japanese. Women registered at the National Center for Child Health and Development gave birth between March 2002 and September 2011 and were followed up until October 2014, those registered at Osaka Women’s and Children’s Hospital gave birth between April 1995 and June 2010 and were followed up until February 2011, and those registered at the National Hospital Organization Nagasaki Medical Center gave birth between January 2003 and February 2014 and were followed up until December 2014.

GDM was diagnosed using a two-step approach. First, women with a positive 50-g glucose challenge test or who were at a high risk of GDM underwent a diagnostic 75-g OGTT. Second, using the results from the 75-g OGTT, and until June 2010, a diagnosis of GDM was made using the Japan Society of Obstetrics and Gynecology criteria [18] (two or more abnormal plasma glucose values during the 75-g OGTT, with abnormal values being defined as ≥5.6 mmol/L (100 mg/dL) when fasted, ≥10.0 mmol/L (180 mg/dL) at 1 h, and ≥8.3 mmol/L (150 mg/dL) at 2 h. In all three facilities, women with one or more abnormal blood glucose values during the 75-g OGTT were managed as though they had GDM during pregnancy, and underwent further 75 g OGTTs postpartum and annually or biennially thereafter. After June 2010, the diagnosis of GDM was made using the IADPSG criteria (one or more abnormal plasma glucose value during the 75-g OGTT, with abnormal values being defined as ≥92 mg/dL fasted, ≥180 mg/dL at 1 h, and ≥153 mg/dL at 2 h) [5]. The IADPSG criteria were adopted by the Japan Society of Obstetrics and Gynecology at this time and used at all three study facilities thereafter.

Those women diagnosed with GDM who were taking corticosteroids or those with any values missing from the 75-g OGTTs were excluded. Women diagnosed with GDM using the Japan Society of Obstetrics and Gynecology criteria before May 2010 were re-evaluated using the IADPSG criteria, and those with overt diabetes in pregnancy, according to IADPSG criteria (fasting plasma glucose [FPG] ≥126 mg/dL or HbA1c ≥6.5%), were excluded.

Therefore, the final analysis was conducted on data from those women diagnosed with GDM using the IADPSG criteria who underwent a 75-g OGTT within 12 weeks of delivery, who had not been diagnosed with T2DM, and who had undergone postpartum follow-up using a 75-g OGTT on more than one occasion. We defined “regular” postpartum follow-up as the perfor-
mance of a 75-g OGTT every 1–2 years. If there were more than 3 years between OGTTs, we regarded the last 75-g OGTT before this period as the final procedure. In women who were followed up for more than 2,000 days after delivery, we used the last 75-g OGTT prior to this 2,000-day time point as the final procedure. Women who were not able to discontinue insulin treatment after childbirth were excluded, because this implied a postpartum diagnosis of T2DM.

Flowchart of study participation

A total of 974 women with GDM and a singleton pregnancy (Tokyo 321, Osaka 336, and Nagasaki 317) were eligible for the study. Of these women, 77 were excluded as follows: one was diagnosed GDM while taking corticosteroids, six had missing OGTT data during pregnancy, and 70 were diagnosed with overt diabetes in pregnancy using the IADPSG criteria. Of the remaining 897 women diagnosed with GDM using the IADPSG criteria, three were diagnosed with clinical postpartum diabetes because insulin treatment could not be stopped after childbirth, 607 underwent a 75-g OGTT within 12 weeks of childbirth, 109 underwent a 75-g OGTT beyond 12 weeks postpartum, and 178 were not followed up postpartum. Of the 607 women who underwent a 75-g OGTT within 12 weeks of giving birth, 25 were diagnosed with diabetes, and 183 did not undergo regular follow-up testing after the first postpartum test. Therefore, data from 399 women were included in the analysis (Fig. 1). 67.6% of women with GDM were evaluated within 12 weeks of delivery using a 75-g OGTT and 65.7% of these were followed up regularly after the early postpartum 75-g OGTT.

Glycemic measurements

A 75-g OGTT was performed within 12 weeks of childbirth, after a 10–12 h overnight fast. Blood samples were obtained for the determination of glucose and insulin at 0, 30, 60, and 120 min, and HbA1c was also measured. NGT was defined by a fasting glucose <100 mg/dL and a 2-h glucose <140 mg/dL, impaired glucose tolerance (IGT) was defined by a 2-h glucose of 140–199 mg/dL, and impaired fasting glucose (IFG) was defined by a fasting glucose of 100–125 mg/dL [19].

Diabetes was diagnosed when a participant’s blood glucose values exceeded one or more of the following

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Fig. 1 Flowchart showing the number of participants
thresholds during the postpartum 75-g OGTT: FPG ≥126 mg/dL, 2-h plasma glucose ≥200 mg/dL, or HbA1c ≥6.5% [19].

As a surrogate measure of insulin resistance, homeostatic model assessment of insulin resistance (HOMA-IR) was calculated, using fasting glucose and insulin values. As a surrogate measure of insulin response, the insulinogenic index (IGI) was calculated as (30 min plasma insulin–fasting plasma insulin) [µU/mL]/(30 min blood glucose–fasting blood glucose) [mmol/L].

Anthropometric and laboratory measurements

Maternal antepartum and postpartum data were obtained from medical records. At the time of GDM diagnosis, maternal age, parity, pre-pregnancy BMI, history of diabetes in first-degree relatives (father, mother, or sibling), and gestational age were recorded. The use of insulin (>20 units/day during pregnancy [20]) and birth weight (macrosomia was defined by a birth weight ≥4,000 g) were also recorded.

This study was conducted with the approval of the Institutional Review Boards of the National Center for Child Health and Development, Osaka Women’s and Children’s Hospital, and the Nagasaki Medical Center for the collection of clinical data (approval number: 894, May 2015). Informed consent was obtained in the form of an opt-out procedure.

Statistical analysis

Data are presented as n (%) for categorical variables and mean ± standard deviation for continuous variables. A Pearson chi-square test or Student’s t-test was used to compare data between the groups two-sided Mann-Whitney U test was used to compare data from women who were or were not followed up. Differences with \( p < 0.05 \) were regarded as statistically significant.

To identify independent predictive factors for T2DM, the following variables were assessed: perinatal facility, maternal age at childbirth, pre-pregnancy BMI, family history of diabetes, GDM diagnosis before 20 weeks of gestation, use of insulin during pregnancy, fetal macrosomia, plasma glucose concentrations (fasting, 1 h, and 2 h) during a 75-g OGTT in the early postpartum period (within 12 weeks of delivery), and HbA1c, IGI, and HOMA-IR in the early postpartum period.

Forward stepwise multivariate logistic regression analysis was performed that included all the clinically important parameters and all the parameters identified as statistically significant in univariate analyses. These variables were dichotomized according to cut-off points determined using receiver operating characteristic (ROC) curves. The results for each predictive factor are presented as odds ratios (ORs) and 95% confidence intervals (CIs). The time to the development of T2DM was described using a Kaplan-Meier curve. Finally, the independent predictive factors identified by our analysis were used to categorize the participants according to their risk of developing T2DM.

All analyses were performed using SPSS version 25 for Windows (IBM Inc., Armonk, NY, USA).

Results

Characteristics of the study participants

Table 1 shows the characteristics of the 399 study participants and those who were excluded from the study who fulfilled the IADPSG criteria and had not developed diabetes by the time they underwent a 75-g OGTT within 12 weeks of giving birth. Those who were excluded from the study were less likely to be using >20 IU/day insulin during pregnancy, and to have lower FPG and higher 1-h glucose concentrations during the early postpartum 75-g OGTT than the 399 study subjects. The values for the other parameters were similar between the two groups. However, the proportion of the study subjects recruited at the Nagasaki facility was higher than at the other two facilities.

Forty-three women (10.8%) were found to have T2DM during the median follow-up period of 737 days (range 127–1,994 days).

Table 2 shows the characteristics of the study participants who developed diabetes and those who had not by the time of the final follow-up appointment. The participants who developed diabetes had higher pre-pregnancy BMIs, were more likely to have a family history of diabetes, and had higher fasting, 1-h, and 2-h plasma glucose concentrations, fasting and 2-h plasma insulin concentrations, and HOMA-IR during the OGTTs, and higher HbA1c values in the early postpartum period. There were no differences in 1-h plasma insulin concentration or IGI. There were significant differences in the prevalence of DM at the final follow-up appointment among the three facilities: 18.9% in Osaka, 10.5% in Nagasaki, and 5.7% in Tokyo, respectively (\( p = 0.02 \)).

Risk of T2DM developing

Table 3a shows the results of the univariate logistic regression analysis. Of the known pre-pregnancy and pregnancy risk factors for the subsequent development of T2DM, high pre-pregnancy BMI, a family history of diabetes, and a diagnosis of GDM made before 20 weeks of pregnancy were significant. The risk factors for subsequent T2DM at the early postpartum evaluation were high fasting, 1-h, and 2-h plasma glucose concentrations, high HbA1c, high HOMA-IR, and a diagnosis of IFG or IGT made by 12 weeks after childbirth.
In the multivariate logistic regression analysis, the following risk factors were included: maternal age at childbirth ≥35 y, pre-pregnancy BMI ≥25 kg/m², a family history of diabetes, a diagnosis of GDM before 20 weeks of pregnancy, use of >20 units/day insulin during pregnancy, early postpartum FPG concentration ≥5.2 mmol/L (93 mg/dL), 1-h plasma glucose concentration ≥9.2 mmol/L (165 mg/dL), and 2-h plasma glucose concentration ≥7.6 mmol/L (136 mg/dL), early postpartum HbA1c ≥5.7 %, IGI ≥0.43, and HOMA-IR ≥1.003. We also adjusted for the facility as a standard categorical variable, because we found differences in the postpartum follow-up method, follow-up rate, and the prevalence of T2DM among the three facilities. As shown in Table 3b, we found three risk factors that were independently associated with the development of diabetes: pre-pregnancy BMI ≥25 kg/m² (OR 5.2, 95% CI: 2.4–11.1), 2-h plasma glucose during the early postpartum OGTT ≥136 mg/dL (IGT; OR 3.9, 1.2–5.7), and HbA1c at the early postpartum assessment ≥5.7% (OR 2.6, 1.2–5.7) (Table 3c). For clinical practice, we decided to use IGT, defined by a plasma glucose concentration ≥140 mg/dL, as a categorical variable in the further analysis, instead of using the cut-off value of 136 mg/dL.

Then as shown in Table 3d, a sensitivity analysis was performed for each center, and the results of two of these (Nagasaki and Osaka) analyses were similar to the overall results. However, it was not possible to perform such an analysis on the Tokyo participants because the incidence of T2DM was too low in this group.

Fig. 2a shows the cumulative prevalence of T2DM in women with a pre-pregnancy BMI ≥25 kg/m² and early postpartum IGT. We categorized women with pre-pregnancy BMI ≥25 kg/m² and IGT as high-risk, those with a pre-pregnancy BMI ≥25 kg/m² but with NGT, or those with a pre-pregnancy BMI <25 kg/m² and IGT as moderate-risk, and those with pre-pregnancy BMI <25 kg/m² and NGT as low-risk, when women with GDM underwent a 75-g OGTT within 12 weeks of giving birth. We combined those with a pre-pregnancy BMI ≥25 kg/m² and NGT with those with a pre-pregnancy BMI <25 kg/m² and IGT because their cumulative incidences of diabetes were similar. Furthermore, by adding HbA1c ≥5.7% (71 mmol/mol) at the early postpartum assessment to the classification, the high-risk group (BMI ≥25 kg/m² and NGT) had an incidence of 1.5% (1/65), moderate-risk group (BMI ≥25 kg/m² and IGT) had an incidence of 1.1% (1/92), and low-risk group (BMI <25 kg/m² and NGT) had an incidence of 0% (0/65).

### Table 1 Characteristics of the 399 study participants and those who were excluded from the study who fulfilled the IADPSG criteria and had not developed diabetes by the time they underwent a 75-g OGTT within 12 weeks of giving birth

| Characteristic                                      | The study participants (n = 399) | The participants who were excluded from the study (n = 470) | p value |
|-----------------------------------------------------|---------------------------------|----------------------------------------------------------|---------|
| Facility                                            |                                 |                                                          | <0.001  |
| Tokyo                                              | 105 (34.2)                      | 202 (65.8)                                               |         |
| Osaka                                              | 74 (26.7)                       | 203 (73.3)                                               |         |
| Nagasaki                                           | 220 (77.2)                      | 65 (22.8)                                                |         |
| Age at childbirth, years                           | 34.1 ± 4.8                      | 34.3 ± 4.8                                               | 0.61    |
| Pre-pregnancy BMI, kg/m²                            | 23.4 ± 5.0                      | 23.8 ± 5.2                                               | 0.35    |
| Primiparous, n (%)                                  | 157 (48.0)                      | 136 (48.9)                                               | 0.79    |
| Family history of diabetes (%)                      | 98 (48.8)                       | 140 (45.2)                                               | 0.43    |
| Antenatal glucose metabolism                        |                                 |                                                          |         |
| GDM diagnosis before 20 weeks of gestation, n (%)   | 60 (15.0)                       | 62 (13.9)                                                | 0.64    |
| apOGTT Fasting plasma glucose, mg/dL                | 86.6 ± 10.2                     | 88.5 ± 10.4                                              | 0.009   |
| apOGTT 1-h plasma glucose, mg/dL                   | 185.9 ± 24.9                    | 181.0 ± 30.0                                             | 0.010   |
| apOGTT 2-h plasma glucose, mg/dL                   | 160.6 ± 25.0                    | 158.7 ± 29.1                                             | 0.31    |
| Use of >20 units/day insulin during pregnancy, n (%)| 87 (21.8)                       | 37 (7.8)                                                 | <0.001  |
| Delivery                                            |                                 |                                                          |         |
| body weight at birth, g                             | 2,963.4 ± 487.8                 | 3,022.2 ± 524.7                                          | 0.09    |
| Macrosomia, n (%)                                   | 5 (1.3)                         | 11 (2.3)                                                 | 0.24    |

Data are mean (SD), or n (%).

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; ap, antepartum.
kg/m² and early postpartum IGT) could be further divided into two groups: those with early postpartum HbA1c <5.7% (71 mmol/mol) (moderately high-risk group) and those with early postpartum HbA1c ≥5.7% (71 mmol/mol) (extremely high-risk group) (Fig. 2b). Thus, women with GDM can be classified into low, moderate, moderately high, and extremely high diabetic risk groups using pre-pregnancy BMI, 2-h plasma glucose concentration during a 75-g OGTT, and HbA1c within 12 weeks of delivery. The proportions of participants in each group were 56.3%, 32.9%, 5.7%, and 5.1%, respectively. Compared with the low risk group, the ORs for the development of T2DM after adjustment for the facility was 3.2 (95% CI: 1.3–7.8, p = 0.01), 9.2 (95% CI: 3.0–28.3, p < 0.00), and 51.4 (95% CI: 16.1–163.9, p < 0.00) for the moderate risk group, the moderately high risk group, and the extremely high risk group, respectively.

### Discussion

Using OGTT data collected during the first 12 weeks after childbirth, we have shown that a pre-pregnancy BMI ≥25 kg/m², early postpartum IGT, and a HbA1c ≥5.7% (71 mmol/mol) are independent risk factors for subsequent T2DM in women with GDM. A pre-pregnancy BMI ≥25 kg/m² carries almost the same risk as IGT in the early postpartum period, and the risk of developing T2DM can be categorized using a combination of these three risk factors.

The present study is the first to categorize women with GDM diagnosed using the IADPSG criteria according to the risk factors for developing T2DM, identified using OGTT data obtained within 12 weeks of delivery. Only two studies conducted many years ago had previously demonstrated a subsequent risk of T2DM in women with GDM by evaluating glucose tolerance in the early postpartum period [15, 16], but the diagnostic criteria used for GDM and postpartum diabetes differed from those

### Table 2 Characteristics of the study participants who had developed diabetes and those who had not at the end of follow-up

| Characteristics | T2DM (n = 43) | NGT/IFG and IGT (n = 356) | p value |
|-----------------|--------------|--------------------------|--------|
| Facility        |              |                          |        |
| Tokyo           | 6 (5.7)      | 99 (94.3)                | 0.019  |
| Osaka           | 14 (18.9)    | 60 (81.1)                |        |
| Nagasaki        | 23 (10.5)    | 197 (89.5)               |        |
| Final follow up date, postpartum day | 657.2 ± 488.8 | 924.3 ± 636.5 | 0.008 |
| Age at childbirth, years | 34.3 ± 4.5 | 34.0 ± 4.9 | 0.70 |
| Pre-pregnancy BMI, kg/m² | 27.0 ± 5.6 | 23.0 ± 4.8 | <0.001 |
| Primiparous, n (%) | 17 (58.6) | 139 (46.8) | 0.22 |
| Family history of diabetes, n (%) | 17 (81.0) | 81 (45.0) | 0.016 |
| Use of >20 units/day insulin during pregnancy, n (%) | 14 (32.6) | 73 (20.5) | 0.071 |
| body weight at birth, g | 2,969.3 ± 498.4 | 2,962.7 ± 487.2 | 0.93 |
| Macrosomia, n (%) | 1 (2.3) | 4 (1.1) | 0.50 |
| ppOGTT |              |                          |        |
| ppOGTT date, postpartum day | 51.6 ± 12.2 | 50.1 ± 11.9 | 0.44 |
| ppOGTT Fasting plasma glucose, mg/dL | 94.2 ± 11.7 | 88.7 ± 8.6 | 0.002 |
| ppOGTT 1-h plasma glucose, mg/dL | 172.7 ± 32.8 | 148.0 ± 32.8 | <0.001 |
| ppOGTT 2-h plasma glucose, mg/dL | 142.7 ± 21.2 | 120.2 ± 26.1 | <0.001 |
| ppOGTT Fasting plasma insulin, ng/mL | 7.3 ± 5.2 | 4.9 ± 3.6 | 0.001 |
| ppOGTT 1-h plasma insulin, ng/mL | 48.6 ± 34.6 | 42.1 ± 25.8 | 0.22 |
| ppOGTT 2-h plasma insulin, ng/mL | 51.6 ± 40.3 | 34.5 ± 22.8 | 0.005 |
| HbA1c, % | 5.7 ± 0.397 | 5.4 ± 0.382 | 0.005 |
| IGI | 0.46 ± 0.29 | 0.62 ± 0.68 | 0.14 |
| HOMA-R | 1.8 ± 1.3 | 1.1 ± 0.84 | 0.002 |

Data are mean (SD), or n (%).

Abbreviations: T2DM, type 2 diabetes mellitus; NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; BMI, body mass index; OGTT, oral glucose tolerance test, IGI, insulinogenic index, pp, postpartum.
Table 3  Odds Ratios for subsequent T2DM in women with GDM

(a) Univariate logistic regression analysis

| Variable                                           | Crude Odds Ratio (95% confidence interval) | p value |
|----------------------------------------------------|--------------------------------------------|---------|
| Age at childbirth ≥35                              | 0.65 (0.34–1.2)                            | 0.20    |
| Pre-pregnancy BMI ≥25 kg/m²                        | 6.4 (3.2–12.7)                             | <0.001  |
| Family history of diabetes                         | 2.2 (1.1–4.3)                              | 0.018   |
| GDM diagnosis before 20 weeks gestation            | 2.1 (1.01–4.5)                             | 0.045   |
| Use of >20 units/day insulin during pregnancy      | 1.9 (0.94–3.7)                             | 0.074   |
| Macrosomia                                         | 2.8 (0.28–27.4)                            | 0.38    |
| ppOGTT                                             |                                            |         |
| ppOGTT Fasting plasma glucose ≥5.2 mmol/L (93 mg/dL) | 2.1 (1.1–3.9)                             | 0.027   |
| ppOGTT 1-h plasma glucose ≥9.2 mmol/L (165 mg/dL)   | 4.6 (2.5–9.7)                              | <0.001  |
| ppOGTT 2-h plasma glucose ≥7.6 mmol/L (136 mg/dL)   | 8.6 (4.2–17.6)                             | <0.001  |
| ppOGTT IFG (Fasting plasma glucose ≥5.6 mmol/L (100 mg/dL) | 3.2 (1.5–6.8)                             | 0.002   |
| ppOGTT IGT (2-h plasma glucose ≥7.8 mmol/L (140 mg/dL) | 6.5 (3.3–12.8)                             | <0.001  |
| HbA1c ≥5.7% (71 mmol/mol)                          | 2.9 (1.5–5.5)                              | 0.001   |
| IGI ≥0.48                                          | 0.53 (0.27–1.03)                           | 0.057   |
| HOMA-IR ≥1.003                                     | 3.5 (1.8–7.1)                              | <0.001  |

(b) Multivariate logistic regression analysis, using a cut off value for fasting and 2-h plasma glucose concentrations 12 weeks postpartum, after adjustment for facility

| Variable                                           | Adjusted Odds Ratio (95% confidence interval) | p value |
|----------------------------------------------------|-----------------------------------------------|---------|
| Pre-pregnancy BMI ≥25 kg/m²                        | 5.2 (2.4–11.1)                               | <0.001  |
| ppOGTT 2-h plasma glucose ≥7.6 mmol/L (136 mg/dL)   | 6.4 (3.0–13.8)                              | <0.001  |
| ppOGTT HbA1c ≥5.7% (71 mmol/mol)                   | 2.6 (1.2–5.7)                               | 0.016   |

(c) Multivariate logistic regression analysis, using the conventional cut off glucose values for IFG and IGT in fasting and 120-min plasma samples 12 weeks postpartum, after adjustment for facility

| Variable                                           | Adjusted Odds Ratio (95% confidence interval) | p value |
|----------------------------------------------------|-----------------------------------------------|---------|
| Pre-pregnancy BMI ≥25 kg/m²                        | 4.3 (1.9–9.7)                                | <0.001  |
| ppOGTT 2-h plasma glucose ≥7.8 mmol/L (140 mg/dL (IGT)) | 3.9 (1.8–8.3)                             | <0.001  |
| ppOGTT HbA1c ≥5.7% (71 mmol/mol)                   | 2.6 (1.2–5.7)                               | 0.015   |

Odds Ratios for subsequent T2DM in women with GDM

(d) Sensitivity analysis

| Variable                                           | Total | Nagasaki | Osaka |
|----------------------------------------------------|-------|----------|-------|
| Pre-pregnancy BMI ≥25 kg/m²                        | 4.3 (1.9–9.7) | 5.8 (2.1–15.8) | 1.9 (0.50–6.8) | 0.35 |
| ppOGTT 2-h plasma glucose ≥7.8 mmol/L (140 mg/dL (IGT)) | 3.9 (1.8–8.3) | 4.5 (1.7–11.7) | 5.4 (1.5–19.7) | 0.011 |
| ppOGTT HbA1c ≥5.7% (71 mmol/mol)                   | 2.6 (1.2–5.7) | 1.9 (0.70–4.9) | 3.4 (0.86–13.5) | 0.082 |

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; pp, postpartum; OGGT, oral glucose tolerance test; IGI, insulinogenic index.

*Because the cut-off value for pre-pregnancy BMI using the receiver operating characteristic curve was 24.7 kg/m², we used 25 kg/m² as the cut-off value, which is commonly used.
used in the present study. In the study conducted in Denmark [15], an OGTT was performed 8 weeks postpartum, and the independent risk factors for T2DM between 2 and 11 years postpartum were high fasting blood glucose at the time GDM was diagnosed, a high 2-h glucose concentration at the same time, a higher area under the OGTT glucose curve postpartum, and maternal pre-pregnancy obesity (BMI $\geq 25$ kg/m$^2$). Thus, the results were partially consistent with those of the present study.

In the other study, which was of Latina women in North America [16], an OGTT was performed 4–16 weeks postpartum, and the independent risk factors for T2DM 5–7 years postpartum were an early diagnosis of GDM, a higher fasting blood glucose during pregnancy, and larger areas under the OGTT glucose curve during pregnancy and postpartum. However, pre-pregnancy BMI
was not found to be an independent risk factor. The study population consisted of GDM women with poor glucose tolerance, indicated, for example, by a FPG ≥140 mg/dL before hospital discharge, and moreover, ~70% of the participants had a pre-pregnancy BMI ≥27 kg/m². In this instance, the selection of the study objectives may have led to pre-pregnancy BMI not being among the independent risk factors identified.

Other previous studies have investigated the relationship between glucose tolerance 1 year postpartum and the risk factors for subsequent T2DM. In these studies, 75-g OGTTs and intravenous glucose tolerance tests were conducted between 15 and 30 months after Hispanic women living in North America had given birth [21] and 12 months after delivery by Korean women [22]. Both studies showed that hyperglycemia and poor pancreatic β-cell function 12–30 months postpartum are associated with the subsequent development of T2DM. In the Korean study [22], high glucose concentrations during the OGTT were a predictor of future diabetes, suggesting that glucose tolerance testing is informative even a year after childbirth in an Asian population.

We have also shown that early postpartum IGT, but not IFG, is associated with a similar risk of T2DM as pre-pregnancy obesity in East Asian women with GDM. Women with postpartum IGT after GDM are reported to have a lower insulin sensitivity index and a weaker insulin response to glucose than women with NGT after GDM [23, 24]. In addition, in obese Latina women, early postpartum IGT was associated with an 84% probability of T2DM 5 years after delivery [16]. Thus, in ethnic groups with a high risk of T2DM, the postpartum evaluation of women with GDM should include glucose tolerance testing.

We have also shown pre-pregnancy obesity to be a potent risk factor for T2DM in women with GDM. A recent meta-analysis found the same, because pre-pregnancy BMI ≥25 kg/m² increased the risk of T2DM (relative risk 3.18 [95% CI: 1.96–5.2]) [10]. In addition, postpartum obesity [25] and postpartum weight gain [21, 25, 26] have been reported to be associated with T2DM after GDM. Therefore, it is important to recognize pre-pregnancy obesity as being associated with a high risk of subsequent T2DM in women with GDM, and to encourage obese women to minimize their weight gain or lose weight postpartum. Maternal BMI at the time of postpartum OGTT is a risk factor for T2DM (OR 4.2, 95% CI: 2.0–8.6) as same as he pre-pregnancy BMI. However, at the time the OGTT was performed, within 12 weeks of giving birth, maternal body weight is still returning to normal, rather than being stable. Therefore, we analyzed the pre-pregnancy BMI data.

We have also identified an early postpartum HbA1c ≥5.7% (71 mmol/mol) as an independent risk factor for T2DM in women with GDM. A similar HbA1c value at the time of GDM diagnosis during pregnancy has also been previously reported to be a risk factor for T2DM [9]. This threshold is similar to that in the general population with regard to T2DM [19, 27].

It is important to prevent or delay the onset of T2DM after GDM, because if T2DM develops before 40 years of age there is a higher risk of diabetic complications than if it develops later [28-30]. Therefore, women diagnosed with GDM during pregnancy should always be followed up postpartum, although various barriers to this may exist, including an underdeveloped follow-up system [31-35].

If all women who suffer from GDM were to be assessed annually or biannually using an OGTT, significant costs and complexity would be involved. To ameliorate these problems, it is very important to categorize women according to their risk of developing T2DM, follow up and receive interventions aimed at preventing T2DM. In the present study, our adopted policy is to calculate pre-pregnancy BMI and assess 2-h plasma glucose concentration during a 75-g OGTT in the early postpartum period in all women with GDM, but if they have both of the risk factors mentioned above, HbA1c should also be measured, to predict their risk of developing T2DM. So women with GDM can be classified into four groups (low, moderate, moderately high, and extremely high diabetic risk groups), and who classified into extremely high diabetic risk groups should be very carefully followed up and receive appropriate interventions, because most will develop T2DM in the near future. A sophisticated and practical method of clinical risk categorization for the follow-up of women with GDM has been described for the first time in this report.

Our study had a number of limitations. First, this was a retrospective study, and the study period, follow-up rate, and the method used to follow up women postpartum differed among the three perinatal centers. This may explain the differences in the incidence of progression of T2DM among these centers. Approximately 70% of the women were in the low risk group in both Tokyo and Nagasaki, while only 50% were in this group in Osaka, which may be the result of differences in socio-economic background in the area where each facility is located. Second, the participants in this study may not have been representative of every woman with GDM diagnosed using the IADPSG criteria, because the participants were regularly followed up after an early postpartum OGTT, were more likely to use insulin during pregnancy, and had higher 1-h glucose concentrations during the early postpartum 75-g OGTT than the women who were excluded from the study. Therefore, individuals who could not
mount a compensatory insulin secretory response during pregnancy may have been more likely to be followed up after the early postpartum OGTT. Third, pre-pregnancy BMI was calculated using self-reported weight, not the actual value. In Japan, self-reported weight has been reported to be slightly less than actual weight in obese people [36]. Fourth, the present study participants were East Asian women, who are considered to be a high-risk ethnic group for T2DM [37], meaning that the results may not be universally applicable. Finally, the presence or absence of lactation could not be analyzed as an explanatory variable, because we obtained data regarding lactation from only a quarter of the women. Recently, it has been shown that lactation may be protective against the development of T2DM [38].

In conclusion, the risk of T2DM in women with GDM should be stratified according to the presence of pre-pregnancy obesity and early postpartum IGT, and if both are present, HbA1c should also be taken into account. According to their risk categorization, women with GDM should be followed up and receive appropriate interventions to prevent T2DM.

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Disclosure

The authors declare no conflicts of interest. This work has not previously been published in any other form.

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