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ORIGINAL ARTICLE

One-hour oral glucose tolerance test plasma glucose at gestational diabetes diagnosis is a common predictor of the need for insulin therapy in pregnancy and postpartum impaired glucose tolerance

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ABSTRACT

Aims/Introduction: Gestational diabetes mellitus (GDM) is a risk for adverse perinatal outcomes, and patients with a history of GDM have an increased risk of impaired glucose tolerance (IGT). Here, we carried out two non-interventional and retrospective studies of GDM patients in Japan.

Materials and Methods: In the first study, we enrolled 529 GDM patients and assessed predictors of the need for insulin therapy. In the second study, we enrolled 185 patients from the first study, and assessed predictors of postpartum IGT.

Results: In the first study, gestational weeks at GDM diagnosis and history of pregnancy were significantly lower, and pregestational body mass index, family history of diabetes mellitus, 1- and 2-h glucose levels in a 75-g oral glucose tolerance test (OGTT), the number of abnormal values in a 75-g OGTT, and glycated hemoglobin were significantly higher in participants receiving insulin therapy. In the second study, 1- and 2-h glucose levels in a 75-g OGTT, the number of abnormal values in a 75-g OGTT, glycated hemoglobin, and ketone bodies in a urine test were significantly higher in participants with OGT. Logistic regression analysis showed that gestational weeks at GDM diagnosis, 1-h glucose levels in a 75-g OGTT and glycated hemoglobin were significant predictors of the need for insulin therapy, and 1-h glucose levels in a 75-g OGTT at diagnosis and ketone bodies in a urine test were significant predictors for postpartum IGT.

Conclusions: Antepartum 1-h glucose levels in a 75-g OGTT was a predictor of the need for insulin therapy in pregnancy and postpartum IGT.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy"[1]. GDM is a common medical complication of pregnancy, and the prevalence is growing with increasing rates of late marriage and childbearing, maternal obesity, and inactivity[2].

Exposure to maternal hyperglycemia during pregnancy, even mild hyperglycemia, is associated with an increased risk of adverse perinatal outcomes, including large size for gestational age, macrosomia, induction of labor and cesarean section[3]. Therefore, strict glycemic control is recommended to prevent neonatal and maternal complications. The first-line treatment of GDM is medical diet therapy and exercise, but if this fails, insulin therapy can be initiated. In order to ensure normal fetal development and better perinatal outcomes, it is important to

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establish whether insulin therapy is required for glycemic control in the early stages of GDM. Some studies have revealed some factors that underlie the need for insulin therapy for glycemic control, but consistent predictive factors have not been found.

Gestational diabetes mellitus is also associated with increased maternal risk for diabetes mellitus. An estimated >10% of women with GDM have impaired glucose tolerance (IGT) soon after delivery. Other women develop diabetes mellitus at rates of 20–60% within 5–10 years after pregnancy[4]. Therefore, patients with GDM are recommended to receive the 75-g oral glucose tolerance test (OGTT) during the 6–12 weeks postpartum visit[5].

We carried out two non-interventional and retrospective studies of GDM patients in Japan. The aim of the first study was to compare the characteristics of GDM patients who required insulin therapy with those who only required diet therapy during their pregnancy, and to identify factors predicting the need for insulin therapy in these patients. The aim of the second study was to compare the characteristics of GDM patients who developed IGT with those who had normal glucose tolerance at the 6–12 weeks postpartum visit, and to identify risk factors that predict the development of IGT in these patients.

METHODS

The study protocol was approved by institutional review boards of the National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan.

Participants

This clinical investigation was a non-interventional and retrospective study. The first study enrolled 529 women with GDM who first visited Kumamoto Medical Center from 1 April 2015 to 31 March 2016. Before delivery, the necessity of a postpartum glucose tolerance test was announced. A total of 185 participants from the first study were subjected to the postpartum 75-g OGTT during the 6–12 weeks postpartum period in our hospital and were then enrolled in the second study.

During the first visit to hospital, the women of the first study received a 75-g OGTT at 32.6 ± 0.2 years-of-age at their estimated 25.0 ± 0.3 gestational weeks at the Obstetrics and Gynecology Hospital in Kumamoto prefecture, including Fukuda Hospital, Kikuyo Ladies' Clinic and Matsubase Ladies' Clinic. Pregnant women were subjected to a two-step screening strategy for GDM in accordance with the clinical recommendations of the Japan Society of Obstetrics and Gynecology at the Obstetrics and Gynecology Hospital in Kumamoto prefecture[6]. Pregnant women with the following clinical risk factors were subjected to a 75-g OGTT as soon as possible: geriatric pregnancy, pregestational obesity, a previous history of GDM, previous history of macrosomia, large for gestational age, glycosuria and a casual plasma glucose level ≥100 mg/dL. Pregnant women with no risk factors or with a normal 75-g OGTT pattern underwent a 1-h 50-g oral glucose challenge test between 24 and 28 weeks-of-gestation. If the glucose challenge test result exceeded 140 mg/dL, a diagnostic 75-g OGTT was then carried out. We diagnosed those with GDM according to International Association of Diabetes and Pregnancy Study Groups criteria (defined as at least one value greater than a fasting glucose level of 92 mg/dL, a 1-h glucose level of 180 mg/dL or a 2-h glucose level of 153 mg/dL in the 75-g OGTT)[1], and excluded those with overt diabetes in pregnancy or with known type 1 or type 2 diabetes mellitus before pregnancy.

Treatments

Patients received dietary education from registered dietitians with 30 kcal/kg weight of ideal bodyweight based on body mass index (BMI) 22 kg/m^2 supplemented with 200 kcal, and were instructed to eat three meals per day and one-to-three snacks[6].

After the first visit, patients visited our hospital every 1–3 weeks to measure 2-h postprandial glucose levels. In addition, patients who were covered to carry out the self-monitoring of blood glucose by the Japanese medical insurance system measured 2-h postprandial glucose levels three times a day by themselves. The Japanese medical insurance system covers the self-monitoring of blood glucose levels by GDM patients who inject themselves with insulin, show two or more abnormal values in a 75-g OGTT or show one abnormal value in a 75-g OGTT with BMI ≥25. If the 2-h postprandial glucose level was >120 mg/dL, they were admitted to our hospital to measure preprandial and 2-h postprandial glucose levels daily, and to receive medical nutrition therapy. After admission, if targeted glucose levels with preprandial glucose <100 mg/dL and 2-h postprandial glucose <120 mg/dL were not achieved continuously for 3 days in the same time zone by medical nutrition therapy, insulin therapy was initiated.

In the first study, we classified patients into two groups: patients who received insulin therapy (Insulin group; $n = 57$) and patients without insulin therapy (Diet group; $n = 472$). In the second study, 41 patients received insulin therapy and 144 patients were treated with diet alone.

Measurements and calculations

Data collected included age and gestational weeks at GDM diagnosis, history of gestation and pregnancy, BMI at 20 years-of-age, pregestational and maximum BMI, family history of diabetes mellitus, prior GDM, plasma glucose levels, and the number of abnormal values in a 75-g OGTT at GDM diagnosis. Fasting plasma glucose, glycated hemoglobin (HbA1c), fasting immunoreactive insulin (IRI) and ketone bodies in a urine test were measured during the first visit to our hospital. The results of ketone bodies in a urine test of negative, ±, 1+, 2+, 3+ and 4+ were scored as 0, 0.5, 1, 2, 3 and 4, respectively. Plasma glucose levels and IRI levels of a postpartum 75-g OGTT at 0, 30, 60, 90 and 120 min were also collected. In addition, we calculated the homeostatic model assessment for

insulin resistance (HOMA-IR; fasting glucose [mg/dL] × fasting IRI [μU/mL]/405)[7], β-cell function (HOMA-β; fasting IRI [μU/mL] × 360/fasting glucose [mg/dL]−63)[7] and the insulinogenic index ([30-min IRI {μU/mL}−fasting IRI {μU/mL}]/[30-min glucose {mg/dL}−fasting glucose {mg/dL}])[8] using established methods.

Statistical analysis

Data are presented as mean ± standard error of the mean. The unpaired *t*-test, the Mann–Whitney *U*-test and the χ^2-test were used to analyze between-group differences for continuous variables, ordinal variables and categorical variables, respectively. Multivariate logistic regression analysis was carried out using selected independent variables that were significantly different in univariate analysis. We also carried out receiver operating characteristic (ROC) curve analysis to identify clinical factors that predicted the need for insulin therapy or the appearance of IGT. We determined a cut-off value by the point on the ROC curve closest to the upper left corner. All analyses were carried out using SPSS 14.0-J (SPSS Japan, Ibaraki, Japan), and all *P*-values were two-sided. A *P*-value <0.05 was considered significant.

RESULTS

Characteristics of GDM in the first study

Data collected during the first visit to our hospital were compared between the Diet and Insulin groups. As shown in Table 1, age at GDM diagnosis, history of gestation, BMI at 20 years-of-age, maximum BMI, prior GDM, fasting IRI, HOMA-IR, HOMA-β and ketone bodies in urine did not significantly differ between the Diet and Insulin groups. Plasma glucose levels in a 75-g OGTT at 0 min and fasting plasma glucose during the first visit were higher in the Insulin group compared with that of the Diet group, but the difference was not significant.

In contrast, gestational weeks at GDM diagnosis and history of pregnancy were significantly lower in the Insulin group compared with that of the Diet group. In addition, pregestational BMI, family history of diabetes mellitus, plasma glucose levels in a 75-g OGTT at 1 and 2 h, number of abnormal values in a 75-g OGTT, and HbA1c were significantly higher in the Insulin group compared with those of the Diet group.

Risk factors for the need for insulin therapy

To identify clinical factors to predict the need for insulin therapy, we carried out logistic regression analysis using independent variables that were significantly different between the Diet and Insulin groups (Table 2). In logistic regression analysis, plasma glucose levels in a 75-g OGTT at 1 h and HbA1c were significant predictors for insulin therapy, and the odds ratios were 1.023 (95% confidence interval [CI] 1.009–1.037) and 3.192 (95% CI 1.177–8.659), respectively. Gestational weeks at GDM diagnosis was identified as a significant protective factor for insulin therapy, and the odds ratio was 0.958 (95% CI 0.921–0.997).

To determine the cut-off values, ROC curve analysis was carried out using independent variables that were significant

Table 1 | Characteristics of gestational diabetes mellitus in the diet and insulin groups

	Diet group (*n*)		Insulin group (*n*)		*P*-value
Age at GDM diagnosis (years)	32.5 ± 0.3	(472)	33.6 ± 0.7	(57)	0.117
Gestational weeks at GDM diagnosis (weeks)	25.32 ± 0.35	(471)	22.18 ± 1.10	(56)	0.004
History of gestation	1.45 ± 0.07	(471)	1.28 ± 0.20	(57)	0.448
History of pregnancy	0.87 ± 0.05	(472)	0.54 ± 0.11	(57)	0.030
BMI at 20 years-of-age	20.97 ± 0.15	(433)	21.01 ± 0.46	(48)	0.933
Pregestational BMI	22.41 ± 0.21	(457)	23.89 ± 0.70	(53)	0.025
Maximum BMI	24.15 ± 0.58	(442)	24.96 ± 0.71	(52)	0.635
Family history of DM, *n* (%)	199 (43.1)	(462)	38 (69.1)	(55)	<0.001
Prior GDM, *n* (%)	25 (5.3)	(469)	5 (8.8)	(57)	0.357
PG in 75-g OGTT at GDM diagnosis (mg/dL)					
Fasting	91.5 ± 0.4	(471)	94.1 ± 1.4	(55)	0.087
At 1 h	155.4 ± 1.5	(471)	184.9 ± 4.4	(55)	<0.001
At 2 h	139.5 ± 1.2	(471)	157.1 ± 4.1	(55)	<0.001
No. abnormal values of 75-g OGTT at GDM diagnosis	1.3 ± 0.0	(471)	1.8 ± 0.1	(55)	<0.001
Fasting PG (mg/dL)	79.4 ± 0.3	(448)	81.9 ± 1.29	(50)	0.061
HbA1c (%)	5.24 ± 0.01	(470)	5.46 ± 0.06	(57)	0.001
Fasting IRI (μU/mL)	5.51 ± 0.18	(437)	6.10 ± 0.53	(46)	0.311
HOMA-IR	1.10 ± 0.04	(437)	1.27 ± 0.12	(46)	0.196
HOMA-β	134.11 ± 4.65	(430)	124.32 ± 1 0.55	(45)	0.508
Ketone bodies in urine	0.91 ± 0.06	(471)	0.93 ± 0.18	(57)	0.828

Data are mean ± standard error of the mean. BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-β, homeostatic model assessment for β-cell function; HOMA-IR, homeostatic model assessment for insulin resistance; IRI, *immunoreactive insulin*; OGTT, oral glucose tolerance test; PG, plasma glucose.

Table 2 | Logistic regression analysis with selected independent variables that were significantly different between the diet and insulin groups

	B	Standard error	*P*-value	Odds ratio (95% CI)
Gestational weeks at GDM diagnosis	−0.043	0.020	0.033	0.958 (0.921–0.997)
History of pregnancy	−0.334	0.196	0.088	0.716 (0.488–1.051)
Family history of DM (1: no, 2: yes)	0.583	0.341	0.087	1.792 (0.919–3.493)
Pregestational BMI	0.025	0.034	0.456	1.026 (0.960–1.096)
PG at 1-h in 75-g OGTT at GDM diagnosis	0.023	0.007	0.001	1.023 (1.009–1.037)
PG at 2-h in 75-g OGTT at GDM diagnosis	0.009	0.007	0.200	1.009 (0.995–1.024)
No. abnormal points in 75-g OGTT at GDM diagnosis	−0.151	0.314	0.632	0.860 (0.464–1.593)
HbA1c	1.161	0.509	0.023	3.192 (1.177–8.659)

BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PG, plasma glucose.

predictors of the need for insulin therapy by logistic regression analysis. The cut-off values of gestational weeks at GDM diagnosis, plasma glucose levels in a 75-g OGTT at 1 h and HbA1c were 25.07 weeks (area under the curve [AUC] 0.613, sensitivity of 61.8% and specificity of 58.9%), 181.5 mg/dL (AUC 0.739, sensitivity of 60.0%, specificity of 75.8%) and 5.35% (AUC 0.650, sensitivity of 54.4%, and specificity of 65.5%), respectively. When we carried out a logistic regression analysis using the cut-off values of all three parameters, AUC, sensitivity and specificity were 0.723, 67.3 and 67.3%, respectively.

Postpartum 75-g OGTT

A total of 185 participants from the first study received a postpartum 75-g OGTT during the 6–12-week postpartum period. According to the diagnosis criteria for diabetes mellitus[5], these participants were divided into two groups based on the results of the postpartum 75-g OGTT: the normal glucose tolerance group (n = 160, 86.5%) and the IGT group (n = 25, 13.5%). The IGT group contained three participants (1.6%) who were diagnosed as diabetes mellitus.

In the IGT group, plasma glucose levels in a 75-g OGTT at 30, 60, 90 and 120 min were significantly higher compared with those of the normal glucose tolerance group (Table 3). In contrast, a difference in plasma glucose levels in a 75-g OGTT at 0 min was not observed between the normal and IGT groups. Similarly, IRI levels in a 75-g OGTT at 90 and 120 min were higher compared with those of the normal glucose tolerance group, whereas IRI levels in a 75-g OGTT at 0, 30 and 60 min did not significantly differ between the normal and IGT groups.

Insulinogenic index, a marker of the early insulin response to glucose, was significantly lower in the IGT group compared

Table 3 | Postpartum 75-g oral glucose tolerance test in the normal and impaired glucose tolerance groups

	All participants (n = 185)	Normal glucose tolerance (n = 160)	Impaired glucose tolerance (n = 25)	*P*-value
PG in 75-g OGTT (mg/dL)				
Fasting	87.7 ± 0.6	86.9 ± 0.5	92.6 ± 3.1	0.082
At 30 min	141.5 ± 1.8	137.6 ± 1.7	166.2 ± 5.5	<0.001
At 60 min	141.5 ± 2.6	134.2 ± 2.3	188.6 ± 6.7	<0.001
At 90 min	128.4 ± 2.4	120.0 ± 2.0	181.7 ± 5.7	<0.001
At 120 min	116.6 ± 2.0	108.4 ± 1.3	169.1 ± 5.3	<0.001
IRI in 75-g OGTT (μU/mL)				
Fasting	3.85 ± 0.15	3.73 ± 0.14	4.65 ± 0.66	0.185
At 30 min	36.83 ± 1.64	36.89 ± 1.83	36.44 ± 3.28	0.927
At 60 min	41.81 ± 1.64	40.57 ± 1.70	49.79 ± 5.15	0.054
At 90 min	36.23 ± 1.56	33.68 ± 1.55	52.56 ± 4.81	<0.001
At 120 min	31.86 ± 1.39	27.89 ± 1.16	57.26 ± 4.62	<0.001
Insulinogenic index	0.70 ± 0.04	0.74 ± 0.04	0.45 ± 0.04	<0.001
<0.4, n (%)	52 (28.3)	42 (26.4)	10 (40.0)	0.161
HOMA-IR	0.86 ± 0.04	0.81 ± 0.03	1.17 ± 0.23	0.135
>1.6, n (%)	12 (6.5)	7 (4.4)	5 (20.0)	0.003
HOMA-β	57.02 ± 1.80	57.31 ± 2.01	55.20 ± 3.67	0.690
<30, n (%)	10 (5.4)	9 (5.6)	1 (4.0)	1.000

Data are mean ± standard error of the mean. HOMA-β, homeostatic model assessment for β-cell function; HOMA-IR, homeostatic model assessment for insulin resistance; OGTT, oral glucose tolerance test; PG, plasma glucose.

with that of the normal glucose tolerance group. In contrast, there were no differences observed in HOMA-IR and HOMA-β between the normal and IGT groups.

Characteristics of GDM in the second study

Data collected during the first visit to our hospital were compared between the normal and IGT groups (Table 4). There were no significant differences in age at GDM diagnosis, history of gestation and pregnancy, BMI at 20 years-of-age, pregestational and maximum BMI, family history of diabetes mellitus, prior GDM, plasma glucose levels in a 75-g OGTT at 0 min, fasting plasma glucose, fasting IRI, HOMA-IR, and HOMA-β between the normal and IGT groups. In contrast, plasma glucose levels in a 75-g OGTT at 60 and 120 min, the number of abnormal values in a 75-g OGTT, HbA1c, and ketone bodies in a urine test were significantly higher in the IGT group compared with those of the normal glucose tolerance group.

In the second study, 41 patients received insulin therapy during gestation, and the patients who received insulin therapy during gestation were more frequent in the IGT group than in the normal glucose tolerance group.

Risk factors for the appearance of IGT

To identify clinical factors to predict postpartum IGT, we carried out logistic regression analysis using independent variables that were significantly different between the normal and IGT groups (Table 5). In logistic regression analysis, plasma glucose levels in a 75-g OGTT at 60 min and ketone bodies in a urine test were significant predictors for IGT, and the odds ratios were 1.027 (95% CI 1.004–1.050) and 1.558 (95% CI 1.091–2.255), respectively.

To determine the cut-off values, ROC curve analysis was carried out using independent variables that were significant predictors for the appearance of IGT by logistic regression analysis. The cut-off values of plasma glucose levels in a 75-g OGTT at 60 min and ketone bodies in a urine test were 184.5 mg/dL (AUC 0.770, sensitivity of 68.0%, specificity of 82.3%) and 0.75 (AUC 0.700, sensitivity of 68.0%, and specificity of 63.1%), respectively.

DISCUSSION

Glucose intolerance during pregnancy, even mild intolerance, is a risk for adverse perinatal outcomes. Therefore, strict glycemic control is required to prevent adverse perinatal outcomes. In contrast, women with a history of GDM also have an increased risk of developing type 2 diabetes mellitus later in life compared with women without GDM. In the present study, we carried out two non-interventional and retrospective studies of GDM patients in Japan. The first was a comparison of the characteristics of GDM patients who required insulin therapy and those who required diet therapy only during pregnancy to identify the factors predicting the need for insulin therapy in

Table 4 | Characteristics of gestational diabetes mellitus in the normal and impaired glucose tolerance groups

	Normal glucose tolerance	(*n*)	Impaired glucose tolerance	(*n*)	*P*-value
Age at GDM diagnosis (years)	33.3 ± 0.4	(160)	34.2 ± 1.0	(25)	0.439
Gestational weeks at GDM diagnosis (weeks)	25.46 ± 0.59	(158)	23.58 ± 1.48	(25)	0.241
History of gestation	1.21 ± 0.10	(160)	1.24 ± 0.26	(25)	0.904
History of pregnancy	0.65 ± 0.06	(160)	0.56 ± 0.15	(25)	0.601
Family history of DM, *n* (%)	77 (49.7)	(155)	16 (66.7)	(24)	0.121
Prior GDM, *n* (%)	2 (1.3)	(158)	2 (8.0)	(25)	0.091
BMI at 20 years old	20.95 ± 0.26	(146)	20.89 ± 0.66	(23)	0.927
Pregestational BMI	22.01 ± 0.32	(155)	23.27 ± 1.01	(24)	0.163
Maximum BMI	23.43 ± 0.32	(148)	23.49 ± 1.46	(23)	0.948
PG in 75-g OGTT at GDM diagnosis (mg/dL)					
Fasting	90.6 ± 0.7	(159)	91.4 ± 2.2	(25)	0.712
At 1 h	155.5 ± 2.4	(159)	187.5 ± 6.4	(25)	< 0.001
At 2 h	141.9 ± 2.0	(159)	161.2 ± 6.9	(25)	0.001
No. abnormal values of 75-g OGTT at GDM diagnosis	1.3 ± 0.0	(159)	1.9 ± 0.2	(25)	< 0.001
Fasting PG (mg/dL)	78.9 ± 0.5	(152)	79.0 ± 2.3	(24)	0.965
HbA1c (%)	5.22 ± 0.03	(160)	5.45 ± 0.09	(25)	0.002
Fasting IRI (μU/mL)	4.73 ± 0.21	(147)	4.67 ± 0.53	(24)	0.914
HOMA-IR	0.94 ± 0.04	(147)	0.96 ± 0.13	(24)	0.871
HOMA-β	115.96 ± 5.41	(146)	125.11 ± 23.30	(22)	0.581
Ketone bodies in urine	0.80 ± 0.09	(160)	1.76 ± 0.29	(25)	0.001
History of insulin therapy, *n* (%)	31 (19.4)	(160)	10 (40.0)	(25)	0.021

Data are mean ± standard error of the mean. BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; HOMA-β, homeostatic model assessment for β-cell function; HOMA-IR, homeostatic model assessment for insulin resistance; OGTT, oral glucose tolerance test; PG, plasma glucose; IRI, *immunoreactive insulin*.

Table 5 | Logistic regression analysis with selected independent variables that were significantly different between the normal and impaired glucose tolerance groups

	B	Standard error	*P*-value	Odds ratio (95% CI)
PG at 1-h in 75-g OGTT at GDM diagnosis	0.026	0.011	0.020	1.027 (1.004–1.050)
PG at 2-h 75-g OGTT at GDM diagnosis	0.001	0.011	0.906	1.001 (0.980–1.023)
No. abnormal points in 75-g OGTT at GDM diagnosis	0.439	0.429	0.306	1.551 (0.669–3.594)
HbA1c	1.091	0.705	0.121	2.978 (0.749–11.847)
Ketone bodies in urine	0.443	0.182	0.015	1.558 (1.091–2.225)
History of insulin therapy (1: no, 2: yes)	−0.250	0.636	0.694	0.779 (0.224–2.708)

GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PG, plasma glucose.

GDM patients. The second was a comparison of the characteristics of GDM patients who developed IGT and those who had normal glucose tolerance at their 6–12 weeks postpartum visit to identify the risk factors for developing IGT.

In the first study, logistic regression analysis showed that gestational weeks at GDM diagnosis, plasma glucose levels in a 75-g OGTT at 1 h and HbA1c were significant predictors for insulin therapy. Similar to the present results, other studies showed that plasma glucose levels in a 75-g OGTT at 1 h[9–11] and HbA1c[9,12–15] were associated with the need for insulin therapy. In particular, Watanabe *et al.*[10] and Ito *et al.*[11] analyzed Japanese GDM patients and reported that only 1-h glucose levels in a 75-g OGTT at diagnosis was an independent predictor of the need for insulin[10,11]. Although sample sizes were not large (37 and 112, respectively) in these two studies, in combination with the present results, 1-h glucose levels in a 75-g OGTT might be a useful parameter in predicting the need for insulin therapy in Japanese GDM patients. In addition, gestational weeks at GDM diagnosis was associated with the need for insulin therapy[9,16]. The cut-off values of gestational weeks at GDM diagnosis was 25.07 weeks in the present study, and in accordance with our results, Pertot *et al.*[9] reported that diagnosis of GDM after 25 weeks was identified as a significant protective factor of the need for insulin therapy. Previous studies also reported diverse possible factors predicting the need for insulin therapy including pregestational BMI[13,14,17], maternal age[17] and family history of diabetes[9,13,14], but these were not associated with the need for insulin therapy in the current study. Because ethnicity was reported to be a key determinant for predicting the need for insulin therapy[9], the differences in risk factors among the previous studies and the current study might be derived from ethnicity, as well as differences of study protocol.

Gestational diabetes mellitus is a heterogeneous pathophysiological state, the main underlying mechanism of which appears to involve a dysfunction in pancreatic β-cells, manifesting itself in the course of increasing insulin resistance during pregnancy. Insulin resistance is an important pathogenic mechanism that precedes the occurrence of GDM. However, the study population of women showed that the value of the HOMA-IR index, which is commonly used as a parameter of insulin resistance, was within the normal range. The exact reason for this phenomenon is unclear. However, Sokup *et al.*[18] reported that 25% of 1,254 Polish Caucasian women with GDM showed a low degree of insulin resistance (HOMA-IR <1.29), and a HOMA-IR index value higher than 1.29 is associated with greater pregestational BMI. In the present study, pregestational BMI was 22.57 ± 0.20. Therefore, the HOMA-IR index was within the normal range in the present study, possibly because of lower pregestational BMI. Differences in ethnicity also need to be considered. Japanese individuals sometimes develop IGT or type 2 diabetes without severe insulin resistance[19,20]. Similarly, severe insulin resistance might not be a requirement for the development of GDM in all Japanese women. Further approaches are required in order to investigate these possibilities.

In the second study, logistic regression analysis showed that 1-h glucose levels in a 75-g OGTT at diagnosis and ketone bodies in a urine test were significant predictors for IGT during the 6–12-week postpartum period. Similarly, other studies have shown that plasma glucose levels in a 75-g OGTT at 1 h were associated with IGT[21–23]. In contrast, HbA1c[23–26], 2-h glucose levels in a 75-g OGTT[24], fasting plasma glucose[27], 2-h plasma glucose[22,28], antepartum insulinogenic index[29], insulin treatment[22], family history of diabetes[22] and ethnicity[26,28] were also reported to be predictors for IGT. Some studies did not evaluate the association between antepartum plasma glucose levels in a 75-g OGTT at 1 h and postpartum IGT. Therefore, the differences in risk factors among studies might be derived from study protocol differences and ethnicity.

To our knowledge, antepartum ketone bodies in a urine test have not been reported as a predictor for postpartum IGT. The exact reason for this phenomenon is unclear, but there might be a few possible explanations. First, the presence of high levels of ketones indicates insufficient intake of food and carbohydrates[30] or impaired insulin secretion and insulin action[31]. Thus, antepartum ketone bodies in urine might predict postpartum impaired insulin secretion and action. Second, participants were instructed to follow an unrestricted diet containing at least 150 g of carbohydrates daily and continue usual physical activity for at least 3 days before the test[32]. However, patients with antepartum ketone bodies in a urine test can

ordinarily have insufficient food and carbohydrate intake, leading to worse glucose tolerance. Finally, starvation as a result of hyperemesis gravidarum can induce ketonuria. In addition, severe hyperemesis gravidarum has been associated with reduced insulin sensitivity in the offspring in childhood[33]. Thus, hyperemesis gravidarum might also affect postpartum-impaired glucose tolerance. Other approaches are required to investigate these possibilities.

In the current study, antepartum plasma glucose levels in a 75-g OGTT at 1 h was a predictor of both the need for insulin therapy in pregnancy and postpartum IGT. The cut-off values of antepartum plasma glucose levels in a 75-g OGTT at 1 h were 181.5 mg/dL or 184.5 mg/dL for the need for insulin therapy in pregnancy or postpartum IGT, respectively. These cut-off values were similar to values for GDM criteria. In addition, 1-h post-load hyperglycemia was reported to be a strong predictor of type 2 diabetes[34], and in Japan it is recommended that patients with a 1-h value of >180 mg/dL should be treated similarly to those with IGT, even if they belong to the normal glucose tolerance group[35]. In the IGT group of the present study, post-load hyperglycemia and a decrease in early insulin response to glucose were observed. A similar tendency was reported in patients with IGT or in the early stages of type 2 diabetes[36,37]. A 1-h value of >180 mg/dL might be a parameter of post-load hyperglycemia and a decrease in early insulin response to glucose.

Potential limitations of the present study need to be considered. Our study cohort does not represent the entire GDM population, and a model constructed from the retrospective data of a single cohort study with possible selection bias needs to be replicated and validated. Furthermore, the present study did not assess other factors, such as weight gain during pregnancy, physical activity and hypertension. In addition, unmeasured fetal or placental factors that influence insulin resistance might also have a marked impact on antenatal insulin treatments. Furthermore, information on BMI at 20 years-of-age, pregestational and maximum BMI, a family history of diabetes mellitus, and prior GDM was based on self-reported data by patients. Another limitation was that while food intake by GDM patients was controlled during hospitalization, dietary compliance before hospitalization and after discharge was not assessed. Furthermore, not all patients were able to measure 2-h postprandial glucose levels daily by themselves, because the present study was carried out within the confines of the Japanese medical insurance system.

In conclusion, gestational weeks at GDM diagnosis, plasma glucose levels in a 75-g OGTT at 1 h and HbA1c were significant predictors of the need for insulin therapy, and 1-h glucose levels in a 75-g OGTT at diagnosis and ketone bodies in a urine test were significant predictors for IGT during the 6–12-week postpartum period. In particular, 1-h glucose levels in a 75-g OGTT antepartum was a predictor for both the need for insulin therapy in pregnancy and postpartum IGT. If a 1-h value of >180 mg/dL in 75-g OGTT is observed in pregnant women, we should diagnose women with GDM and give a careful consideration to both their need for insulin therapy in pregnancy and postpartum IGT.

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DISCLOSURE

The authors declare no conflict of interest.

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