were also excluded. Each woman underwent a universal two-step screening for GDM: a casual glucose test or 50-g glucose challenge test (GCT) between 24 and 30 weeks of gestation. Then, women who had a venous plasma glucose ≥100 mg/dL on a casual glucose test or ≥140 mg/dL by 50-g GCT were scheduled for a diagnostic, 75-g OGTT after an overnight fast. JSOG criteria for GDM were applied (fasting, 100 mg/dL: 1 h, 180 mg/dL; 2 h, 150 mg/dL) [11]. GDM was defined as present when at least two plasma glucose measurements were at or above the cut-off points. In the present study, we used cases whose diagnosis was based on only one abnormal 75-g OGTT value, termed OAV, to assess the effects of treating mild GDM. Underweight, overweight, and obese were defined as a body mass index (BMI) of less than 18.5 kg/m^2, between 25 kg/m^2 and 29 kg/m^2, and 30 kg/m^2 or more, respectively. The definition of obesity in Japan is a BMI of 25 kg/m^2 or higher [13]. Therefore, overweight and obese women are categorized as being obese in Japan.

Data collected included maternal age, parity, pre-pregnancy BMI, chronic hypertension, pregnancy-induced hypertension (PIH) including pre-eclampsia, gestational age at delivery, delivery characteristics including spontaneous or induced delivery, vaginal delivery or caesarean section, and newborn characteristics such as birth weight, sex, Apgar score, perinatal mortality and major congenital malformations. Pre-gestational weight was self-reported at the first prenatal visit. Gestational age was defined by number of weeks since the last menstrual period or the ultrasound assessment of crown-rump length if discordancy was recognized. Chronic hypertension was defined as hypertension treated with medication before pregnancy or arterial blood pressure ≥140/90 mm Hg before 20 weeks of pregnancy. Macrosomia was defined as a birth weight at or above 4000 g. LGA was defined as sex- and delivery-specific birth weight for gestational age being above the 90th percentile of Japanese fetal growth curves [14]. Major congenital malformations were defined as those causing significant functional impairment, requiring surgery or being life-threating.

The non-intervention group received routine obstetrical care in 21 institutions. Of the nine with interventions, three institutions provided routine obstetrical care with diet therapy alone from a registered dietitian, while six provided routine obstetrical care with dietary management plus self-monitoring of blood glucose (SMBG) and insulin therapy, if needed. Dietary therapy was based on a woman's pre-pregnancy BMI, and dietary intake and gestational weight gain guidance were provided to these women. Also, the intervention group received guidance on how to determine SMBG levels 4–6 times a day. In this group, if targeted glucose levels (i.e., preprandial glucose levels of less than 100 mg/dL and levels 2 h postprandially that were less than 120 mg/dL) were not achieved, insulin therapy was initiated.

Care for pregnant women was provided in the same manner in all participating institutions.

2.2. *Study outcomes*

The composite study outcome included perinatal mortality (stillbirth or neonatal death) and complications associated with maternal hyperglycemia: congenital malformation, LGA, macrosomia, hypoglycemia, hyperbilirubinemia, shoulder dystocia, respiratory distress syndrome, and admission to the neonatal intensive care unit.

Neonatal blood for measuring glucose was collected 1 h or 2 h after birth and before feeding; hypoglycemia was defined as a glucose value of less than 35 mg/dL [15]. Hyperbilirubinemia was defined as a requirement for phototherapy.

Maternal outcomes included weight gain from the time of enrollment to delivery, PIH including gestational hypertension and pre-eclampsia, cesarean delivery, labor induction, and shoulder dystocia. Gestational hypertension was defined as a systolic pressure of 140 mm Hg or more or a diastolic pressure of 90 mm Hg or more on two occasions at least 4 h apart. Pre-eclampsia was defined as blood pressure elevation (according to the definition of gestational hypertension) together with proteinuria (300 mg of protein or more in a 24-h urine collection or a result of 2+ or greater on a dipstick test when a 24-h collection was not available). Shoulder dystocia was defined clinically, and the providers were required to document the specific maneuvers used to release the fetal shoulders.

2.3. *Statistical analysis*

Baseline characteristics and laboratory measurements are presented as means ± SD, as median or as percentages. Univariate tests for differences in values between any two groups were carried out using the chi-square test. Multiple logistic regression analysis was performed to identify variables possibly contributing to difference between any two groups. All reported P values are two-tailed and $P < 0.05$ was taken to indicate a statistically significant difference. All statistical analyses were performed using general-purpose statistical software, StatFlex version 6.0 (Artech Inc., Osaka, Japan).

3. Results

From 2006 through 2010, we retrospectively recruited 948 OAV subjects from 30 institutions in Japan. Although 948 of these women were enrolled, 893 were studied, as shown in Fig. 1. Among them, 543 women with OAV received routine obstetrical routine care without GDM treatment (non-treatment group) and 350 received routine obstetrical routine care

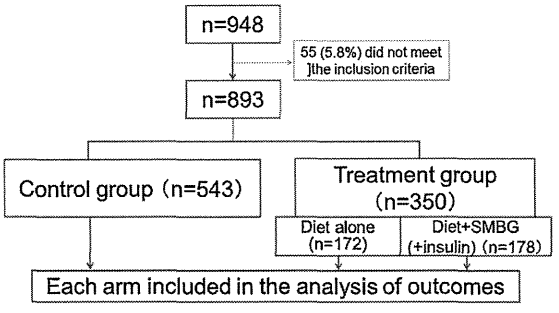

Fig. 1 – Enrollment, assignment, and follow-up of study participants.

Table 1 – Basal characteristics, maternal complications, and neonatal complications.

	Non-treatment group ($n = 543$)	Treatment group ($n = 350$)	
		Diet alone ($n = 172$)	Diet + SMBG (+insulin) ($n = 178$)
Nullipara – no. (%)	277 (51.0)	78 (45.3)	77 (43.3)
Age (yr)	33.7 ± 4.9	34.5 ± 4.8	33.7 ± 4.7
Pre-gestational BMI	21.6 ± 6.1	22.6 ± 5.3	22.7 ± 4.8
Gestational weight gain (kg)	8.9 ± 11.1	8.6 ± 9.6	7.7 ± 4.5
Gestational age at diagnosis (wk)	27.8 ± 3.5	27.6 ± 4.1	26.9 ± 5.6
Glucose levels of 75 g-OGTT (mg/dL)			
Fasting	83.5 ± 9.5	83.0 ± 9.1	82.8 ± 7.9
1-h	164.3 ± 25.4	170.3 ± 20.3*	171.5 ± 22.9*
2-h	148.0 ± 21.4	148.5 ± 23.9	149.8 ± 22.4
PIH – n (%)	16 (2.9)	8 (4.7)	11 (6.2)
Induction of labor – n (%)	92 (16.9)	48 (27.9*)	51 (28.7*)
Total cesarean section – n (%)	185 (34.1)	57 (33.1)	65 (36.5)
Primary cesarean section – n (%)	65 (12.0)	21 (12.2)	24 (13.5)
Gestational age at delivery (wk)	38.3 ± 2.0	38.6 ± 1.6	38.4 ± 2.1
Birth weight (g)	2973.1 ± 510.9	2977.6 ± 404.6	2992.2 ± 467.8
LGA (%)	71 (13.1)	15 (8.7)	17 (9.6)
Macrosomia (%)	11 (2.0)	1 (0.6)	1 (0.6)
Shoulder dystocia (%)	3 (0.6)	0 (0)	0 (0)
RDS (%)	48 (8.8)	9 (5.2)	12 (6.7)
Hypoglycemia (%)	33 (6.1)	12 (7.0)	14 (7.9)
Jaundice (%)	52 (9.6)	25 (14.5)	15 (8.4)
NICU (%)	60 (11.0)	19 (11.0)	29 (16.3)

PIH: pregnancy-induced hypertension.
* $P < 0.05$ vs. the control group.

with GDM treatment (treatment group): diet therapy alone for 172 women and diet therapy and SMBG with or without insulin therapy for 178 (Fig. 1). The baseline characteristics of the 893 women in this retrospective study are shown in Table 1. Weight gain during pregnancy was significantly lower and glucose levels 1 h after 75-g OGTT were higher in the treatment than in the non-treatment group. There were no significant differences in other demographic variables. When we separated the treated patients into subgroups based on differences in therapeutic management, i.e., diet alone vs. diet plus SMBG with or without insulin therapy, there were no significant differences between these two subgroups.

There was no significant difference between the treatment and non-treatment groups in the frequency of PIH (2.9% and 5.4%, respectively) or cesarean section (34.1% and 34.9%, respectively), as shown in Table 1. After excluding cases with abnormal presentations, placenta previa, oligohydramnios, and previous cesarean delivery, the primary cesarean delivery rates were similar in the treatment and non-treatment groups (12.0% and 12.8%, respectively). The rate of labor induction was significantly higher in the treatment than in the non-treatment group. There were no perinatal deaths in either group. The individual neonatal complication rates did not differ significantly between the two groups (Table 1). Neither mean birth weight nor the frequencies of LGA and macrosomia differed significantly between the treatment and non-treatment groups. Likewise, there were no significant differences in neonatal complications including respiratory distress syndrome (RDS), hypoglycemia, and jaundice between the diet alone and diet plus SMBG with or without insulin therapy subgroups (Table 1).

In terms of neonatal complication, the incidence of LGA tended to be lower in the treatment than that in the non-treatment group (13.1% and 8.7% [$P = 0.07$], 13.1% and 9.6% [$P = 0.08$]). Therefore, we focused on LGA. Multiple logistic regression analysis (MLRA) to detect factors associated with the birth of LGA infants to OAV women showed pre-gestational BMI and weight gain during gestation to be independently associated with LGA (Table 2).

Next, we examined maternal and perinatal outcomes in overweight and obese OAV women. The definition of obesity in Japan is a BMI of 25 kg/m^2 or higher [13]. Maternal weight gain during gestation was significantly smaller in the treatment than in the non-treatment group (4.6 kg and 6.6 kg, respectively,

Table 2 – Risk factors for LGA in OAV.

Variables	β	SE(β)	P value	Odds ratio	95% CI
Treatment	−0.3300	0.23909	0.1675	–	–
Pre-gestational BMI*	0.1234	0.02352	0.00001	1.853	1.473–2.334
Gestational weight gain	0.1362	0.02651	0.00001	1.146	1.089–1.207
75 g-OGTT 1 h	−0.0026	0.00457	0.5620	–	–

AIC = 576.399, AUC = 0.714.
* Odds ratio was computed for a change of BMI by 5 kg/m^2.

Table 3 – Basal characteristics, maternal complications and neonatal complications in overweight and obese women.

	Non-treatment group (n = 102)	Treatment group (n = 88)	
		Diet alone (n = 44)	Diet + SMBG (+insulin) (n = 44)
Nullipara – no. (%)	62 (61.4)	21 (47.7)	23 (52.3)
Age (yr)	34.7 ± 4.6	35.1 ± 4.8	34.4 ± 5.1
Pre-gestational BMI	30.0 ± 6.0	29.8 ± 4.4	30.6 ± 3.8
Gestational weight gain (kg)	6.6 ± 5.3	4.9 ± 6.9	4.2 ± 4.7*
Gestational age at diagnosis (wk)	27.2 ± 4.4	27.4 ± 5.7	25.0 ± 6.7*,#
Glucose levels of 75 g-OGTT (mg/dL)			
Fasting	86.3 ± 8.2	87.8 ± 9.1	86.4 ± 8.2
1-h	169.5 ± 24.6	174.5 ± 19.1	178.0 ± 19.9*
2-h	140.7 ± 23.0	140.0 ± 21.1	149.6 ± 22.3
PIH – n (%)	9 (8.9)	5 (11.4)	3 (6.8)
Induction of labor – n (%)	26 (25.7)	13 (29.5)	14 (31.8)
Total cesarean section – n (%)	185 (44.6)	18 (40.9)	22 (50.0)
Primary cesarean section – n (%)	17 (16.7)	8 (18.1)	9 (20.4)
Gestational age at delivery (wk)	38.2 ± 2.3	38.3 ± 1.8	38.0 ± 2.8
Birth weight (g)	3094.6 ± 585.7	2938.8 ± 501.9	2992.2 ± 467.8
LGA (%)	26 (25.5)	4 (9.1)	4 (9.1)
Macrosomia (%)	2 (2.0)	1(2.3)	0 (0)
Shoulder dystocia (%)	1 (1.0)	0 (0)	0 (0)
RDS (%)	12 (11.8)	5 (11.4)	7 (15.9)
Hypoglycemia (%)	11 (10.8)	3 (6.8)	5 (11.4)
Jaundice (%)	13 (12.7)	6 (13.6)	7 (15.9)
NICU (%)	17 (16.7)	8 (18.2)	9 (20.5)

PIH: pregnancy-induced hypertension.
* $P < 0.05$ vs. the control group.
# $P < 0.05$ vs. the diet alone group.

P = 0.01), as shown in Table 3. However, maternal weight gains during gestation did not differ significantly between the diet alone subgroup and that receiving diet plus SMBG with or without insulin therapy (Table 3). OAV was diagnosed significantly earlier in the subgroup receiving diet plus SMBG with or without insulin therapy than in that given dietary guidance alone (25.0 ± 6.7 wk and 27.2 ± 4.4 wk, P = 0.01). Glucose levels 1 h after 75-g OGTT were significantly higher in the diet plus SMBG with or without insulin therapy subgroup than in the non-treatment group (178.0 ± 19.9 mg/dL and 169.5 ± 24.6 mg/dL, P = 0.04). However, glucose levels 1 h after 75-g OGTT did not differ significantly between the diet alone subgroup and the diet plus SMBG subgroup. Although maternal complications did not differ significantly between the two groups, the LGA incidence was significantly lower in the treatment than in the non-treatment group (25.5% and 9.1%, respectively, P = 0.02) (Table 3). There were no significant differences in maternal and neonatal outcomes between the diet alone subgroup and that given dietary guidance plus SMBG with or without insulin therapy.

MLRA to detect factors associated with the birth of LGA infants to OAV women with obesity showed treatment to be negatively associated with the LGA incidence (Table 4).

4. Discussion

The present retrospective study demonstrated that although intervention for OAV was not associated with adverse pregnancy outcomes, intervention for obese Japanese women with GDM was associated a lower incidence of LGA.

The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial is a well-known randomized controlled trial for management of mild GDM, which used WHO diagnostic criteria. The mean fasting and 2-h plasma glucose levels were 86 mg/dL and 154 mg/dL, respectively [15]. Therefore, most of the ACHOIS trial subjects might have had one abnormal GDM based on the IADPSG criteria (meeting at least one of three threshold values from a 75-g OGTT; fasting plasma glucose ≥92 mg/dL, 1-h plasma glucose ≥180 mg/dL,

Table 4 – Risk factors for LGA in OAV with overweight and obese women.

Variables	β	SE(β)	P value	Odds ratio	95% CI
Treatment	−1.101	0.4483	0.0050	0.292	0.138–0.800
Pre-gestational BMI	0.0518	0.0530	0.3287	–	–
Gestational weight gain	0.0629	0.0414	0.1282	–	–
75 g-OGTT 1 h*	0.0221	0.0100	0.0276	3.024	1.130–8.088

AIC = 169.02863, AUC = 0.718.
* Odds ratio was computed for a change of OGTT by 50 mg.

and 2-h plasma glucose ≥153 mg/dL) for GDM. On the other hand, the mean fasting, 1-h and 2-h plasma glucose levels in the present study were 83 mg/dL, 172 mg/dL, and 149 mg/dL, respectively. Thus, although the 75-g OGTT profile showed no major difference, pregnancy outcomes differed modestly. For instance, the incidences of PIH, LGA, macrosomia, and shoulder dystocia in the non-intervention group in the ACHOIS trial were 18.2%, 21.9%, 21.0%, and 3.1%, respectively [15]. In contrast, the corresponding prevalences in our non-intervention group were 3.4%, 13.1%, 2.0%, and 0.6%, respectively. Although intervention in the ACHOIS trial significantly reduced all of the above complications, the present study revealed no improvements in these pregnancy outcomes. Interestingly, pre-gestational BMI in the ACHOIS trial and the present study were 26.0–26.8 and 22.2–22.7, respectively. Of course, we cannot compare a randomized trial with the present retrospective study. However, we can speculate that BMI as a baseline characteristic of subjects independently contributes to pregnancy outcomes. Obesity is well known to have an independent impact on pregnancy outcomes. For instance, a large prospective study from Spain found that the upper quartile of maternal BMI was responsible for 23% of macrosomia, while gestational diabetes accounted for 3.8% [16]. Of course, an interrelation between BMI and glucose is not precluded. Recently, a sub-analysis of the HAPO study by Catalano et al. showed that obesity independently impacts pregnancy outcomes such as pre-eclampsia, LGA, macrosomia, and shoulder dystocia [17].

The present study also suggested pre-gestational BMI and gestational weight gain to be independently associated with LGA with one abnormal glucose value in Japanese GDM patients. Blacks et al. examined the effects of maternal BMI and gestational weight gain on the frequency of LGA using women with normal glucose tolerance and GDM based on the IADPSG diagnostic criteria [18]. Both BMI and gestational weight gain were associated with the LGA incidence even in women with normal glucose tolerance and, of these two parameters. GDM had a much greater effect on the incidence of LGA. Although their study was not limited to OAV, also including other types of GDM, our results partially support the relationship between maternal BMI and LGA incidence.

We also demonstrated intervention for obese OAV subjects to be associated with a reduced incidence of LGA. Multiple regression analysis confirmed intervention to be independently associated with reduced LGA. This result is reasonable. Because most ACHOIS trial subjects were overweight or obese, as mentioned above, the incidence of adverse pregnancy outcomes would be high, such that the effects of intervention would be much greater. The present study revealed no impacts on adverse pregnancy outcomes. However, it is intuitively clear that dietary intervention alone would yield effects similar to those of the intervention group receiving dietary therapy plus SMBG with or without insulin.

The present study identified no changes in neonatal complications. The HAPO study results suggested that a threshold for an increased risk of neonatal hypoglycemia may not be apparent until fasting maternal glucose levels exceed 100 mg/dL [3]. Therefore, the present results are consistent with those of the HAPO study. As for study of the obese subgroups, the present sample size makes it difficult to obtain significant results.

In conclusion, this is the first demonstration that maternal overweight impacts the incidence of LGA and that interventions such as dietary therapy alone or with SMBG and/or insulin may reduce the rate of births of LGA infants in the Japanese population. Further studies including an intervention trial and an evaluation of cost effectiveness using the IADPSG criteria are required for milder forms of GDM. Further prospective RCTs including cost performance are required to assess appropriate managements for mild GDM.

5. Conflict of interest

The authors declare that they have no conflict of interest.

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CLINICAL ARTICLE

Risk factors associated with abnormal glucose tolerance in the early postpartum period among Japanese women with gestational diabetes

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ABSTRACT

Objective: To identify the risk factors associated with abnormal glucose tolerance (AGT) on the first postpartum oral glucose tolerance test (OGTT) among Japanese women with gestational diabetes (GDM). *Methods:* In a retrospective study, data were analyzed from women with GDM who underwent their first postpartum OGTT 6–8 weeks post partum at a center in Omura, Japan, between January 1, 2007, and December 31, 2011. Women with diabetes or impaired glucose tolerance were deemed to have postpartum AGT. The association between postpartum AGT and various risk factors was analyzed. *Results:* Among 169 women who underwent a postpartum OGTT, 58 (34.3%) had AGT. The significant risk factors associated with postpartum AGT in univariate analysis were pre-pregnancy body mass index ($P = 0.096$), 1-hour plasma glucose ($P = 0.006$), hemoglobin A_{1c} ($P < 0.001$), insulinogenic index ($P = 0.05$), an insulinogenic index of less than 0.4 ($P = 0.006$), and insulin therapy during pregnancy ($P < 0.001$). Independent risk factors identified by multivariate logistic regression models were insulinogenic index (odds ratio [OR] 0.10, 95% confidence interval [CI] 0.01–0.74; $P = 0.002$), an insulinogenic index of less than 0.4 (OR 5.70, 95% CI 1.69–21.66; $P = 0.005$), and insulin therapy during pregnancy (OR 3.43, 95% CI 1.03–12.55; $P = 0.044$). *Conclusion:* Among Japanese women with GDM, a lower insulinogenic index and use of insulin therapy during pregnancy are associated with early postpartum AGT.

1. Introduction

A history of gestational diabetes (GDM) is an important risk factor associated with diabetes later in life. In the late 1970s, it was reported to take more than 20 years for women with GDM to develop diabetes after the index pregnancy [1]. Recent lifestyle changes in high-income countries have shortened this interval to a few years [2,3]. Owing to the pandemic of obesity and diabetes in both high- and low-income countries, prevention of diabetes in women with a history of GDM is of crucial importance.

Various maternal and pregnancy characteristics among women with GDM are considered to be risk factors for the onset of diabetes in later life. These risk factors include an advanced maternal age, a family history of diabetes, obesity, an early gestational age at diagnosis, the severity of hyperglycemia, elevated hemoglobin A_{1c} (HbA_{1c}), an abnormal insulin profile at the time of oral glucose tolerance test (OGTT), the need for insulin therapy during pregnancy, and delivery of a macrosomic newborn [3–5]. Ideally, all pregnant women with GDM should be screened in the early postpartum period, but less than half undergo postpartum glucose screening [6–8].

The aim of the present study was to investigate risk factors associated with abnormal glucose test results on the first postpartum OGTT among Japanese women who had been diagnosed with GDM.

2. Materials and methods

In a retrospective study, data were obtained for women with GDM who underwent a postpartum 75-g OGTT 6–8 weeks post partum at the National Hospital Organization Nagasaki Medical Center (Omura, Japan) between January 1, 2007, and December 31, 2011. To eliminate the possibility of pregestational diabetes, women who had overt diabetes during pregnancy were excluded in accordance with the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria [9], such as a fasting plasma glucose level of more than 7.0 mmol/L (126 mg/dL) or an HbA_{1c} level of more than 6.5% on an OGTT during pregnancy. In addition, only women of Japanese ethnic origin were included in the study. The institutional review board of the study center approved the investigation. All eligible women were contacted and asked to provide written informed consent for the use of their data in the present study.

Before July 2010, GDM was defined according to the previous criteria of the Japan Society of Obstetrics and Gynecology (JSOG) [10]; the new

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JSOG criteria (i.e. the IADPSG criteria) were applied to data obtained after July 2010 (Table 1). WHO criteria [11] were used to assess abnormal glucose tolerance (AGT) in the postpartum period (Table 1). Women with diabetes or impaired glucose tolerance were deemed to have postpartum AGT.

The associations between postpartum AGT and risk factors during the index pregnancy were analyzed. Candidate risk factors included maternal age, pre-pregnancy body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), plasma glucose and HbA_{1c} levels on OGTT during the index pregnancy, diagnostic criteria of GDM, and insulin therapy during pregnancy.

The standard practice of treatment for women with GDM included diet and insulin therapy. On the basis of the results of blood glucose self-monitoring, insulin therapy was prescribed if the patient exhibited fasting hyperglycemia (>5.3 mmol/L [95 mg/dL]) or 2-hour postprandial hyperglycemia (>6.7 mmol/L [120 mg/dL]). The patients did not receive any oral hypoglycemic agents.

The insulinogenic index—a surrogate for first-phase insulin secretion from the pancreas—was also determined using results of the OGTT during the index pregnancy. It was calculated by the following equation: insulinogenic index = Δimmunoreactive insulin$_{(30\ min)}$/Δplasma glucose$_{(30\ min)}$. An insulinogenic index of less than 0.4 is considered to be abnormal [12].

Homeostasis model assessment–insulin resistance (HOMA-IR) was calculated with the following equation: HOMA-IR = (fasting plasma glucose) × (fasting immunoreactive insulin)/405. Homeostasis model assessment–β-cell function (HOMA-B) was also calculated by the following equation: HOMA-B = 360 × (fasting immunoreactive insulin)/(fasting plasma glucose − 63).

Statistical analysis was performed with JMP9 software (SAS Institute, Cary, NC, USA). The association between each risk factor and postpartum AGT was assessed by a univariate logistic regression analysis, and risk factors exhibiting an association with a P value of less than 0.10 were considered as candidates for the multivariate analysis. Independent associations between the risk factor candidates and postpartum AGT results were then tested using multivariate logistic regression models. $P < 0.05$ was considered to be statistically significant.

3. Results

During the 5-year study period, 208 Japanese women were diagnosed with GDM, of whom 169 (81.3%) underwent a postpartum OGTT. Mean time from delivery to OGTT was 6.9 ± 1.5 weeks. Overall, 111 (65.7%) women exhibited normal test results, and 58 (34.3%) women had AGT. Among the women with AGT, 52 (89.7%) had impaired glucose tolerance and 6 (10.3%) had diabetes. Postpartum AGT was recorded in 44 (34.6%) of 127 women diagnosed according to pre-2010 JSOG criteria and 14 (33.3%) of 42 women diagnosed in accordance with the new JSOG (IADPSG) criteria; this difference was not statistically significant.

Significant differences between women with normal results and those with AGT were recorded in 1-hour plasma glucose ($P = 0.004$), HbA_{1c} ($P < 0.001$), and insulinogenic index values ($P = 0.039$) on OGTT at the diagnosis of GDM during pregnancy (Table 2). Additionally, the proportion of women with an insulinogenic index of less than 0.4 was greater among those with AGT than among those with normal postpartum OGTT results ($P < 0.001$) (Table 2). Similarly, the proportion of women who had received insulin therapy during pregnancy was greater among women with postpartum AGT ($P < 0.001$) (Table 2). More than half the women in both groups had a BMI of 18.5–24.9 before the index pregnancy (Fig. 1).

Significant risk factor candidates identified in the univariate logistic analysis were pre-pregnancy BMI ($P = 0.096$), 1-hour plasma glucose ($P = 0.006$), HbA_{1c} ($P < 0.001$), insulinogenic index as a continuous variable ($P = 0.05$), an insulinogenic index of less than 0.4 ($P = 0.006$), and insulin therapy during pregnancy ($P < 0.001$). In multivariate logistic regression models, the insulinogenic index, an insulinogenic index of less than 0.4, and insulin therapy during pregnancy were found to be independent risk factors associated with abnormal postpartum test results (Table 3).

4. Discussion

The present study has demonstrated that the insulinogenic index determined at the time of diagnostic OGTT during pregnancy and the use of insulin therapy during pregnancy are significant risk factors associated with abnormal results on OGTT at 6–8 weeks post partum, independent of maternal age, pre-pregnancy obesity, and plasma glucose level during pregnancy. Women with an insulinogenic index of less than 0.4 and women treated with insulin therapy during pregnancy are more likely to have AGT at their first postpartum test.

It is well established that women with a history of GDM have a significant risk of developing diabetes later in life [1,2]. With respect to predicting the development of diabetes 5–7 years after delivery, Kjos et al. [13,14] demonstrated that an early postpartum OGTT is the best measurement for prediction of later diabetes, and that early postpartum AGT defined by WHO criteria is superior to other routine clinical variables (including maternal age, parity, pre-gravid BMI, and glucose values) among Latino women with GDM. Accordingly, identifying risk factors associated with early postpartum AGT is worthwhile.

Cao et al. [15] investigated risk factors for early postpartum AGT in a Chinese population, and found that pre-pregnancy BMI, and fasting and 2-hour plasma glucose levels on OGTT during pregnancy were independent contributors to AGT at 6–8 weeks post partum. In the present study, neither pre-pregnancy obesity nor any plasma glucose level on OGTT in pregnancy was independently associated with early postpartum AGT after adjustment for confounders. In the Chinese study [15], β-cell function during pregnancy (e.g. the insulinogenic index) was not assessed because insulin was not measured during pregnancy; however, the insulinogenic index was measured at 6–8 weeks post partum and found to be the only independent contributor to AGT at 6–12 months post partum.

Obesity is a key characteristic of the development of diabetes post partum [1]. However, the present study did not find an independent association between pre-pregnancy BMI and early postpartum AGT. Although the Japanese population is the least obese among high-income

Table 1
Diagnostic criteria based on 75-g OGTT during the index pregnancy and at the first postpartum screening.

Glucose test	GDM criteria in pregnancy		WHO criteria in the postpartum period	
	Former JSOG criteria[a]	New JSOG (IADPSG) criteria[b]	Diabetes	Impaired glucose tolerance
Fasting, mmol/L[c]	5.55 (100)	5.1 (92)	7.0 (126)	6.1 (110)
1 h, mmol/L[c]	10.0 (180)	10.0 (180)	N/A	N/A
2 h, mmol/L[c]	8.3 (150)	8.5 (153)	11.1 (200)	7.8 (140)

Abbreviations: OGTT, oral glucose tolerance test; GDM, gestational diabetes mellitus; JSOG, Japan Society of Obstetrics and Gynecology; IADPSG, International Association of Diabetes and Pregnancy Study Group; N/A, not addressed.

[a] Before July 2010, GDM was defined as ≥2 abnormal values.

[b] After July 2010, GDM was defined as ≥1 abnormal value.

[c] Measurements in mg/dL are given in parentheses.

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Table 2
Maternal characteristics and 75-g OGTT results during the index pregnancy.[a]

Variable	All women (n = 169)	Postpartum OGTT		
		Normal (n = 111)	AGT (n = 58)	*P* value
Maternal age, y	32.6 ± 5.1	32.5 ± 5.1	32.7 ± 5.3	0.824
Nulliparous	71 (42.0)	44 (39.6)	27 (46.6)	0.387
Pre-pregnancy BMI	23.5 ± 4.9	23.0 ± 4.7	24.4 ± 5.2	0.094
Pre-pregnancy BMI ≥25	52 (30.8)	23 (39.7)	29 (26.1)	0.081
Gestational age at OGTT, wk	24.2 ± 7.2	24.5 ± 7.2	23.6 ± 7.4	0.487
GDM diagnosed by the IADPSG criteria	42 (24.9)	28 (25.2)	14 (24.1)	0.877
OGTT results during pregnancy				
Fasting plasma glucose, mmol/L [b]	4.9 ± 0.6 (88 ± 11)	4.8 ± 0.6 (87 ± 11)	4.9 ± 0.6 (89 ± 11)	0.234
1-h plasma glucose, mmol/L [b]	10.6 ± 1.5 (191 ± 27)	10.3 ± 1.4 (186 ± 26)	11.1 ± 1.4 (200 ± 25)	0.004
2-h plasma glucose, mmol/L [b]	9.1 ± 1.4 (164 ± 25)	9.0 ± 1.3 (162 ± 24)	9.3 ± 1.5 (168 ± 27)	0.265
HbA_{1c}	5.5 ± 0.4	5.4 ± 0.4	5.7 ± 0.5	<0.001
Fasting immunoreactive insulin, μU/mL	7.6 ± 3.8	7.2 ± 3.3	8.3 ± 4.4	0.156
Insulinogenic index	0.54 ± 0.32	0.63 ± 0.4	0.45 ± 0.3	0.039
Insulinogenic index <0.4	59 (34.9)	28 (25.2)	31 (53.4)	<0.001
HOMA-IR	1.68 ± 0.94	1.55 ± 0.77	1.87 ± 1.55	0.104
HOMA-B	121 ± 73	122.1 ± 68.2	118.8 ± 80.7	0.826
Insulin therapy in pregnancy	76 (45.0)	37 (33.3)	39 (67.2)	<0.001

Abbreviations: OGTT, oral glucose tolerance test; AGT, abnormal glucose tolerance; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); IADPSG, International Association of Diabetes and Pregnancy Study Group; HbA_{1c}, hemoglobin A_{1c}; HOMA-IR, homeostasis model assessment–insulin resistance; HOMA-B, homeostasis model assessment–β-cell function.
[a] Values are given as mean ± SD or number (percentage), unless indicated otherwise.
[b] Measurements in mg/dL are given in parentheses.

countries, Japanese individuals have a high risk of diabetes [16]. This paradox reflects the ethnic characteristics of the Japanese population. It has been reported that Japanese individuals with impaired glucose tolerance exhibit decreased early-phase insulin secretion, as assessed by the insulinogenic index [12]. Although there is no doubt that obesity is a key feature of the development of diabetes worldwide, impaired β-cell function—not obesity—is the primary contributor among Japanese people [17–21]. Such studies reported that worsening from normal glucose tolerance to IGT in Japanese individuals is associated with decreased early-phase insulin secretion in both non-obese and obese individuals and that impaired early-phase insulin secretion is the initial abnormality observed in the development of glucose intolerance among Japanese individuals.

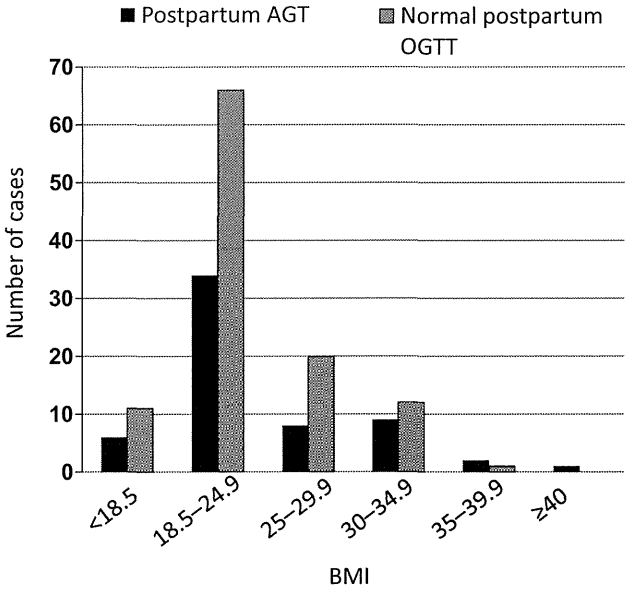

Fig. 1. Pre-pregnancy BMI among women with GDM. Abbreviations: AGT, abnormal glucose tolerance; OGTT, oral glucose tolerance test; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

Japanese women with GDM frequently also have impaired β-cell function [22]. In the present study, the mean pre-pregnancy BMI and its distribution did not differ between women with postpartum AGT and those with normal postpartum test results. A recent Japanese study [21] showed that isolated impaired insulin secretion (defined as a low insulinogenic index without insulin resistance) was a factor in approximately 50% of cases of incident type 2 diabetes in Japanese population, independent of sex. In that study, individuals with isolated impaired insulin secretion had low BMIs and small waist circumferences; moreover, obesity was not found to be a predictor in the isolated impaired insulin secretion group [21]. The present study results are consistent with these findings.

Both insulin resistance and β-cell dysfunction are characteristics of women with GDM, especially those who are obese [23]. Because these features are pathophysiological characteristics of the development of type 2 diabetes, they are also associated with postpartum diabetes [24,25]. Regarding insulin resistance, HOMA-IR—a surrogate index of insulin resistance—was not found to be associated with early postpartum AGT in the present study. In addition, there was no association between HOMA-B—a surrogate index of whole β-cell function—and early

Table 3
Multivariate logistic regression models testing the association between the risk factors and postpartum AGT.[a]

Variables	Model 1[b]		Model 2[c]	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Pre-pregnancy BMI	1.05 (0.93–1.20)	0.43	0.90 (0.92–1.18)	0.70
1-h plasma glucose, mg/dL	0.99 (0.97–1.01)	0.50	0.99 (0.97–1.01)	0.42
HbA_{1c}	1.71 (0.46–6.64)	0.42	1.96 (0.50–8.24)	0.33
Insulinogenic index	0.10 (0.01–0.74)	0.002	–	–
Insulinogenic index <0.4	–	–	5.70 (1.69–21.66)	0.005
Insulin therapy in pregnancy	3.39 (1.04–12.01)	0.004	3.43 (1.03–12.55)	0.044

Abbreviations: AGT, abnormal glucose tolerance; CI, confidence interval; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HbA_{1c}, hemoglobin A_{1c}.
[a] The models were adjusted for maternal age, gestational age at oral glucose tolerance test, and fasting and 2-h plasma glucose levels.
[b] Insulinogenic index used as a continuous variable.
[c] Insulinogenic index used as a categorical variable.

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postpartum AGT. These findings are consistent with those of previous studies in Japanese non-pregnant adults [12,18–20].

The strength of the present study is the high postpartum follow-up rate—approximately 81% of women diagnosed with GDM underwent a postpartum OGTT—which might eliminate bias associated with follow-up, such as socioeconomic factors. The American College of Obstetrics and Gynecology recommends that all pregnant women with a diagnosis of GDM should receive follow-up tests at 6–12 weeks post partum and be managed appropriately [26]. However, it has previously been reported that the rate of postpartum follow-up tests in the early postpartum period is low (less than 50%) [6–8]. Against this background, risk-oriented procedures would be more practical.

One limitation of the present study is that it included women diagnosed with GDM according to two sets of criteria in different periods. However, the difference in criteria did not affect the diagnosis of early postpartum AGT. Another limitation was the small sample size. Morimoto et al. [21] reported that approximately one-quarter of the incidence of type 2 diabetes in the Japanese cohort in their study could be attributed to insulin resistance associated with obesity. Therefore, the sample size used in the present study might be too small to demonstrate whether obesity is a predictor of early postpartum AGT.

In conclusion, among Japanese women who were diagnosed with GDM during pregnancy, the insulinogenic index at GDM diagnosis and the use of insulin therapy during pregnancy were found to be independent risk factors associated with early postpartum AGT. Measurements of insulin levels on OGTT during pregnancy in the Japanese population would be useful, and low insulin responders (defined as patients with an insulinogenic index of <0.4) and women who require insulin therapy during pregnancy should be targeted for postpartum screening tests.

Conflict of interest

The authors have no conflicts of interest.

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Clinical impact of women with gestational diabetes mellitus by the new consensus criteria: two year experience in a single institution in Japan

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Abstract. There is a paucity of information on perinatal data regarding gestational diabetes mellitus (GDM) by the new criteria from a real experience because the number of health care associations implementing the new criteria is still limited. The aim of this study is to investigate perinatal features of the new criteria-defined GDM. We reviewed a total of 995 women with singleton pregnancy that underwent GDM screening followed by a diagnostic oral glucose tolerance test (OGTT). All women found to have GDM underwent self-monitoring of blood glucose measurements as well as dietary management. Insulin treatment was initiated when dietary treatment did not achieve the glycemic goal. Of the 995 women, 141 had GDM (14.2%): 104 with one, 27 with two, and 10 with three abnormal OGTT values. Women with two or three abnormal OGTT values needed insulin treatment more frequently than those with one abnormal OGTT value (1-AV) (70.3% vs 23.1%, $P < 0.0001$). After adjustment for age, pregravid overweight, gestational weeks at diagnosis, a first-degree family history of diabetes was correlated with the implementation of insulin treatment in women with 1-AV (adjusted odds ratio 3.9; 95% Confidence Interval 1.7-9.2; $P = 0.001$). When compared perinatal outcomes between women with normal glucose tolerance and GDM, fetal growth and the occurrence of pregnancy-induced hypertension were comparable between the two groups. Our data suggest that the IADPSG-defined GDM with 1-AV show less severe glucose intolerance, but might be at risk of insulin requirement when a first-degree family history of diabetes exists.

Key words: The new consensus criteria, Gestational diabetes mellitus, Large-for gestational age, Gestational hypertension

IN 2010, International Association of Diabetes and Pregnancy Study Group (IADPSG) proposed new criteria for diagnosing and classifying gestational diabetes mellitus (GDM), based on data of the observational hyperglycemia and adverse pregnancy outcomes (HAPO) study [1]. Since the new diagnostic criteria would increase the frequency of GDM diagnosis without a detailed cost-effectiveness analysis, the number of health care associations implementing the new criteria is still limited [2]. Thus, there is a paucity of information on the IADPSG-defined GDM from a real experience. Especially, clinical significance of GDM by one abnormal value under the IADPSG criteria remains unknown [3].

In Japan, the IADPSG recommendation was adopted in July 2010 [4], and is commonly used in the obstetric practice, although the screening strategy varies in hospitals. With this background, we have investigated perinatal outcomes of the IADPSG-defined GDM in our hospital. First, maternal clinical and metabolic features were compared between women with a single and two or three abnormal oral glucose tolerance test (1- and 2/3-AV) values. Second, factors associated with insulin treatment in women with 1-AV were investigated. Third, perinatal outcomes were compared between women with normal glucose tolerance and IADPSG-defined GDM.

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Materials and Methods

Subjects

We conducted a retrospective cohort study of 995 consecutive pregnant Japanese women who were cared for at the perinatal unit of Keio University Hospital from 2011 to 2012. Gestational age was confirmed in the first trimester by crown-rump length measurements. Excluded from this study were women with multi-fetal pregnancies and women whose neonates exhibited congenital anomalies. Women with a medical history indicating either impaired glucose tolerance or diabetes mellitus (DM), or the use of medications known to affect glucose metabolism were also excluded. The research was performed in accordance with the Declaration of Helsinki and informed consent was obtained from patients where appropriate. This study was approved by the institutional review board at Keio University School of Medicine.

GDM screening and glycemic control

Each woman underwent a two-step screening for GDM: universal early testing and a standard 1-h 50g oral glucose challenge test (GCT) in early and late pregnancy, respectively, based on the clinical recommendation by Japan Society of Obstetrics and Gynecology (JSOG) [4]. The universal early testing included the clinical risk factors, as follows: (1) pregravid overweight (BMI $\geq$ 25), (2) prior GDM, (3) past history of macrosomia (birth weight $\geq$ 4000g), (4) a family history of DM in the first-degree relatives, (5) random plasma glucose $\geq$ 95 mg/dl. Levels of HbA1c and glycoalbumin (GA) were also examined as early testing in our institution (cut-off values: HbA1c $\geq$ 5.9%, GA $\geq$ 15.8%). Women with positive early testing underwent a diagnostic 75-g OGTT with the measurement of plasma glucose (mg/dl) and insulin concentration (mU/l) in the fasting state and at 30 min, 1 h, and 2 h after the glucose load. Plasma glucose and insulin levels were measured by a glucose oxidase method and enzyme immunoassay, respectively. Women with negative early testing or normal OGTT results underwent a standard GCT between 24 and 27 weeks of gestation. If the GCT result exceeded 140 mg/dl, the diagnostic 75-g OGTT was then performed. Based on the IADPSG criteria, GDM was diagnosed if one or more values reached or exceeded the following thresholds: fasting, 92 mg/dl; 1 h, 180 mg/dl; 2 h, 153 mg/dl [1]. Overt diabetes in pregnancy was defined as HbA1c $\geq$ 6.5% or fasting plasma glucose $\geq$ 126 mg/dl or random plasma glucose exceeded 200 mg/dl, the latter needing to be confirmed by one of the former [1]. The normal glucose tolerance (NGT) group comprised women with normal GCT or normal OGTT results.

All women found to have IADPSG-defined GDM underwent self-monitoring of blood glucose (SMBG) measurements as well as dietary management (daily calorie intake: early, 30 kcal/kg + 150 kcal; late, 30 kcal/kg + 350 kcal; if obese, 30 kcal/kg throughout pregnancy). Dietary management includes three meals and three snacks. Daily capillary glucose profiles were obtained seven times a day under dietary management: fasting, 2 h-post-breakfast, before lunch, 2 h-post-lunch, before dinner, 2 h-post-dinner, and bedtime. Capillary glucose levels were measured with a Medisafe Fit Pro blood glucose meter (Terumo Corporation, Tokyo, Japan). Insulin treatment was initiated when dietary treatment did not consistently maintain fasting and pre-meal capillary glucose $\leq$ 100 mg/dl and 2 h postprandial capillary glucose $\leq$ 120 mg/dl, respectively. Regular, or rapid acting, and NPH insulin were used to achieve the glycemic target and insulin dose was adjusted according to insulin algorithm based on SMBG values.

Assessment of insulin sensitivity, insulin secretion and beta cell function

Insulin sensitivity and insulin secretion were evaluated using measurements from the diagnostic OGTT [5, 6]. The insulin sensitivity was estimated by the whole-body insulin sensitivity index derived from the OGTT (IS_{OGTT}). The IS_{OGTT} was calculated by the following formula: 10,000 / square root $\{Glu_0 \times Ins_0 \times (Glu_0 + Glu_{60} \times 2 + Glu_{120}) / 2 \times (Ins_0 + Ins_{60} \times 2 + Ins_{120}) / 2\}$, where Glu_y and Ins_y represent plasma glucose (mg/dl) and insulin values (mU/l), respectively, at time y min during the OGTT. Insulin secretion was assessed by the ratio of the total area under the insulin curve to the total area under the glucose curve ($AUC_{ins/glu}$) during the OGTT. To evaluate beta cell function, we calculated the OGTT-derived disposition index using the following measures: Insulin Secretion-Sensitivity Index-2 (ISSI-2: the $AUC_{ins/glu}$ multiplied by IS_{OGTT}) [7].

Perinatal outcomes

Maternal characteristics and perinatal outcomes were collected from the patients' hospital records. Gestational hypertension was defined as a blood pres-

sure of at least 140/90 mmHg occurring for the first time after mid-pregnancy, without proteinuria or pre-existing hypertension. Proteinuria was defined as urinary excretion of at least 0.3 g in a 24-hour period. A diagnosis of preeclampsia was made in women who developed gestational hypertension and proteinuria. Using the Japanese standard sex- and parity-specific birthweight percentile curves, birthweight ≥ 90th percentile was defined as large-for-gestational age (LGA), and birthweight < 10th percentile was designated small-for-gestational age (SGA). Macrosomia was defined as birthweight above 4000 g.

Statistical analysis

Data were presented as mean ± SD or percentage in text and tables, where appropriate. Continuous data were compared between groups by Student's *t* test. Categorical variables were analyzed with the chi-square test or Fisher's exact test. Statistical analysis was performed using the JMP (SAS Institute, Cary, NC, USA). A value of $P < 0.05$ was considered statistically significant.

Results

Among 995 pregnant women, 141 (14.2%) were diagnosed to have GDM: 104 with a single abnormal value, 27 with two abnormal values, and 10 with three abnormal values. Of women with GDM, 68 were diagnosed by universal early testing in the first trimester. Two women (2/995 cases, 0.02%) had overt diabetes in pregnancy.

When compared the clinical features between women with 1- and 2/3-AV, there were no significant differences in maternal age, pregravid overweight (BMI ≥ 25), prior GDM, a family history of DM, and gestational weeks at diagnosis (Table 1). Compared with 1-AV, women with 2/3-AV showed significantly lower levels of IS_{OGTT} ($P < 0.01$), although insulin secretion assessed by $AUC_{ins/glu}$ was comparable between the two groups. As a result, levels of ISSI-2 in women with 2/3-AV were significantly lower than those with 1-AV ($P < 0.0001$). To achieve glycemic goal, women with 2/3-AV needed insulin treatment more frequently than those with 1-AV (70.3% vs 23.1%, $P < 0.0001$, Table 1).

With respect to clinical features in the 1-AV group, there were no significant differences in metabolic phenotypes (insulin sensitivity, insulin secretion, and beta cell function) as well as maternal age, pregravid overweight (BMI ≥ 25), prior GDM, gestational weeks at diagnosis between women with and without insulin treatment (Table 2). Of interest, a family history of DM was more prevalent in women requiring insulin treatment (41.7% vs. 15.0%, $P < 0.01$, Table 2). The time point showing abnormal values as well as levels of plasma glucose and insulin at the diagnostic OGTT were not associated with the implementation of insulin treatment (Table 3). After adjustment for age, pregravid overweight, gestational weeks at diagnosis, a family history of DM was significantly correlated with insulin treatment in women with 1-AV (adjusted odds ratio 3.9; 95% Confidence Interval 1.7-9.2; $P = 0.001$).

Table 1 Maternal clinical features in women with a single and two/three abnormal oral glucose tolerance test results

		A single abnormal OGTT result (n=104)	Two/three abnormal OGTT results (n=37)
Maternal age	, years	35.7 ± 4.4	35.8 ± 4.8
Pregravid BMI	, kg/m^2	20.7 ± 3.4	22.3 ± 5.1*
Pregravid overweight		10 (9.6%)	8 (21.6%)
Prior GDM		1 (1.0%)	2 (5.4%)
A family history of diabetes		22 (21.2%)	11 (29.7%)
Gestational age at diagnosis	, weeks	21 ± 8	22 ± 7
Diagnosed before 20 weeks' pregnancy		51 (49.0%)	17 (46.0%)
HbA1c at diagnosis	, %	5.4 ± 0.3	5.4 ± 0.3
IS_{OGTT}		6.4 ± 3.0	4.8 ± 2.7 #
$AUC_{ins/glu}$		0.34 ± 0.21	0.41 ± 0.22
ISSI-2		2.1 ± 0.62	1.6 ± 0.49 ##
Insulin treatment		24 (23.1%)	26 (70.3%) ##

OGTT, oral glucose tolerance test; BMI, body mass index; overweight, BMI ≥ 25; GDM, gestational diabetes mellitus; IS_{OGTT}, insulin sensitivity index derived from the oral glucose tolerance test; $AUC_{ins/glu}$, the ratio of the total area under the insulin curve to the total area under the glucose curve during the oral glucose tolerance test; ISSI-2, Insulin Secretion-Sensitivity Index-2 (i.e. the $AUC_{ins/glu}$ multiplied by IS_{OGTT}); *, $P < 0.05$; #, $P < 0.01$; ##, $P < 0.0001$

Table 2 Maternal characteristics in women with a single abnormal oral glucose tolerance test result

		Insulin Treatment (n=24)	Dietary management only (n=80)
Maternal age	, years	36.1 ± 5.0	35.9 ± 4.3
Pregravid BMI	, kg/m^2	21.1 ± 2.6	20.5 ± 3.6
Pregravid overweight		3 (12.5%)	7 (8.8%)
Prior GDM		0 (0.0%)	1 (1.25%)
A family history of diabetes		10 (41.7%)	12 (15.0%) #
Gestational age at diagnosis	, weeks	20 ± 8	22 ± 8
Diagnosed before 20 weeks' pregnancy		13 (54.2%)	38 (47.5%)
HbA1c at diagnosis	, %	5.4 ± 0.3	5.4 ± 0.3
IS_{OGTT}		6.6 ± 3.4	6.3 ± 2.9
$AUC_{ins/glu}$		0.37 ± 0.18	0.40 ± 0.22
ISSI-2		2.1 ± 0.74	2.1 ± 0.58

OGTT, oral glucose tolerance test; BMI, body mass index; overweight, BMI ≥ 25; GDM, gestational diabetes mellitus; IS_{OGTT}, insulin sensitivity index derived from the oral glucose tolerance test; $AUC_{ins/glu}$, the ratio of the total area under the insulin curve to the total area under the glucose curve during the oral glucose tolerance test; ISSI-2, Insulin Secretion-Sensitivity Index-2 (i.e. the $AUC_{ins/glu}$ multiplied by IS_{OGTT}); #, $P < 0.01$

Table 3 Profiles of the diagnostic oral glucose tolerance test in women with a single abnormal result

		Insulin Tratment (n=24)	Dietary management only (n=80)
Plasma glucose (mg/dl)			
	0 min	89.3 ± 7.1	88.9 ± 7.4
	30 min	145.2 ± 17.8	141.7 ± 22.4
	60 min	152.8 ± 29.0	153.7 ± 27.3
	120 min	146.6 ± 29.6	135.8 ± 26.2
Plasma insulin (mU/l)			
	0 min	6.4 ± 3.2	6.6 ± 4.3
	30 min	58.9 ± 30.6	60.5 ± 38.9
	60 min	62.0 ± 34.7	71.4 ± 47.3
	120 min	69.2 ± 37.9	64.3 ± 41.5
Abnormal value of plasma glucose#			
	0 min	9 (37.5%)	40 (50%)
	60 min	3 (12.5%)	14 (17.5%)
	120 min	12 (50%)	26 (32.5%)

#, Cases showing abnormal plasma glucose values at each time point in the diagnostic oral glucose tolerance test

The overall perinatal features of this study cohort were as follows: the mean maternal age was 34.9 ± 4.8 years, pregravid BMI 19.8 ± 4.6, gestational age at delivery 38.0 ± 2.4 weeks, mean birthweight 2841 ± 551 g, and 680 (68.0%) were primiparas. Twenty-five women (2.5%) developed gestational hypertension, and 19 (2.9%) preeclampsia. The occurrence of SGA and LGA was 6.9% (69/995 cases) and 6.0% (60/995 cases), respectively.

The baseline characteristics and pregnancy outcomes of women with NGT or GDM are shown in Table 4. There were significant differences in maternal age, pregravid overweight, and a family history of DM among subjects with NGT and GDM. With regard to fetal growth, the prevalence of LGA and SGA were comparable between the NGT and GDM groups. Additionally, no significant differences in the occurrence of pregnancy-induced hypertension (i.e. gestational hypertension and preeclampsia) were found between the two groups.

Discussion

Currently, prospective data on the potential frequency of GDM with the IADPSG criteria has been slow. To the best of our knowledge, this is the first report on perinatal features of women with GDM in the clinical situations that adopted the IADPSG consen-

Table 4 Baseline characteristics and perinatal outcomes in women with normal glucose tolerance or gestational diabetes mellitus

		NGT (n=852)	GDM (n=141)
Maternal age	, years	34.7 ± 4.8	36.1 ± 4.6 *
Nulliparous		591 (69.4%)	89 (63.1%)
Pregravid BMI	, kg/m^2	19.6 ± 4.7	21.1 ± 4.0 #
Pregravid overweight		36 (4.2%)	18 (12.8%) ##
Prior GDM		5 (0.6%)	3 (2.1%)
A family history of diabetes		57 (6.7%)	33 (23.4%) ##
Gestational age at delivery	, weeks	38.1 ± 2.4	37.8 ± 2.8
Birth weight	, g	2845 ± 548	28121 ± 573
LGA		59 (6.9%)	10 (7.1%)
Macrosomia		9 (1.1%)	1 (0.7%)
SGA		53 (6.2%)	7 (5.0%)
Gestational hypertension		21 (2.5%)	4 (2.8%)
Preeclampsia		17 (2.0%)	2 (1.4%)

NGT, normal glucose tolerance, defined as negative screen for gestational diabetes mellitus or normal oral glucose tolerance results. GDM, gestational diabetes mellitus; BMI, body mass index, overweight, BMI ≥ 25; LGA, large-for-gestational age, defined as birth weight ≥ 90th percentile for gestational age; SGA, small-for-gestational age, defined as birth weight < 10th percentile for gestational age; Macrosomia, birth weight ≥ 4000g. *, $P < 0.05$; #, $P < 0.001$; ##, $P < 0.0001$.

sus criteria. In our institution, the prevalence of GDM by the former JSOG criteria was 2.3%, as previously reported [8]. Compared with the former situations, the IADPSG criteria lead to an increase in the frequency of GDM diagnosis in our hospital. Additionally, the majority (104/141 cases, 74%) of women with GDM showed 1-AV, which was consistent with data in the complete HAPO cohort [1]. Our results demonstrated that the frequency of GDM would increase significantly with the IADPSG criteria, mainly by those with 1-AV.

The implementation of insulin treatment was based on daily glucose profile during dietary management in our hospital. In this retrospective analysis, more women with 2/3-AV needed the addition of insulin treatment to achieve the glycemic control, compared with 1-AV. With respect to beta cell function, levels of ISSI-2 in women with 2/3-AV were significantly lower than those with 1-AV. The level of beta cell function is associated with the severity of glucose intolerance in GDM [9]. Additionally, our previous investigation demonstrated that beta cell dysfuntion in women with 2/3-AV appeared more severe than those with 1-AV [10]. Taken altogether, our data indicated women with 2/3-AV had more severe levels of glucose intolerance, compared with 1-AV.

Approximately one-quarter of women with 1-AV needed the insulin treatment. Most women with the IADPSG-defined GDM have 1-AV and factors associated with insulin treatment are needed in the clinical practice. The insulin treatment did not depend on which glucose result met or exceeded single IADPSG-defined OGTT threshold. When analyzed maternal characteristics, a family history of DM was correlated with the induction of insulin treatment. Of women with the IADPSG-defined GDM, therefore, those with 1-AV appear less severe glucose intolerant, but might be at risk of insulin requirement when a family history of DM exists.

There were significant differences in pregravid overweight, prior GDM, and a family history of DM among subjects with NGT and GDM, as were noted in the former situations [11]. Of note, no significant differences were found in the occurrence of perinatal outcome including LGA and pregnancy-induced hypertension between the NGT and GDM groups in this study cohort. Previous analysis based on reevaluated data before the adoption of the IADPSG criteria has shown increased risk of the development of LGA and gestational hypertension in the IADPSG-defined GDM [12]. Additionally, Black *et al.* have shown that IADPSG-defined GDM could be at risk of adverse outcomes including LGA, gestational hypertension and shoulder dystocia/birth injury [13]. To date, two trials have demonstrated the advantages of treatment for women with mild degree glucose intolerance, although inclusion criteria for the trial were different from the

IADPSG recommendation [14, 15, 16]. Our results suggest that intervention for women with IADPSG-defined GDM could contribute to the improvement of pregnancy outcomes, although further studies on the clinical and cost-effective management are needed.

Benefit of treatment of IADPSG-defined GDM remains unknown because no randomized control trial has been conducted using the IADPSG criteria and additional well-designed trial and other clinical studies will be needed to determine the optimal treatment targets [1]. In the clinical settings, therefore, appropriate management of IADPSG-defined GDM remains unclear. Our data is only a local experience but could be useful for other healthcare professionals considering the IADPSG criteria.

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Disclosure

Authors declare no conflict of interest with regard to this manuscript.

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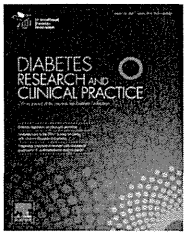

Comparison of pregnancy outcomes between women with gestational diabetes and overt diabetes first diagnosed in pregnancy: A retrospective multi-institutional study in Japan

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ABSTRACT

Aims: To determine differences in pregnancy outcomes including diabetic complications, maternal and perinatal complications between gestational diabetes mellitus and overt diabetes in pregnancy in Japan.

Methods: A multi-institutional retrospective study compared pregnancy outcomes between gestational diabetes mellitus and overt diabetes in pregnancy. We examined pregnant women who met the former criteria for gestational diabetes mellitus and received dietary intervention with self-monitoring of blood glucose with or without insulin. Overt diabetes in pregnancy was defined as ≥2 abnormal values on 75-g oral glucose tolerance test, fasting

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glucose ≥126 mg/dl (7.0 mmol/l) and 2-h postprandial glucose ≥200 mg/dl (11.1 mmol/l), or glycated hemoglobin levels ≥6.5% (48 mmol/mol).

Results: Data were collected on 1267 women with gestational diabetes and 348 with overt diabetes in pregnancy. Pregestational body mass index was higher (26.2 ± 6.1 vs. 24.9 ± 5.7 kg, $P < 0.05$) and gestational age at delivery was earlier (37.8 ± 2.5 weeks vs. 38.1 ± 2.1 weeks, $P < 0.05$) in overt diabetes than in gestational diabetes. Glycated hemoglobin (6.8 ± 1.1% [51 mmol/mol] vs. 5.8 ± 0.5% [40 mmol/mol], $P < 0.05$) and glucose on 75-g oral glucose tolerance test and prevalence of retinopathy (1.2% vs. 0%, $P < 0.05$) and pregnancy-induced hypertension (10.1% vs. 6.1%, $P < 0.05$) were higher in overt diabetes than in gestational diabetes. Pregnancy-induced hypertension was associated with pregestational body mass index, gestational weight gain, chronic hypertension, and nulliparity but not with 75-g oral glucose tolerance test.

Conclusions: Overt diabetes in pregnancy is significantly associated with maternal complications such as retinopathy and pregnancy-induced hypertension.

1. Introduction

Gestational diabetes mellitus (GDM) is associated with maternal complications such as pregnancy-induced hypertension (PIH) and cesarean section, and neonatal complications, such as macrosomia, hypoglycemia, jaundice, and respiratory distress syndrome [1,2]. GDM is significantly associated with large-for-gestational age (LGA) infants [3,4], and mean glucose concentration is strongly associated with neonatal birth weight in women with GDM [5]. The Hyperglycemia Adverse Pregnancy Outcome (HAPO) study showed a positive correlation between maternal hyperglycemia level and adverse maternal, fetal, and/or neonatal outcomes [3]. The International Association of Diabetes in Pregnancy Study Group (IADPSG) recently proposed new criteria for diagnosing GDM [6]. The new criteria are based primarily on glucose levels that are associated with a 1.75-fold increased risk of giving birth to a LGA infant according to the HAPO study [1].

GDM is defined as glucose intolerance that first occurs or is first identified during pregnancy [7]. The possibility that unrecognized glucose intolerance antedated the pregnancy is therefore not excluded, and this has become a more significant problem as the prevalence of obesity and subsequent development of type 2 diabetes in young women has increased worldwide [8]. Furthermore, ethnicity is associated with risk factors for GDM [8]. For instance, Asian people have a high risk of developing GDM. We previously reported that more than 50% of GDM cases in Japan are diagnosed in the first trimester of pregnancy [9]. The IADPSG proposed the following definition for overt diabetes during pregnancy (ODM): pregnant women who meet the criteria for diabetes in the nonpregnant state but were not previously diagnosed with diabetes. Thus, 2 types of glucose intolerance are identified in pregnancy: GDM and ODM. The clinical significance of ODM has been reported. The risk of congenital malformations and of maternal complications such as retinopathy and nephropathy is increased in diabetes. Rapid management and follow-up may also be required during pregnancy [10,11].

Our hypothesis is that overt diabetes would have a more severe glycemic disturbance and increased risk of both maternal and neonatal complications; however, little has been reported regarding differences in pregnancy outcomes between these groups. Therefore, the Japan Diabetes and Pregnancy Study (JDPS) Group conducted a multi-institutional retrospective review to assess and compare pregnancy outcomes between ODM and GDM in Japan.

2. Materials and methods

2.1. Study design

The present retrospective study was conducted in 40 general hospitals in Japan from 2003 to 2009. The individual ethics committees at each of the 40 collaborating centers approved the protocol. All women with singleton pregnancy and no prior diagnosis of diabetes mellitus were included. Women with multiple fetal gestations, pre-gestational diabetes, history of previous treatment for gestational diabetes, active chronic systemic disease other than chronic hypertension, and those with the second of 2 pregnancies within the same year were excluded. All women underwent a universal 2-step screening for GDM, i.e. a casual glucose test or 50-g glucose challenge test (GCT) between 24 and 30 weeks of gestation. Women who had random plasma glucose ≥100 mg/dl (5.5 mmol/l) or plasma glucose ≥140 mg/dl (7.8 mmol/l) on GCT were then scheduled for a diagnostic 75-g 2-h oral glucose tolerance test (OGTT) after an overnight fast, using JSOG criteria (fasting, 100 mg/dl [5.5 mmol/l]; 1 h, 180 mg/dl [10 mmol/l]; 2 h, 150 mg/dl [8.3 mmol/l]) [12]. GDM was diagnosed when at least 2 plasma glucose measurements were the same as or higher than the cut-off points. Overweight or obese pregnant women are recommended to undergo a 75-g OGTT at any time during gestation. HbA1c measurements was shown in NGSP units (%).

Overt diabetes first diagnosed in pregnancy (ODM) was defined as ≥2 abnormal values on 75-g oral glucose tolerance test, fasting glucose ≥126 mg/dl (7.0 mmol/l) and 2-h postprandial glucose ≥200 mg/dl (11.1 mmol/l), glycated hemoglobin levels ≥6.5% (48 mmol/mol), random glucose ≥200 mg/dl (11.1 mmol/l), or diabetic retinopathy recognized in pregnancy.

Collected data included maternal age; parity; pre-pregnancy BMI; chronic hypertension; pregnancy-induced hypertension

(PIH), including pre-eclampsia; gestational age at delivery; delivery characteristics, including spontaneous or induced delivery, vaginal delivery, or cesarean section; and newborn characteristics such as birth weight, sex, Apgar score, perinatal mortality, and major congenital malformations. Pregestational weight was self-reported at the first prenatal visit. Gestational age was defined by the number of weeks since the last menstrual period or the ultrasound assessment of crown-rump length if discordance was recognized. Chronic hypertension was defined as hypertension treated with medication before pregnancy or arterial blood pressure ≥140/90 mm Hg before 20 weeks of pregnancy. Macrosomia was defined as a birth weight ≥4000 g. LGA was defined as sex- and delivery-specific birth weight for gestational age above the 90th percentile on Japanese fetal growth curves [13]. Major congenital malformations were defined as those that caused significant functional impairment, required surgery, or were considered life threatening.

In all institutes, GDM women received dietary management along with self-monitoring of blood glucose (SMBG) and insulin therapy, if needed. Dietary therapy, including guidance on intake and gestational weight gain, was provided to these women based on their pre-pregnancy BMI. They also received guidance on how to determine SMBG levels 4–6 times a day. Insulin therapy was initiated if targeted glucose levels (i.e., preprandial glucose levels <100 mg/dl [5.5 mmol/l] and 2-h postprandial levels <120 mg/dl [6.7 mmol/l]) were not achieved.

2.2. Study outcomes

The composite study outcome included perinatal mortality (stillbirth or neonatal death) and complications associated with maternal hyperglycemia, including congenital malformation, LGA infant, macrosomia, hypoglycemia, hyperbilirubinemia, shoulder dystocia, respiratory distress syndrome, and admission to the neonatal intensive care unit.

Neonatal blood was collected for glucose measurement at 1 or 2 h after birth and before feeding. Hypoglycemia was defined as a blood glucose value <35 mg/dl [1.9 mmol/l] [14]. Hyperbilirubinemia was defined as an elevated serum bilirubin requiring phototherapy.

Maternal outcome parameters included weight gain from the time of enrollment to delivery, PIH including gestational hypertension and preeclampsia, cesarean delivery, labor induction, and shoulder dystocia. Gestational hypertension was defined as a systolic pressure of ≥140 mm Hg or a diastolic pressure of ≥90 mm Hg, recorded on 2 occasions at least 4 h apart. Preeclampsia was defined as blood pressure elevation (according to the definition of gestational hypertension) along with proteinuria (24-h urine protein ≥300 mg, or a dipstick test result of ≥2+ when a 24-h collection was not available). Shoulder dystocia was defined clinically, and the providers were required to document the specific maneuvers used to release fetal shoulders.

2.3. Statistical analysis

Baseline characteristics and laboratory measurements are presented as means ± SD, medians, or percentages. The chi-square test was used for univariate analysis of differences in values between any 2 groups. Multiple logistic regression analysis (MLRA) was performed to detect variables that differentiate any 2 groups. All reported P values are two-tailed, and $P < 0.05$ was considered a statistically significant difference. All statistical analyses were performed using a general-purpose statistical software, StatFlex version 6.0 (Artech Inc., Osaka, Japan).

3. Results

From 2003 through 2009, we retrospectively examined 2011 GDM subjects from 40 institutions in Japan. Of the 2011 women, 1615 were studied and divided into 2 groups based on the degree of carbohydrate intolerance: GDM ($n = 1267$) and ODM ($n = 348$). 520 (41.0%) women with GDM and 172 (49.4%) women with ODM received 75 g OGTT before 24weeks of gestation, respectively. If they screened normal in the first trimester, they are re-tested between 24 and 30 weeks of gestation. If screening test was positive, HbA1c levels were tested at the time of 75 g OGTT.

The baseline characteristics of women with GDM and ODM are shown in Table 1. There was no significant difference in maternal age and frequency of nulliparity between the 2 groups. Pregestational BMI was higher in ODM than in GDM, but gestational weight gain was not significantly different between these groups. Gestational age at diagnosis was earlier in women with ODM than in those with GDM. In the 75 g OGTT, the plasma glucose level at all time-points was significantly higher in the ODM group than in the GDM group. In addition, ODM patients had significantly higher HbA1c levels than GDM patients. Prevalence of insulin treatment was higher in the ODM group than that in the GDM group.

Maternal complications are shown in Table 2. The prevalence of retinopathy and PIH was significantly higher in the ODM group than in the GDM group. However, the prevalence of chronic hypertension, primary cesarean section, and induction of labor was similar between groups. MLRA for PIH risk factors showed that pregestational BMI, gestational

Table 1 – Baseline characteristics.

	GDM ($n = 1267$)	ODM ($n = 348$)
Age (y)	33.6 ± 4.8	33.1 ± 5.3
Nullipara – no. (%)	598 (47.2)	183 (52.7)
Pregestational BMI	24.9 ± 5.7	26.2 ± 6.1*
Gestational weight gain (kg)	6.4 ± 5.4	5.8 ± 5.6
Gestational age at diagnosis (wk)	23.5 ± 8.2	22.0 ± 9.0*
Glucose levels of 75 g-OGTT (mg/dl)		
Fasting	90.5 ± 11.8	114.5 ± 32.2*
1-h	200.8 ± 32.1	237.2 ± 47.1*
2-h	177.7 ± 34.2	227.6 ± 43.5*
HbA1c (%)	5.8 ± 0.5	6.8 ± 1.1*
Insulin therapy – no. (%)	432 (34.1)	298 (85.6)*

ODM, overt diabetes in pregnancy; HbA1c (NGSP) *$p < 0.05$ vs. GDM.

Table 2 – Maternal complications.

	GDM (n = 1267)	ODM (n = 348)
Retinopathy – n (%)	0 (0)	4 (1.2)*
Chronic hypertension – n (%)	57 (4.5)	24 (6.9)
Pregnancy induced hypertension – n (%)	77 (6.1)	35 (10.1)*
Cesarean section – n (%)	426 (33.6)	119 (34.2)
Primary cesarean section – n (%)	193 (15.2)	60 (17.2)
Induction of labor – n (%)	294 (23.2)	94 (27.0)

ODM, overt diabetes in pregnancy; *$p < 0.05$ vs. GDM.

weight gain, chronic hypertension, and nulliparity were associated with the onset of PIH (Table 3).

Neonatal complications in the study population are shown in Table 4. Gestational age at delivery was significantly earlier in the ODM group than in the GDM group. Prevalence of congenital malformations was higher in the ODM group, but the difference between groups was not significant. The groups were also similar with respect to other neonatal parameters, including birth weight, small-for-gestational-age (SGA) infants, LGA infants, respiratory distress syndrome (RDS), hypoglycemia, and jaundice.

4. Discussion

The present study examined the difference in pregnancy outcomes between women with GDM and ODM in Japan. The results showed that the prevalence of PIH and diabetes complications such retinopathy was higher in women with ODM than in those with GDM.

The degree of carbohydrate intolerance is more severe in ODM compared with GDM and may include undiagnosed pregestational diabetes. As expected the present study showed that HbA1c and plasma glucose levels in the 75 g OGTT at the time of diagnosis were higher in the ODM group than in the GDM group. Among maternal complications, the prevalence of PIH was higher in ODM than GDM. Multiple linear logistic analysis showed that pregestational BMI, gestational weight gain, chronic hypertension, and nulliparity were associated with the onset of PIH. A recent sub-analysis of the HAPO study by Catalano et al. showed that obesity independently affects pregnancy outcomes such as pre-eclampsia, LGA infant, macrosomia, and shoulder dystocia [2]. The HAPO study subjects included women who had normal glucose tolerance or mild carbohydrate intolerance. Blacks et al. examined the effects of maternal BMI and gestational weight gain on the frequency of LGA infants among women with normal glucose tolerance and GDM based on the IADPSG diagnostic criteria [14]. These reports suggest that pregestational BMI is associated with pregnancy outcome. Therefore, the impact of maternal pregestational BMI may be strong in the present study. Chronic hypertension is another well-known risk factor for preeclampsia [15]. The present study demonstrates that chronic hypertension is a risk factor for PIH in women with GDM and those with ODM. Howarth et al. showed that women with type 1 diabetes and vascular disease are at greater risk of preeclampsia and pathological fetal growth [16]. The ODM group in the present study included 4 women with diabetic retinopathy, none of whom had type 1 diabetes. It is noteworthy that 2 of the women with retinopathy developed PIH in the third trimester of gestation. Although multiple linear logistic analysis showed no clear relationship between diabetic retinopathy and PIH, the results suggest that health care providers should consider the potential for development of PIH in women with ODM and diabetic retinopathy.

Table 4 – Neonatal complications.

	GDM (n = 1267)	ODM (n = 348)
Gestational age at delivery (wk)	38.1 ± 2.1	37.8 ± 2.5*
Birth weight (g)	2977.3 ± 653.8	2974.6 ± 551.0
SGA – n (%)	202 (15.9)	61 (17.5)
LGA – n (%)	290 (22.9)	70 (20.1)
Macrosomia – n (%)	35 (2.8)	11 (3.2)
Shoulder dystocia – n (%)	15 (1.2)	3 (0.9)
Congenital malformations – n (%)	65 (5.1)	22 (6.4)
RDS – n (%)	148 (11.7)	33 (9.5)
Hypoglycemia – n (%)	158 (12.5)	48 (13.8)
Jaundice – n (%)	185 (14.6)	50 (14.4)
NICU – n (%)	451 (35.6)	117 (33.6)

ODM, overt diabetes in pregnancy; *$p < 0.05$ vs. GDM.

No significant differences in neonatal outcomes were observed between the GDM and ODM groups. LGA infants are a well-recognized and significant complication of GDM [3,4], and there is a strong association between mean maternal glucose concentration and neonatal birth weight [5]. Furthermore, if glycemic control during pregnancy is too strict, the prevalence of SGA is increased [17]. In the present study, there was no significant difference between the GDM and ODM groups in the prevalence of SGA and LGA infants, suggesting that management for both GDM and ODM were appropriate

Table 3 – Risk factors for pregnancy-induced hypertension.

Variables	β	SE (β)	z	P	Odds Ratio	95% CI
Pregestational BMI	0.108	0.018	6.22	<0.001	1.114	1.077–1.153
Gestational weight gain	0.079	0.017	4.15	<0.001	1.114	1.077–1.153
75-g OGTT 1 h	0.005	0.003	1.81	0.07	1.005	0.999–1.010
Chronic hypertension	1.650	0.287	5.74	<0.001	5.208	2.966–9.144
Nullipara	0.692	0.214	3.231	<0.001	2.001	1.329–1.762

AIC = 724.648.
AUC = 0.7668.

after diagnosis. Recently, Wong T et al. showed that the prevalence of LGA was higher in the overt diabetes group than that in the GDM group [18]. A difference between the present study and the Australian study is pre-pregnancy BMI. The absolute maternal BMI has been shown to be associated with the prevalence of LGA. In the present study, although BMI showed a significant difference between the GDM and the ODM groups, BMI in both groups was lower than subject in the Australian study. Pregestational diabetes mellitus is also associated with an increase in congenital malformations [19]. We expected that the frequency of congenital malformations would be higher in the ODM group than in the GDM group, because ODM includes pregestational diabetes mellitus. However, the frequency of congenital malformations was not significantly different between the 2 groups. The mean HbA1c level in the ODM group was 6.8% ± 1.1% [51 mmol/mol]. We speculate that glucose levels were not high enough to cause congenital malformations in our study population.

The present study has several limitations that could affect data interpretation. First, it was not possible to determine whether glycemic control in each group was appropriate. We also could not determine whether glycemic control was similar in the third trimester of gestation. In addition, subjects were recruited using the previous JSOG criteria for GDM. Therefore, we cannot compare GDM as defined by the IADPSG criteria with ODM. If the IADPSG criteria for GDM were used to recruit study subjects, the number of mildly carbohydrate intolerant women would presumably be increased, magnifying the differences between GDM and ODM in pregnancy outcomes. Also, follow-up data on maternal glucose tolerance in both the GDM and ODM group were not examined in the present study.

In summary, the current study shows that ODM has a greater negative impact on pregnancy outcomes, including PIH and diabetic complications such as diabetic retinopathy, than does GDM.

Conflict of interest

The authors have no potential conflict of interest to declare.

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Appendix

The contributors of the Japan Diabetes and Pregnancy Study Group are follows:

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