Table 2 Adjusted odds ratios of HOMA-IR for giving birth to a large-for-gestational age infant in the multivariate logistic regression models

Predictive variables	Model I adjusted for FPG		Model II adjusted for 1-hour PG		Model III adjusted for 2-hour PG		Model IV adjusted for all PG	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
HOMA-IR	1.55 (1.11-2.17)	0.0099	1.49 (1.11-2.00)	0.008	1.46 (1.09-1.95)	0.012	1.53 (1.10-2.15)	0.012
Pre-pregnancy BMI (kg/m^2)	1.08 (1.00-1.16)	0.044	1.08 (1.00-1.16)	0.044	1.08 (1.00-1.15)	0.042	1.12 (1.00-1.16)	0.041
Weight gain during pregnancy (kg)	1.11 (1.05-1.18)	0.0003	1.11 (1.05-1.18)	0.0003	1.12 (1.05-1.18)	0.0002	1.19 (1.06-1.19)	0.0001

OR, odds ratio; CI, confidence interval; BMI, body mass index; GA, gestational age; FPG, fasting plasma glucose; PG, plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance.

fasting PG (r^2=0.35, p<0.001), 1-hour PG (r^2=0.34, p <0.001), 2-hour PG (r^2=0.34, p<0.001), and HOMA-IR (r^2=0.36, p<0.001) were significantly associated with neonatal birthweight. We examined the association between HOMA-IR and neonatal birthweight using multivariate regression analysis adjusting for these confounders including GA at delivery, parity, pre-pregnancy BMI, weight gain during pregnancy, fasting PG, 1-hour PG, and 2-hour PG levels. Maternal HOMA-IR was significantly and positively associated with neonatal birthweight after adjusting for these confounders (p<0.05). In this multivariate regression model, the parity (p<0.001), the pre-pregnancy BMI (p<0.0001), and the weight gain during pregnancy (p<0.001) were also independent variables associated with neonatal birthweight. On the other hand, we did not find any association between maternal PG levels and neonatal birthweight.

Ninety-one women (13.9%) had an LGA infant (Table 1). We examined multivariate logistic models regarding the risk of delivery of an LGA infant (Table 2), in which the GA at delivery, parity, pre-pregnancy BMI, weight gain during pregnancy, and each PG (in models I to III) and all PG (in model IV) were controlled as confounders. In each model, HOMA-IR was a significant independent risk factor of giving birth to an LGA infant after controlling for the confounders. For example, in model IV, HOMA-IR was an independent risk factor of giving birth to an LGA infant with an adjusted odds ratio (OR) of 1.53 (95% confidence interval [CI], 1.10-2.15; p=0.012) per 1 unit of HOMA-IR. In each model, the pre-pregnancy BMI and the gestational weight gain remained significantly associated with giving birth to an LGA infant (Table 2). However, neither the parity nor the PG levels were associated with LGA infants in the models.

Discussions

In healthy non-diabetic singleton pregnancies, we found that the maternal HOMA-IR in the second and third trimesters was significantly and positively associated with the neonatal birthweight after adjusting for the parity, pre-pregnancy BMI, weight gain during pregnancy, and PG levels. Elevated maternal HOMA-IR was an independent risk factor of giving birth to an LGA infant after controlling for these confounding variables. To the best of our knowledge, this is the first report to demonstrate a significant association between maternal HOMA-IR and fetal growth independent of maternal obesity and PG levels in normal pregnancy.

In previous studies, investigators did not find any independent association between maternal insulin resistance during pregnancy and neonatal birthweight in subjects with or without GDM. Voldner *et al.* [8] investigated the relationship between fetal macrosomia and maternal metabolic measures, including their fasting PG, fasting insulin, and HOMA-IR at 30-32 weeks of gestation in 553 non-GDM Caucasian females. They found that only the fasting PG, and neither the fasting insulin nor HOMA-IR, was associated with macrosomia after adjusting for covariates including maternal BMI. Bomba-Opon *et al.* [9] examined the association between maternal HOMA-IR in the third trimester and neonatal birthweight in 121 patients with GDM, and could not find any association. Das *et al.* found a significant association between maternal HOMA-IR and ultrasonographically-determined fetal growth at 24-28 weeks of gestation in 86 women with normal glucose tolerance [10]. Although they adjusted for maternal PG levels, they did not control for maternal obesity and did not address neonatal birthweight. The Japanese pop-

ulation is the least obese among developed countries [11], and in this study the subjects had a mean standard pre-pregnancy BMI of 22.0 kg/m^2. It is possible that the difference in basic obesity between Japanese and other ethnic populations may contribute to a difference between our study and other studies. Maternal BMI is strongly associated with neonatal birthweight independent of maternal glucose levels [12], and obesity is also significantly associated with insulin resistance. Therefore, to determine whether maternal insulin resistance is associated with fetal growth independent of maternal obesity in the obese population rather than less obese population like Japanese subjects, much more sample size would be necessary.

We combined the HOMA-IR data from the second and third trimesters, because there were no significant differences between them. Maternal insulin resistance is already increased in early gestation in comparison with the pre-pregnant state in healthy pregnant subjects [2]. Although the change in insulin resistance between the second and third trimesters has not been well documented in normal pregnancy, some authors have reported that no significant change was observed in the maternal HOMA-IR between the trimesters in either non-obese or obese women with normal glucose tolerance [13]. Cohen *et al.* reported that the HOMA-IR is appropriate for use during the second and third trimesters of pregnancy even in obese patients [14].

In terms of the association between maternal hyperglycemia and neonatal birthweight, Voldner *et al.* [8] reported that the maternal fasting PG was the only independent risk factor associated with neonatal macrosomia. A large multicenter prospective observational study called the HAPO study [15] confirmed that each maternal PG level during 75 g OGTT in mid-pregnancy was independently associated with giving birth to an LGA neonate, and that the fasting PG showed the strongest association. In the HAPO study, however, they did not address maternal insulin status. In the univariate analyses in our study, we also found that each PG during 75 g OGTT was significantly associated with neonatal birthweight, and that the fasting PG was the strongest. However, the association was no longer significant in the multivariate regression models including HOMA-IR and the pre-pregnancy BMI as covariates. While the association between maternal PG levels and neonatal birthweight cannot be independent from maternal HOMA-IR, since there is a link between maternal PG levels and insulin resistance in normal pregnancy, HOMA-IR in mid-pregnancy could well be a better predictive variable for neonatal birthweight and macrosomia than maternal PG levels because of its lack of reproducibility during OGTT in uncomplicated pregnancies. Again, the lack of statistical power may have affected the identification of such a modest association in non-diabetic healthy pregnant subjects in a previous study [8].

It is well-documented that maternal pre-pregnancy BMI and excessive gestational weight gain are independently associated with fetal macrosomia in non-diabetic pregnancy [16-18]. A subanalysis of the HAPO study showed that maternal obesity was significantly associated with macrosomia, independent of maternal PG levels [19]. In our study, we found that maternal pre-pregnancy BMI and gestational weight gain were individually associated with having an LGA infant, independent of not only maternal glycemic levels, but also insulin resistance status. Although maternal obesity, excessive gestational weight gain and insulin resistance during pregnancy are interrelated [20, 21], our results showed that these three factors may independently influence fetal overgrowth during normal pregnancy.

There are several limitations to this study. Firstly, we did not directly measure insulin resistance. Although the gold standard used to measure insulin resistance *in vivo* is the euglycemic glucose clamp method [22], because of the complexity of the clamp method, we were obliged to use surrogate indices of insulin resistance which are often used in the clinical setting. HOMA-IR is known to show a good linear correlation to insulin resistance directly measured by glucose clamp technique in non-pregnant adults [23-25]. Although HOMA-IR during pregnancy is less correlated to directly measured insulin resistance by clamp method in comparison with females in a non-pregnant state, it is still a significant predictor of total insulin sensitivity throughout pregnancy and may be a useful tool to assess maternal insulin status [14, 26]. Secondly, we did not measure neonatal adiposity. Neonatal adiposity is well recognized in infants born from diabetic and gestational diabetic mothers and is a very sensitive marker of abnormal fetal overgrowth [27, 28]. Walsh *et al.* [29] reported that the maternal fasting PG concentration at 24 weeks of gestation was significantly associated with both infant birthweight and adiposity in healthy non-diabetic mothers. Although further examinations are necessary, maternal HOMA-IR, a surrogate marker of insulin resistance, is expected to provide a

new predictor of neonatal adiposity in diabetic and/or non-diabetic healthy mothers.

In terms of clinical significance, we were able to use HOMA-IR levels to assess the risk of having a macrosomic infant in women without GDM. Although we did not include patients with gestational diabetes in this study due to therapeutic bias, HOMA-IR levels may also be useful to estimate the risk of macrosomia in such patients. It has been reported that the prevalence of GDM has increased since applying the new IADPSG diagnostic criteria [6], and it may be possible to make triage decisions based on HOMA-IR level in order to assess the risk of macrosomia.

In summary, maternal HOMA-IR in the second and third trimesters was significantly associated with neonatal birthweight and the risk of giving birth to an LGA infant after controlling for GA at birth, maternal parity, pre-pregnancy BMI, weight gain during pregnancy, and PG levels in uncomplicated pregnancies. Our findings suggest that the degree of insulin resistance in mid-pregnancy plays an important role in fetal growth in normal healthy pregnancies, independent of maternal obesity and glucose levels.

Disclosure

None of the authors have any potential conflict of interest to disclose associated with this research.

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A retrospective multi-institutional study of treatment for mild gestational diabetes in Japan

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ABSTRACT

Aims: To determine whether treating mild gestational diabetes mellitus (GDM) is associated with improvement of pregnancy outcomes in Japan.

Methods: In a multi-institutional retrospective study, we examined pregnant women meeting the criteria for mild GDM (i.e., only one abnormal value [OAV] for 75-g OGTT; fasting glucose ≥100 mg/dL, 1-h postprandial glucose ≥180 mg/dL, and 2-h postprandial glucose ≥150 mg/dL), receiving either routine prenatal care (non-treatment group) or dietary intervention alone or dietary intervention with self-monitoring of blood glucose and/or insulin therapy, if necessary (treatment group). Pregnancy outcomes were compared between these groups.

Results: Data from 893 eligible women were collected from 30 institutions. Participants included 542 untreated and 351 treated women. Although there were no significant differences in baseline clinical characteristics or maternal and perinatal outcomes between these groups, the incidence of large-for-gestational-age (LGA) infants was lower in the treatment group ($P = 0.07$). Multiple logistic regression analysis (MLRA) revealed that pre-pregnancy BMI and gestational weight gain were associated with LGA infants, while 75-g OGTT results were unrelated to LGA. When overweight and obese women were the subjects, the number of LGA infants was significantly lower in the intervention than in the control group, and gestational weight gain was significantly lower in the treatment than in the control group. MLRA showed that intervention was significantly related to a lower incidence of LGA infants.

Conclusions: Our study suggests that maternal BMI impacts fetal growth and that treatment for overweight or obese mothers with OAV is associated with a lower frequency of LGA infants.

1. Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that first occurs or is first identified during pregnancy [1]. New criteria for diagnosing GDM were recently proposed by the International Association of Diabetes in Pregnancy Study Group (IADPSG) [2]. Maternal hyperglycemia correlates with adverse maternal, fetal, and/or neonatal outcomes [3]. The new criteria are based primarily on glucose levels associated with a 1.75-fold increased risk of giving birth to a large-for-gestational-age (LGA) infant in the Hyperglycemia Adverse Pregnancy Outcome (HAPO) study [3]. The frequency of this condition is increasing worldwide. In fact, the new criteria will result in a GDM prevalence of 17.8% [2], doubling the numbers of pregnant women currently diagnosed. LGA infants are well known to be a significant obstetrical complication of GDM [4,5]. The neonatal complications of GDM, including hypoglycemia and hypocalcemia, are due mainly to fetal hyperinsulinemia, which results from maternal hyperglycemia. The long-term complications of GDM are type 2 diabetes development in the mother [6,7] and diabetes and/or obesity in their offspring [8,9].

In 2010, the criteria for diagnosing GDM proposed by the IADPSG were adopted in Japan. The frequency of GDM consequently increased 2–4-fold as compared with the previous criteria [10], i.e., meeting at least two of three threshold values from a 75-g oral glucose tolerance test (OGTT); fasting glucose ≥100 mg/dL, 1-h postprandial glucose ≥180 mg/dL, and 2-h postprandial glucose ≥150 mg/dL, as proposed by the Japan Society of Obstetrics and Gynecology (JSOG) [11]. These criteria are similar to those proposed by the IADPSG (meeting at least two of three threshold values from a 75-g OGTT; fasting plasma glucose ≥92 mg/dL, 1-h plasma glucose ≥180 mg/dL, and 2-h plasma glucose ≥153 mg/dL) [10] and the American Diabetes Association (meeting at least two of three threshold values from a 75-g OGTT; fasting plasma glucose ≥95 mg/dL, 1-h plasma glucose ≥180 mg/dL, and 2-h plasma glucose ≥155 mg/dL) [12]. Among women with newly diagnosed GDM, most had only one abnormal value (OAV) based on the JSOG criteria [our unpublished data, under submission]. A multi-institutional retrospective review was thus performed by the Japan GDM Study Group (JGSG) to assess whether the treatment of mild GDM, i.e., one abnormal OGTT value, improves pregnancy outcomes in Japan.

2. Materials and methods

2.1. Study design

The present retrospective study was conducted in 30 general hospitals in Japan from 2005 to 2010. The protocol was approved by the ethics committee at each of the 30 collaborating centers. All women with a singleton pregnancy and no prior diagnosis of diabetes mellitus were included. Women with multi-fetal gestations, pre-gestational diabetes, previous treatment for gestational diabetes or an active chronic systemic disease other than chronic hypertension, and those with the second of two pregnancies in the same year

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

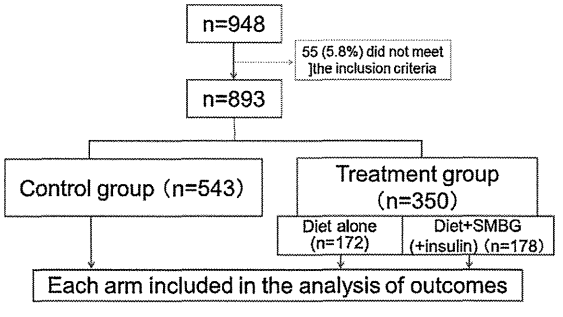

Fig. 1 – Enrollment, assignment, and follow-up of study participants.

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.

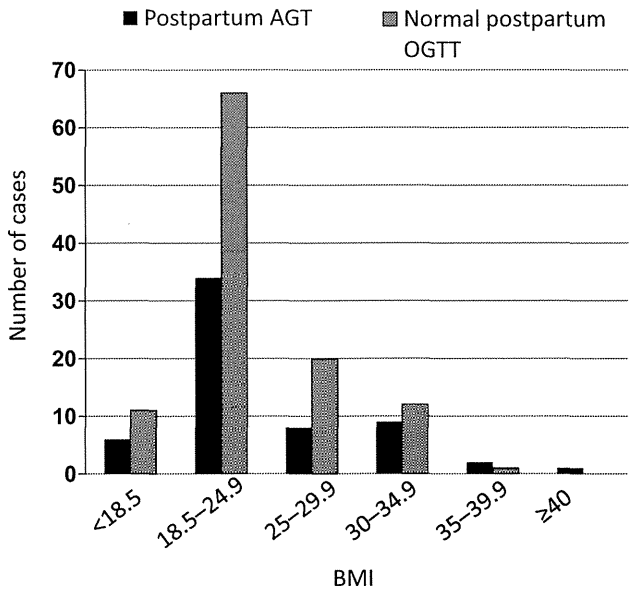

Fig. 1. Pre-pregnancy BMI among women with GDM. Abbreviations: AGT, abnormal glucose tolerance; OGTT, oral glucose tolerance test; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

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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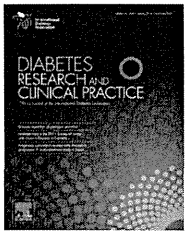

Comparison of pregnancy outcomes between women with gestational diabetes and overt diabetes first diagnosed in pregnancy: A retrospective multi-institutional study in Japan

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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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Keywords:
Gestational diabetes mellitus
Pregnancy outcome
LGA

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

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.

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.

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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