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


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
Keywords: Gestational diabetes mellitus  
Pregnancy outcome  
LGA

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 non-pregnant 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; and other maternal complications such as retinopathy and polyhydramnios.
(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 24 weeks 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 ODM 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>
<thead>
<tr>
<th>Table 1 - Baseline characteristics.</th>
<th>GDM (n = 1267)</th>
<th>ODM (n = 348)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>33.6 ± 4.8</td>
<td>33.1 ± 5.3</td>
</tr>
<tr>
<td>Nullipara – no. (%)</td>
<td>598 (47.2)</td>
<td>183 (52.7)</td>
</tr>
<tr>
<td>Pregestational BMI</td>
<td>24.9 ± 5.7</td>
<td>26.2 ± 6.1*</td>
</tr>
<tr>
<td>Gestational weight gain (kg)</td>
<td>6.4 ± 5.4</td>
<td>5.8 ± 5.6</td>
</tr>
<tr>
<td>Gestational age at diagnosis (wk)</td>
<td>23.5 ± 8.2</td>
<td>22.0 ± 9.0*</td>
</tr>
<tr>
<td>Glucose levels of 75 g-OGTT (mg/dl)</td>
<td>90.5 ± 11.8</td>
<td>114.5 ± 32.2*</td>
</tr>
<tr>
<td>Fasting</td>
<td>200.8 ± 32.1</td>
<td>237.2 ± 47.1*</td>
</tr>
<tr>
<td>1-h</td>
<td>177.7 ± 34.2</td>
<td>227.6 ± 43.5*</td>
</tr>
<tr>
<td>2-h</td>
<td>5.8 ± 0.5</td>
<td>6.8 ± 1.1*</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>432 (34.1)</td>
<td>298 (85.6)*</td>
</tr>
</tbody>
</table>

ODM, overt diabetes in pregnancy; HbA1c (NGSP) *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 as 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.

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.

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

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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