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Pregnancy outcomes of gestational diabetes mellitus according to pre-gestational BMI in a retrospective multi-institutional study in Japan

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Abstract. The aim of this study was to determine the effects of pre-gestational body mass index on pregnancy outcomes of women with gestational diabetes in Japan. A multi-institutional retrospective study was performed. We examined pregnant women who met the former criteria for gestational diabetes in Japan, receiving dietary intervention with self-monitoring of blood glucose with or without insulin therapy. Women with gestational diabetes were divided into three groups according to pre-gestational body mass index: body mass index <25 (control group), $25 \leq$ body mass index <30 (overweight group), body mass index ≥ 30 (obese group). Data from a total of 1,758 eligible women were collected from 40 institutions. Participants included 960 controls, 426 overweight women, and 372 obese women with gestational diabetes. Gestational weight gain was highest in the control and lowest in the obese group. The prevalences of chronic hypertension and pregnancy induced hypertension were higher in the overweight and obese groups than in the control group. Multiple logistic regression analysis revealed pre-gestational body mass index, gestational weight gain, chronic hypertension, and nulliparity to be associated with the onset of pregnancy induced hypertension, while the 75-g OGTT results were unrelated to pregnancy induced hypertension. The prevalence of large-for-gestational age was lower in infants born to obese women than in those born to overweight or control women. The present results suggest that medical interventions for obese women with gestational diabetes may contribute to reducing the prevalence of large-for-gestational age but would not achieve marked reductions in maternal complications.

Key words: Gestational diabetes mellitus, Pregnancy outcome, Body mass index

GESTATIONAL DIABETES MELLITUS (GDM) is defined as glucose intolerance that first occurs or is

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first identified during pregnancy [1]. GDM has been recognized as being associated with not only maternal complications including pregnancy induced hypertension (PIH) and cesarean section, but also neonatal complications such as macrosomia, hypoglycemia, jaundice, and respiratory distress syndrome (RDS) [2-3]. Most notably, large-for-gestational age (LGA) infants are well known to be a significant obstetrical compli-

cation of GDM [4-5] and mean glucose concentration is strongly associated with neonatal birth weight in women with GDM [6].

The Hyperglycemia Adverse Pregnancy Outcome (HAPO) study showed the maternal hyperglycemia level to definitely correlate with adverse maternal, fetal, and/or neonatal outcomes [2]. On the other hand, sub-analyses of HAPO study showed that the combination of GDM and obesity showed substantially higher odds ratio compared with those for either GDM or obesity alone, suggesting that both maternal overweight and obesity are independently associated with adverse pregnancy outcomes [7]. Also, Blanc *et al.* reported that prepregnancy overweight and obesity account for a high proportion of LGA, even in the absence of GDM [8].

We hypothesized that overweight or obese GDM women should be at high risk of adverse pregnancy outcomes, however, appropriate pregnancy management of these women is anticipated to decrease somewhat the degrees of maternal and/or neonatal morbidity. Therefore, a multi-institutional retrospective review was performed by the Japan Diabetes and Pregnancy Study (JDPS) Group to assess whether the maternal pre-gestational body mass index (BMI) affects pregnancy outcomes of Japanese women with GDM.

Materials and Methods

Study design

The present retrospective study was conducted using data from 40 general hospitals in Japan for the period from 2003 through 2009. The protocol was approved by the ethics committee at each of the 40 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, previously treated for gestational diabetes or active chronic systemic disease other than chronic hypertension, and those with the second of two pregnancies in the same year were excluded. Each woman underwent a universal two-step screening process for GDM: a casual glucose test or 50-g glucose challenge test (GCT) between 24 and 30 weeks of gestation. Then, women who had random plasma glucose measurements ≥ 100 mg/dL or plasma glucose of GCT ≥ 140 mg/dL were scheduled for a diagnostic, 75 g, 2-h oral glucose tolerance test (OGTT) after an overnight fast. JSOG criteria were applied (fasting, 100 mg/dL: 1 h, 180 mg/dL; 2 h, 150 mg/dL) [9]. GDM was defined

as present when at least two plasma glucose measurements were the same as or higher than the cut-off points. Overweight or obese women are recommended to undergo a 75-g OGTT at any time in gestation. Underweight, overweight, and obese were defined as a BMI of less than 18.5 kg/m², between 25 and 29 kg/m², and 30 kg/m² or more, respectively. Underweight women were categorized as normal weight for the purposes of these analyses.

Data collected included maternal age, parity, pre-pregnancy BMI, chronic 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. Pre-gestational weight was self-reported at the first prenatal visit. Gestational age was defined as the 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 $\geq 140/90$ mm Hg before 20 weeks of pregnancy. Macrosomia was defined as a birth weight at or above 4,000 g. LGA was defined as sex- and parity-specific birth weight for gestational age being above the 90th percentile of Japanese fetal growth curves [10]. Also, small-for-gestational age (SGA) was defined as sex- and parity-specific birth weight for gestational age being below the 10th percentile of Japanese fetal growth curves [10]. Major congenital malformations were defined as those causing significant functional impairment, requiring surgery or being life-threatening.

In all institutes, women with GDM received dietary management with self-monitoring of blood glucose (SMBG) and, if needed, insulin therapy. Dietary therapy was based on a woman's pre-pregnancy BMI, and dietary intake and gestational weight gain guidance were provided as necessary. The JSOG recommends that 250 kcal is added as an additional energy intake during pregnancy to 30 kcal/kg for ideal body weight at non-pregnancy in non-obese subjects [11]. Ideal body weight is defined by the data of the Japan Ministry of Health, Labour, and Welfare's [12]. In the case of obese GDM women, an additional calorie intake during pregnancy was not prescribed. Also, these women received guidance on how to determine SMBG levels 4 to 6 times a day. In this study, if targeted glucose lev-

els (i.e., preprandial glucose levels of less than 100 mg/dL and levels 2 hours postprandially that were less than 120 mg/dL) were not achieved, insulin therapy was initiated.

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, RDS, and admission to the neonatal intensive care unit.

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

Maternal outcomes included weight gain from the time of enrollment until delivery, PIH including gestational hypertension and preeclampsia, cesarean delivery, and labor induction. Gestational hypertension was defined as a systolic pressure of 140 mm Hg or more and/or a diastolic pressure of 90 mm Hg or more on two occasions at least 4 hours apart. Preeclampsia 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.

HbA1c values were defined by the National Glycohemoglobin Standardization Program (NGSP)

standards [13].

Statistical analyses

Baseline characteristics and laboratory measurements are presented as means \pm SD, as either medians or percentages. Univariate tests for differences in values between any two groups were performed employing the chi-square test. Also, Tukey-Kramer test was used to compare continuous variables. Multiple logistic regression analysis (MLRA) was performed to explore variables contributing to differentiation of 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).

Results

From 2003 through 2009, we retrospectively collected 1,806 GDM subjects from 40 institutions in Japan. One thousand, seven hundred and fifty eight women with GDM were studied. These women were divided into three groups based on their BMI: the normal group (< 25, *n* = 960), the overweight group (25-30, *n* = 426), and the obese group (\geq 30, *n* = 372).

The 1,758 women received diet therapy and SMBG with or without insulin therapy after the diagnosis of GDM. The baseline characteristics of women with GDM in this retrospective study are shown in Table 1. Maternal age in the obese group was younger than that in the normal and overweight groups. Gestational weight gain was highest in the control, followed by the overweight group and lowest in the obese group.

Table 1 Baseline characteristics

	Body mass index		
	< 25 (<i>n</i> = 960)	25-30 (<i>n</i> = 426)	\geq 30 (<i>n</i> = 372)
Age (yrs)	33.5 \pm 4.9	33.9 \pm 5.0	32.9 \pm 4.9* [†]
Nulliparity – <i>n</i> (%)	471 (49.1)	190 (44.6)	179 (48.2)
Pre-gestational body mass index (kg/m ²)	21.1 \pm 2.2	27.3 \pm 1.4*	34.4 \pm 3.7* [†]
Gestational weight gain (kg)	7.9 \pm 4.3	5.6 \pm 5.4*	2.8 \pm 6.3* [†]
Gestational age at diagnosis (wks)	24.3 \pm 8.0	22.5 \pm 8.3*	20.6 \pm 8.8* [†]
Glucose levels on 75-g OGTT (mg/dL)			
Fasting	91.5 \pm 18.7	98.3 \pm 21.4*	104.5 \pm 21.9* [†]
1-h	200.8 \pm 32.1	209.9 \pm 37.4*	212.6 \pm 33.7*
2-h	177.7 \pm 34.2	182.2 \pm 41.1	176.0 \pm 35.9 [†]

Data are mean \pm SD or *n*. *, *P* < 0.05 vs. BMI <25; [†], *P* < 0.05 vs. BMI 25-30

Table 2 Maternal complications

	Body mass index		
	< 25 (n = 960)	25-30 (n = 426)	≥ 30 (n = 372)
Chronic hypertension – n (%)	15 (1.6)	34 (8.0)*	43 (11.6)*
Pregnancy induced hypertension - n (%)	14 (1.5)	46 (10.8)*	55 (14.8)*
Cesarean section – n (%)	269 (28.1)	167 (39.2)*	172 (46.2)*†
Primary cesarean section – n (%)	95 (9.9)	93 (21.8)*	109 (29.3)*†
Induction of labor – n (%)	210 (21.9)	103 (24.2)	113 (30.4)*†

*, $P < 0.05$ vs. BMI <25; †, $P < 0.05$ vs. BMI 25-30

Table 3 Risk factors for pregnancy induced hypertension

Variables	β	SE (β)	z	P	Odds Ratio	95% CI
Pre-gestational BMI	0.11	0.02	6.39	< 0.001	1.12	1.08-1.15
Gestational weight gain	0.08	0.02	4.21	< 0.001	1.08	1.04-1.12
75-g OGTT 1-h	0.93	0.60	1.56	0.118		
Chronic hypertension	1.65	0.29	5.76	< 0.001	5.20	3.00-9.10
Nulliparity	0.72	0.21	3.39	< 0.001	2.06	1.36-3.12
Age at delivery	0.03	0.02	1.4	0.146	1.03	0.90-1.07

AIC = 742.22176, AUC = 0.76648

Table 4 Risk factors for primary cesarean section

Variables	β	SE (β)	z	P	Odds Ratio	95% CI
Age at delivery	0.06	0.01	5.63	<0.001	1.06	1.04-1.09
Pre-gestational BMI	0.06	0.01	6.36	< 0.001	1.06	1.04-1.09
Gestational weight gain	0.03	0.20	4.20	0.001	1.03	1.01-1.06
PIH	0.82	0.20	4.20	<0.001	2.28	1.56-3.34
Chronic hypertension	0.51	0.23	2.19	0.029	1.67	1.06-2.65

AIC = 2155.56897, AUC = 0.65143

Gestational age at diagnosis of GDM was slightly earlier in the obese group than in the overweight group and was latest in the control group. Fasting plasma glucose levels on 75-g OGTT were lowest in the control, somewhat higher in the overweight and highest in the obese group. Glucose levels 1 hour after 75-g OGTT were higher in the overweight and obese groups than in the control group. Glucose levels 2 hours after 75-g OGTT were higher in the obese group than in the control and overweight groups.

Maternal complications are shown in Table 2. The prevalences of chronic hypertension were higher in the overweight and obese groups than in the control group. Similarly, the prevalences of PIH were significantly higher in the overweight and obese groups than in the control group. The primary cesarean sec-

tion rate was highest in the obese women. Induction of labor was very common in the obese group. Table 3 shows the risk factors for PIH identified by MLRA. Pre-gestational BMI, gestational weight gain, chronic hypertension, and nulliparity were found to be associated with the onset of PIH. Also, Pre-gestational BMI, gestational weight gain, PIH, and chronic hypertension were found to be associated with primary cesarean section (Table 4).

Neonatal complications in the present study are shown in Table 5. Gestational ages at delivery and birth weights did not differ significantly among the three groups. The prevalence of SGA did not differ among the three groups. The prevalence of LGA was significantly lower in infants born to obese women than to overweight or normal weight women. Other neonatal

Table 5 Neonatal complications

	Body mass index		
	< 25 (n = 960)	25-30 (n = 426)	≥ 30 (n = 372)
Gestational age at delivery (wks)	38.1±2.0	37.9±2.4	37.8±2.6
Birth weight (g)	2988.9 ±637.9	2975.2±603.2	2909.1±597.6
Small-for gestational age – n (%)	160 (16.7)	73 (17.1)	58 (16.0)
Large-for-gestational age – n (%)	216 (22.5)	101 (23.7)	57 (15.3)*†
Macrosomia – n (%)	31(3.2)	10 (2.3)	5 (1.3)
Shoulder dystocia – n (%)	68 (7.1)	24 (5.6)	31 (8.3)
Congenital malformations – n (%)	59 (6.1)	17 (4.1)	20 (5.3)
Respiratory distress syndrome – n (%)	119 (12.4)	38 (9.0)	39 (10.4)
Hypoglycemia – n (%)	121 (12.6)	61 (14.4)	45 (12.2)
Jaundice – n (%)	151 (15.7)	58 (13.6)	49 (13.3)
Neonatal intensive care unit – n (%)	357 (37.2)	150 (35.2)	120 (32.3)

*, $P < 0.05$ vs. BMI <25; †, $P < 0.05$ vs. BMI 25-30

complications such as congenital malformations, RDS, hypoglycemia, and jaundice showed no significant differences among the three groups.

Discussion

This is the first large-scale study of pregnancy outcomes of women with GDM according to pre-gestational BMI in Japan. Our results revealed the prevalences of baseline features of GDM according to pre-gestational BMI, as well as maternal and neonatal complications. Thus, we focus mainly on these points in the following discussion.

Characteristics of women with GDM

In the present study, plasma glucose levels on 75-g OGTT showed a gradual increase according to pre-gestational BMI. This trend is consistent with observations in previous reports. For instance, Black *et al.* reported that glucose levels on 75-g OGTT gradually increased according to pre-gestational BMI [8].

In this study, gestational age at diagnosis was earlier in overweight and obese women. This result is likely attributable to the recommendation that 75-g OGTT is performed at any time a pregnant woman is found to be overweight or obese in Japan [14]. On the other hand, gestational weight gain was decreased according to pre-gestational BMI, suggesting that diet therapy intervention ameliorated excessive weight gain during pregnancy. As the strategies for managing women with GDM were similar among the institutes participating in this study, the present results suggest diet ther-

apy to effectively reduce maternal weight gain during pregnancy. Langer *et al.* also showed that gestational weight gain was decreased according to pre-gestational BMI [15]. There are no available data for ideal body weight gain in women with GDM. The Japan Ministry of Health, Labour, and Welfare's recommended nutritional requirements do not list restrictions dependent on a pregnant woman's physique. In the nutritional guidelines for pregnancy in the "Healthy Family 21" of the Ministry of Health, Labour, and Welfare, weight gain is basically about 5 kg in women with a BMI of 25 or higher, with individual consideration to be given [16]. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), a randomized trial of treatment for GDM, concluded that treatment reduces serious perinatal complications with significant reduction of maternal weight gain during pregnancy [17]. In that trial, intervention included individualized dietary advice from a registered dietitian. Researchers considered a woman's pre-gestational body weight, dietary intake, activity level, and weight gain. In another randomized controlled trial in the United States, the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (NCHD) trial [18], nutritional counseling and diet therapy were provided based on nutritional recommendations made by the American Diabetes Association (ADA). Although the content of dietary counseling in the ACHOIS trial [17] is not clear, another trial by the NCHD trial [18] used the ADA guidelines in their protocol. Briefly, the ADA recommends nutritional counseling, if possible by a registered dietitian, with indi-

vidualization of a nutrition plan based on height and weight [19].

Therefore, the protocol of diet therapy for women with GDM in Japan is not so different from the protocol of other countries.

Maternal and neonatal complications

Maternal complications including the prevalences of chronic hypertension, PIH, primary cesarean section, and induction of labor were higher in overweight or obese women with GDM than in normal weight women with GDM. The MLRA revealed pre-gestational BMI, gestational weight gain, chronic hypertension, and nulliparity to be associated with the onset of PIH, while the 75-g OGTT results were unrelated to PIH. Also, the MLRA revealed that pre-gestational BMI, gestational weight gain, PIH, and chronic hypertension were associated with primary cesarean section. These results suggest maternal complications to be more closely associated with maternal pre-gestational BMI than with blood glucose levels. Catalano *et al.* also showed both maternal GDM and obesity to be independently associated with adverse pregnancy outcomes [7].

On the other hand, it is noteworthy that the only significant difference identified was in the prevalence of LGA, a neonatal complication. The prevalence of LGA in the obese group was the lowest among the three groups and the prevalences of LGA were similar in the normal weight and overweight groups, suggesting intervention for women with GDM to be effective. Langer *et al.* also reported that obese and overweight GDM patients achieving targeted levels of glucose control with insulin therapy showed no increased risk for LGA and macrosomia [15]. As the prevalences of SGA were similar among the three groups in the present study, glycemic control was apparently not excessively strict. Because mean glucose levels less than 87 mg/dL indicate strict control, the prevalence of SGA is reported to be increased [5]. Ben-Haroush *et al.* reported that both the severity of GDM and maternal weight are independent predictors of infant birth weight [20]. Most *et al.* reported that different thresholds used for different maternal BMI categories in addition to the achievement of glycemic control and pharmacological therapy will enhance pregnancy outcomes [21]. As the MLRA showed that gestational weight gain was not associated with LGA in the present study (data not shown), improvement of maternal lipid metabolism through

reduction of excessive gestational weight gain during pregnancy might reduce excessive fetal growth. Taken together from these findings, glycemic control under control of gestational weight gain by diet therapy may be effective for obese women with GDM.

The present study has limitations that must be taken into account when interpreting the data. First, as there are no data from women with normal glucose tolerance in this study, we cannot compare real pregnancy outcomes between women with normal glucose tolerance and those with GDM. Second, we cannot ascertain whether glycemic control for GDM in each group was appropriate or whether glycemic control was similar in the third trimester of gestation. Also, the subjects were recruited based on the previous JSOG criteria for GDM, such that we cannot compare our GDM groups with subjects studied using the IADPSG criteria. Furthermore, as gestational age at diagnosis of GDM is earlier in the obese group compared with the overweight group, duration of treatments were longer in the obese group than those in the overweight group. Therefore, we should consider the possibility that the intervention could vary by obesity status.

In summary, in the current study we found that medical interventions such as diet therapy and SMBG with or without insulin therapy for obese GDM women may contribute to reducing the prevalence of LGA but do not markedly reduce maternal complications. Prevention of LGA is important because these infants are at risk for metabolic syndrome in later life [22-23]. Therefore, the essential strategy for preventing GDM and LGA should include an appropriate diet prior to conception. Further study focusing on such a pre-conception program for overweight and obese women is required. Also, further study on the effects of ketone body by diet therapy for obese women with GDM on offspring in later life.

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Conflict of Interests

None of the authors have any potential conflicts of interest associated with this study.

Appendix

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

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