Comparison of pregnancy outcomes between women with early-onset and late-onset gestational diabetes in a retrospective multi-institutional study in Japan

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INTRODUCTION
Gestational diabetes mellitus (GDM) is known as glucose intolerance that first develops or is found during pregnancy; however, the gestational age at diagnosis of GDM is not always reported1.

Recently, the prevalence of obesity and type 2 diabetes mellitus among childbearing women has increased significantly, because some women are diagnosed with pre-existing diabetes at their first visit to a hospital or clinic. These changes have led the American Diabetes Association to redefine GDM to include only glucose intolerance diagnosed in the second or third trimester of gestation. This definition excludes women with pre-existing diabetes or those diagnosed before the second trimester2.

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Gestational diabetes mellitus can lead to maternal complications, such as hypertensive disorders of pregnancy (HDP) and cesarean delivery, as well as infant complications, such as large-for-gestational-age (LGA) infants, macrosomia, respiratory distress syndrome, neonatal hypoglycemia and neonatal jaundice. LGA infants often experience perinatal complications of GDM, and the mean glucose concentration of a mother with GDM has a strong impact on birthweight. The Hyperglycemia Adverse Pregnancy Outcome study has shown that the level of maternal hyperglycemia is correlated with adverse maternal and perinatal outcomes. On the basis of the Hyperglycemia Adverse Pregnancy Outcome study, new criteria for the GDM diagnosis were proposed by the International Association of Diabetes in Adverse Pregnancy Outcome study, and protocol. Other studies based on clinical questions have been published previously using the same database as that used in the Japan Diabetes and Pregnancy Study. All pregnant women participating in the present study underwent a universal two-step screening process for diagnosis of GDM both in early and late pregnancy. This test included a random glucose test in early pregnancy and a random glucose test or a 50-g glucose challenge test between 24 and 32 weeks of gestation, respectively. Those with a random glucose test result \( \geq 100 \text{ mg/dL} \) or glucose challenge test result \( \geq 140 \text{ mg/dL} \) required a diagnostic test for GDM; that is, 75-g OGTT. On the basis of the former Japan Society of Obstetrics and Gynecology (JSOG) criteria, women meeting more than two of the following OGTT cut-off points were considered to have GDM: fasting 100 mg/dL; 1 h 180 mg/dL; and 2 h 150 mg/dL. The database of clinical background characteristics included parity, maternal age, pre-pregnancy body mass index (BMI), gestational weight gain, gestational age at delivery, delivery mode including vaginal delivery or cesarean section, and infant parameters including infant sex, birth weight, Apgar score (1 and 5 min after birth), perinatal mortality and congenital malformations. In terms of maternal pregnancy complications, HDP, including pre-eclampsia, gestational hypertension and chronic hypertension, were examined. Pre-pregnancy body weight was determined based on self-reporting at the first prenatal visit. Gestational age was determined based on the last menstrual period or measurement of crown–rump length using ultrasound in early pregnancy. Gestational hypertension was defined as sustained blood pressure readings of \( \geq 140/90 \text{ mmHg} \) during pregnancy after 20 weeks of gestation after a previously normotensive status without the feature of pre-eclampsia, which normalized by 12 weeks postpartum. Pre-eclampsia was defined as a condition of hypertension accompanied by at least one of the complications as shown, following new onset after 20 weeks of gestation, with all symptoms normalizing by 12 weeks postpartum: proteinuria; other maternal organ dysfunctions, such as liver involvement without any underlying chronic diseases, progressive kidney dysfunction, stroke and neurological complications; hematological complications; and uteroplacental dysfunction. Chronic hypertension was defined as a condition of hypertension diagnosed before pregnancy or before 20 weeks of gestation without features of superimposed pre-eclampsia. Macrosomia was defined as a birthweight of \( \geq 4,000 \text{ g} \). LGA infants were defined as those with a birthweight within or above the 90th percentile of the birthweight of Japanese infants. Small-for-gestational-age infants were defined as those
with a birthweight less than the 10th percentile of the birthweight of Japanese infants\textsuperscript{13}. Congenital malformations were defined as having a morphological abnormality with functional impairment. For instance, congenital malformations included congenital heart diseases, such as atrial septal defect and ventricular septal defect, neural tube defects including spina bifida with or without meningocoele, and atresia of the upper digestive tract.

Women with GDM received guidance regarding self-monitoring of blood glucose levels three to six times a day from a licensed nurse. Dietary counseling was provided for each woman with GDM. Briefly, a registered dietician examined the daily dietary intake of women with GDM using the recollection method and instructed women on the appropriate gestational weight gain on the basis of their pre-pregnancy BMI. The JSOG recommends an additional 200 kcal per day for non-obese women during pregnancy in addition to 30 kcal/kg of non-pregnant ideal bodyweight\textsuperscript{14}. No additional caloric intake was prescribed during pregnancy for overweight and obese women with GDM. Ideal bodyweight was defined by the data of the Japan Ministry of Health, Labor and Welfare\textsuperscript{15}. On the basis of self-monitoring of blood glucose, insulin therapy was started if fasting glucose levels <95 mg/dL and 2-h postprandial levels <120 mg/dL were not achieved.

### Study outcomes

Maternal adverse outcomes included HDP comprising gestational hypertension, pre-eclampsia, chronic hypertension and cesarean section. Neonatal adverse outcomes included neonatal death and complications associated with maternal hyperglycemia, such as delivery of LGA infants, macrosomia, infant hypoglycemia, infant jaundice, respiratory distress syndrome and admission to the neonatal intensive care unit. Blood sampling for neonatal glucose measurement was collected 1 or 2 h after birth. Neonatal hypoglycemia was defined as blood glucose levels <35 mg/dL. Neonatal hyperbilirubinemia was defined as the requirement of phototherapy.

### Statistical analysis

Baseline clinical characteristics and measurements of biomarkers in both the early GDM group and the late GDM group are presented as the mean ± standard deviation and as either medians or percentages. Univariate tests to assess differences between groups were carried out using the \( \chi^2 \)-test. Also, variables with a significant difference between any two groups were then included in multiple logistic regression analysis. \( P \)-values <0.05 (two-tailed) were considered statistically significant. Statistical analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA).

### RESULTS

A total of 1,806 women in 40 institutions were diagnosed with GDM from 2003 through 2009. Of the 1,806 pregnancies, 325 were excluded because of inadequate data, multiple pregnancies or chromosomal abnormalities in infants. In total, 1,481 women with GDM were included in the study. These women were divided into two groups on the basis of gestational age at GDM diagnosis: the early group (<24 weeks; \( n = 600 \)) and the late group (≥24 weeks, \( n = 881 \)).

Table 1 shows the baseline characteristics of the women. Maternal age in the early GDM group was older than in the late GDM group (34.0 ± 4.9 years vs 33.4 ± 4.8 years, \( P = 0.032 \)). The prevalence of nullipara showed no significant differences between groups. Pre-pregnancy BMI was significantly higher in the early group than in the late group (26.2 ± 6.2 vs 24.1 ± 5.2, \( P < 0.001 \)). Gestational weight gain was lower in the early group than in the late group (4.9 ± 5.8 kg vs 7.3 ± 4.8 kg, \( P = 0.032 \)). Gestational age at diagnosis of GDM was different between groups (14.4 ± 4.2 weeks vs 29.6 ± 3.4 weeks, \( P < 0.001 \)). Although gestational age showed no significant difference between groups, birthweight was heavier in the late group than in the early group (2928.2 ± 641.2 g vs 3012.2 ± 640.8 g, \( P = 0.013 \)). Both fasting plasma glucose levels and plasma glucose levels at 1 h after 75-g OGTT were higher in the early group than in the late group (202.4 ± 30.2 mg/dL vs 198.4 ± 26.7 mg/dL, respectively, \( P = 0.005 \)).

Maternal and neonatal complications are shown in Table 2. The prevalence of HDP (9.3% vs 4.8%, \( P < 0.001 \)) and cesarean section (34.2% vs 32.0%, \( P < 0.001 \)) were higher in the early group than in the late group. The prevalence of small-for-gestational-age infants was not significantly different between groups. The prevalence of LGA infants was higher in the late group than in the early group (19.7% vs 24.6%, \( P = 0.025 \)). Other neonatal complications, such as neonatal death, congenital malformation, macrosomia, neonatal hypoglycemia, neonatal

### Table 1 | Clinical characteristics

|                      | Early group (\( n = 600 \)) | Late group (\( n = 881 \)) | \( P \)-value |
|----------------------|-----------------------------|-----------------------------|--------------|
| Maternal age (years) | 34.0 ± 4.9                   | 33.4 ± 4.8                  | 0.032        |
| Nullipara, n (%)     | 421 (47.8%)                  | 459 (52.2%)                 | 0.672        |
| Pre-pregnancy BMI    | 26.2 ± 6.2                   | 24.1 ± 5.2                  | <0.001       |
| Gestational weight gain (kg) | 4.9 ± 5.8                   | 7.3 ± 4.8                  | <0.001       |
| Gestational age at diagnosis (weeks) | 14.4 ± 4.2                   | 29.6 ± 3.4                  | <0.001       |
| Gestational weeks at delivery (weeks) | 38.0 ± 2.2                   | 38.1 ± 2.0                  | 0.267        |
| Birthweight (g)      | 2928.2 ± 641.2               | 3012.2 ± 640.8              | 0.013        |
| Results of 75 g OGTT (mg/dL) |                       |                             |              |
| Fasting PG           | 92.2 ± 12.0                  | 90.8 ± 12.8                 | 0.035        |
| 1-h PG               | 202.4 ± 30.2                 | 198.4 ± 26.7                | 0.005        |
| 2-h PG               | 1750.0 ± 29.4                | 1726.0 ± 26.7               | 0.104        |

Data are expressed as mean (standard deviation) or percentages unless otherwise noted. Large-for-gestational-age was defined as a birthweight greater than the 90th percentile for Japanese infants. BMI, body mass index; OGTT, oral glucose tolerance test; PG, plasma glucose.
Large-for-gestational-age (LGA) was defined as a birthweight greater than the 90th percentile for Japanese infants. HDP, hypertensive disorders of pregnancy; NICU, neonatal intensive care unit; SGA, small-for-gestational-age.

jaundice and admission to the neonatal intensive care unit, showed no significant difference between the two groups.

Table 3 shows the risk factors for HDP described on a cohort identified as having GDM identified by multiple logistic regression analysis. Maternal age at delivery, nulliparity, early group, pre-gestational BMI, gestational weight gain and plasma glucose levels at 2 h after 75-g OGTT were associated with the onset of HDP.

Table 4 shows the associated factors for LGA infants based on a cohort identified as having GDM by multiple logistic regression analysis. Maternal age at delivery, nulliparity, early group, pre-pregnancy BMI, gestational weight gain and plasma glucose levels at 2 h after 75-g OGTT were not associated with LGA infants.

DISCUSSION

The present study showed that women with GDM diagnosed in early pregnancy had a higher prevalence of maternal complications, including HDP and cesarean section, whereas women with GDM diagnosed in late pregnancy had a higher prevalence of LGA infants. These findings might be due to the possibility that earlier initiation of treatment results in a reduction in LGA infants.

The results of the present study are partially in agreement with those of previous reports. For instance, Sweeting et al. reported that despite early diagnostic OGTT and current treatment for GDM, women with GDM diagnosed before 24 weeks of gestation had more adverse pregnancy outcomes, including a higher prevalence of HDP, preterm delivery, cesarean section and neonatal jaundice compared with women with GDM diagnosed after 24 weeks of gestation. However, in their study, women who underwent an OGTT early in pregnancy also had multiple risk factors for GDM. Thus, women diagnosed with GDM before 24 weeks of gestation were at high risk for GDM, unlike participants in the present study who underwent routine screening for GDM.

There is no clear evidence of a reduction in the prevalence of poor pregnancy outcomes with early treatment in women with GDM diagnosed early in pregnancy. In a subanalysis of a multi-institutional randomized trial for a mild degree of GDM, Palatnik et al. reported that earlier intervention for mild GDM was not related to pregnancy outcomes compared with non-intervention. However, in their study, treatment was initiated from 24 weeks of gestation. Therefore, we cannot know the effects of treatment for women with GDM diagnosed before 24 weeks of gestation.

In the present study, the frequency of LGA infants was higher in the late group than in the early group. Notably, duration of treatment in women in the early group was longer than that in the late group. As a result, gestational weight gain in the early group was lower than that in the late group, leading to a higher frequency of LGA in the late group. In addition, although the prevalence of HDP was higher in the early group than the late group, there was no significant difference in the prevalence of LGA infants between the two groups. Therefore, the reason the frequency of LGA infants is lower in the early group than in the late group would not be related to HDP causing small-for-gestational-age infants. The prevalence of LGA infants in the early group was still high (19.7%) compared with the general population. This might have resulted from the
effect of maternal BMI, because maternal BMI is known to be independently associated with birthweight and delivery of LGA infants.\textsuperscript{16,4} In contrast, in the late group, the gestational weeks at diagnosis was almost 30 weeks of gestation. In this case, most of the women with GDM diagnosed in the first half of pregnancy received treatment from 31 or 32 weeks of gestation, suggesting that good glycemic control could not be achieved at 32 weeks of gestation. Lin et al.\textsuperscript{20} and Sameshima et al.\textsuperscript{21} showed that if women with diabetes achieve good glycemic control before 32 weeks of gestation, the number of LGA infants can be reduced\textsuperscript{20,21}. In the present study, there is a possibility that good glycemic control was not achieved until delivery in the late group. Therefore, earlier intervention in the first half of gestation could reduce the prevalence of LGA infants.

The pathophysiological aspect of GDM is also important. It has been reported that both early and late GDM were associated with impairments in β-cell function\textsuperscript{22,23}. Obesity can lead to insulin resistance, which might result in early GDM\textsuperscript{24}. A similar pathophysiological condition might have existed in the current study, as the early group included women with higher BMI compared with the late group. Being overweight (25 \leq \text{pre-gestational BMI} < 30) or obese (pre-gestational BMI \geq 30) has also been known to have additional negative outcomes on pregnancy, such as HDP and cesarean section, as well as perinatal complications, such as delivery of LGA infants\textsuperscript{25}. In the present study, the early group included women with higher BMI, perhaps leading to a higher prevalence of HDP. In fact, the early group and pre-pregnancy BMI were risk factors for HDP in the present study. Therefore, a screening test for GDM early in pregnancy might be an effective tool to identify the high-risk group for HDP. The reason maternal age was associated with LGA infants is unclear. Past reports have not shown a positive association between maternal age and LGA infants in women with GDM. In contrast, pre-gestational BMI and gestational weight gain, which are important risk factors for LGA infants, were not associated with delivery of LGA infants in this study, suggesting that glycemic control at the time of delivery might be different between the two groups. This is one of the limitations of the present study.

Maternal and perinatal adverse outcomes are directly associated with the degree of hyperglycemia\textsuperscript{26}. In this regard, the degree of glucose intolerance was different between women who met the former JSOG criteria for GDM in the present study compared with that in those who met the IADPSG criteria. Women with GDM who meet the IADPSG criteria could have a milder form of GDM compared with women who meet the JSOG criteria used in the present study. In fact, Hagiwara et al.\textsuperscript{27} reported that treatments started after GDM diagnosis in early pregnancy based on IADPSG criteria showed no effectiveness compared with treatments initiated after GDM diagnosis in the latter half of gestation. However, they did not compare the therapeutic method between early in pregnancy and late in pregnancy in the early-onset GDM. Therefore, another limitation of this retrospective study is that their results cannot provide the effectiveness of treatment for the early group. In contrast, Alumni et al.\textsuperscript{28} showed that women with GDM diagnosed early in pregnancy on the basis of the IADPSG criteria require pharmacotherapy more frequently than those diagnosed later in pregnancy, implying a more severe form of hyperglycemia. These results are not in agreement. The present results also cannot provide evidence of usefulness of early intervention for the early GDM group. Therefore, prospective, randomized, controlled trials are necessary to delineate which women require intervention in early pregnancy.

Some limitations must be considered in interpreting the data in the present study. First, we could not compare pregnancy outcomes between women with GDM and women with normal glucose tolerance, because we only included women with GDM. Second, we could not ascertain whether glycemic control for GDM in the two groups was appropriate or similar at the time of delivery. Therefore, we could not assess the exact effect of glycemic control on the incidence of LGA infants. Also, as the participants were recruited on the basis of the former JSOG criteria for GDM, we did not compare real pregnancy outcomes between women with GDM based on the previous JSOG criteria and women with GDM based on the IADPSG criteria.

In summary, in the present study, maternal complications, such as HDP and cesarean section, were associated with early GDM. The use of self-monitoring of blood glucose, dietary counseling and insulin therapy could possibly reduce the incidence of LGA infants. A reduction in the number of LGA infants is particularly important, because LGA not only places the infants at a high risk for perinatal complications, but also might contribute to metabolic syndrome later in life. Further studies focusing on weight control before conception, dietary counseling in terms of specific nutrients and recommendations regarding diet for LGA infants are required. In addition, randomized controlled trials on the treatment of early-onset GDM are required to ascertain the effectiveness of such treatment.

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DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012; 35(Suppl. 1): S64–S71.
2. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes – 2018. Diabetes Care 2018; 41(Suppl1): S13–S27.
3. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008; 358: 1991–2002.
4. Catalano PM, McIntyre HD, Cruickshank JK, et al. The hyperglycemia and adverse pregnancy outcome study: association of GDM and obesity with pregnancy outcomes. *Diabetes Care* 2012; 35: 780–786.

5. Blank A, Grave G, Metzger BE. Effects of gestational diabetes on perinatal morbidity reassessed: report of the International Workshop on Adverse Perinatal Outcomes of Gestational Diabetes Mellitus, December 3–4, 1992. *Diabetes Care* 1995; 18: 127–129.

6. Langer O, Yogev Y, Most O, et al. Gestational diabetes: the consequences of not treating. *Am J Obstet Gynecol* 2005; 192: 989–997.

7. Langer O, Levy J, Brustman L, et al. Glycemic control in gestational diabetes—how tight is tight enough: small for gestational age versus large for gestational age? *Am J Obstet Gynecol* 1989; 61: 646–653.

8. Metzger BE, Gabbe SG, Persson B, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; 33: 676–682.

9. Sugiyama T, Metoki H, Sato H, et al. Comparison of pregnancy outcomes between women with gestational diabetes and overt diabetes in a retrospective multi-institutional study in Japan. *Diabetes Res Clin Pract* 2014; 103: 20–25.

10. Sugiyama T, Nagao K, Metoki H, et al. Pregnancy outcomes of gestational diabetes mellitus according to pre-gestational BMI in a retrospective multi-institutional study in Japan. *Endocr J* 2014; 61: 373–380.

11. Sato T, Sugiyama T, Nagase S, et al. Pregnancy outcomes in women with type 1 and type 2 diabetes mellitus in a retrospective multi-institutional study in Japan. *Endocr J* 2014; 61: 759–764.

12. Kuzuya T, Nakagawa S, Satoh J, et al. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *Diabetes Res Clin Pract* 2002; 55: 65–85.

13. Itabashi K, Fujimura M, Kusuda S, et al. New normative birthweight among Japanese infants according to gestational week at delivery. *Acta Paediatr Jpn* 2010; 114: 1271–1293. (Japanese).

14. Minakami H, Maea T, Fuji T, et al. Guidelines for obstetrical practice in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2014 edition. *J Obstet Gynaecol Res* 2014; 40: 1469–1499.

15. National Institute of Health and Nutrition. Summary report from the Scientific Committee of “Dietary reference intakes for Japanese”. Ministry of Health, Labour and Welfare, 2015.

16. Sweeting AN, Ross GP, Hyett J, et al. Gestational diabetes mellitus in early pregnancy: evidence for poor pregnancy outcomes despite treatment. *Diabetes Care* 2016; 39: 75–81.

17. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009; 361: 1339–1348.

18. Palatnik A, Mele L, Landon MB, et al. Timing of treatment initiation for mild gestational diabetes mellitus and perinatal outcomes. *Am J Obstet Gynecol* 2015; 213: e1–e8.

19. Black MH, Sacks DA, Xiang AH, et al. The relative contribution of prepregnancy overweight and obesity, gestational weight gain, and IADPSG-defined gestational diabetes mellitus to fetal overgrowth. *Diabetes Care* 2013; 36: 56–62.

20. Lin CC, River J, River P, et al. Good diabetic control early in pregnancy and favorable fetal outcome. *Obstet Gynecol* 1986; 67: 51–56.

21. Sameshima H, Kamitomo M, Kajya S, et al. Early glycem control reduces LGA infants in 250 Japanese gestational diabetes pregnancies. *Am J Perinatol* 2000; 17: 371–376.

22. Ryan EA, Imes S, Liu D, et al. Defects in insulin secretion and action in women with a history of gestational diabetes. *Diabetes* 1995; 44: 506–512.

23. Buchanan TA. Pancreatic B-cell defects in gestational diabetes: implications for the pathogenesis and prevention of type 2 diabetes. *J Clin Endocrinol Metab* 2001; 86: 989–993.

24. Bozkurt L, Göbl CS, Pfli gl L, et al. Pathophysiologica characteristics and effects of obesity in women with early and late manifestation of gestational diabetes diagnosed by the International Association of Diabetes and Pregnancy Study Groups criteria. *J Clin Endocrinol Metab* 2015; 100: 1113–1120.

25. Marchi J, Berg M, Dencker A, et al. Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. *Obes Rev* 2015; 16: 621–638.

26. Ehrlich SF, Crites YM, Hedderson MM, et al. The risk of large for gestational age across increasing categories of pregnancy glycemia. *Am J Obstet Gynecol* 2011; 204: e1–e6.

27. Hagiwara Y, Kasa j I, Nakanishi S, et al. Should the IADPSG criteria be applied when diagnosing early-onset gestational diabetes? *Diabetes Res Clin Pract* 2018; 140: 154–161.

28. Alunni ML, Roeder HA, Moore TR, et al. First trimester gestational diabetes screening – change in incidence and pharmacotherapy need. *Diabetes Res Clin Pract* 2015; 109: 135–140.

**APPENDIX**

The contributors of the Japan Diabetes and Pregnancy Study Group include Hirosaki University Graduate School of Medicine; Nishisaitama-Chuo National Hospital; Asahi General Hospital; NTT East Hospital; Keio University School of Medicine; Tokyo Medical and Dental University; Tokyo Women’s University School of Medicine; Tokyo Medical School of Medicine Hachioji Medical Center; National Center for Child Health and Development; Saiseikai Yokohamashi Tobu Hospital; St. Marianna University School of Medicine; Yokohama City University Medical Center; Toyama University Graduate School.
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