Glycemic and metabolic features in gestational diabetes: singleton versus twin pregnancies

Yohei Akiba1), Kei Miyakoshi1), Satoru Ikenoue1), Yoshifumi Saisho3), Yoshifumi Kasuga1), Daigo Ochiai1), Tadashi Matsumoto1) and Mamoru Tanaka1)

1) Department of Obstetrics and Gynecology, Keio University School of Medicine, Tokyo, Japan
2) Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Abstract. A number of data on gestational diabetes mellitus (GDM) in singleton pregnancy is available, however, little is known about the glycemic characteristics of twin pregnancy with GDM. The aim of this study was to compare the severity of dysglycemia between twin and singleton pregnancies with GDM (T-GDM and S-GDM). We retrospectively analyzed pregnancies with GDM defined by the Japan Diabetes Society criteria (T-GDM, n = 20; S-GDM, n = 451) in our hospital. During the study period, women with GDM underwent self-monitoring of blood glucose measurements as well as dietary management. Insulin treatment was initiated when dietary treatment did not achieve the glycemic goal. The glycemic and metabolic characteristics were compared between T-GDM and S-GDM, as follows: gestational week at the diagnosis of GDM, 75 g oral glucose tolerance test (OGTT) results, HbA1c, insulin secretion (i.e. insulinogenic index [IGI] and Insulin Secretion-Sensitivity Index-2 [ISSI-2]), and insulin requirement before delivery. The rate of one abnormal OGTT value in T-GDM was similar to that in S-GDM (60% vs. 71%). There were no significant differences in gestational week and levels of HbA1c at diagnosis, levels of IGI and ISSI-2 between T-GDM and S-GDM (median, 20 weeks vs. 17 weeks, 5.0% vs. 5.2%, 0.58 vs. 0.71, 1.7 vs. 1.8, respectively). The rate of insulin treatment and a median dosage of insulin needed before delivery was comparable between the two groups (T-GDM vs. S-GDM: 45% vs. 32% and 14 vs. 13 unit/day). Our data suggested that the severity of dysglycemia in T-GDM was similar to that in S-GDM during pregnancy.

Key words: Gestational diabetes mellitus, Twin pregnancy, Severity of dysglycemia

THE GLYCEMIC CONTROL plays an important role in the improvement of perinatal outcomes in gestational diabetes mellitus (GDM). Since twin pregnancies showed higher levels of human placental hormones (i.e. lactogen, estrogen, and progesterone) related to insulin resistance [1], the metabolic disturbance appears more remarkable in twins, compared with singletons. To date, several studies demonstrated that glucose tolerance was comparable between twin and singletons in women without GDM [2-4]. In contrast to singleton pregnancies, however, the information on the glycemic features of twin pregnancies with GDM is limited. With this background, we compared the degree of glucose intolerance between twin and singleton pregnancies with GDM (T-GDM and S-GDM, respectively) in our hospital cohort.

Material and Methods

Subjects

With the approval of ethical committee of Keio University School of Medicine, consecutive 529 Japanese women with GDM (T-GDM, n = 24; S-GDM, n = 505) were retrospectively analyzed. All were cared for at the perinatal unit of Keio University Hospital from 2011 to 2016. Gestational age was confirmed in the first trimester by crown-rump length measurements. Excluded from this study were women treated with medications known to affect glucose metabolism (e.g. ritodorine hydrochloride) and with a medical history indicating either impaired glucose tolerance or diabetes mellitus (DM).

GDM diagnosis and glycemic control

During the study period, each woman underwent a two-step screening for GDM: universal early testing and a standard 1-h 50 g oral glucose challenge test (GCT) in early and late pregnancy, respectively, based on the clinical recommendation by Japan Society of Obstetrics and Gynecology (JSOG) [5]. Women with positive screen
underwent a diagnostic 75 g oral glucose tolerance test (OGTT) with the measurement of plasma glucose (PG, mg/dL) and insulin concentration (Ins, mU/L) in the fasting state and at 30 min, 1 h, and 2 h after the glucose load. Levels of PG and Ins were measured by a glucose oxidase method and enzyme immunoassay, respectively. Based on the criteria by Japan Diabetes Society, GDM was diagnosed if one or more values reached or exceeded the following thresholds: fasting, 92 mg/dL; 1 h, 180 mg/dL; 2 h, 153 mg/dL [5].

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

Baseline characteristics, glycemic and metabolic features, and insulin treatment

Insulin sensitivity and insulin secretion were evaluated using measurements from the diagnostic OGTT [6, 7]. The insulin sensitivity was estimated by the whole-body insulin sensitivity index derived from the OGTT (ISOGTT). The ISOGTT was calculated by the following formula: 10,000/square root \{PG_0 \times \text{Ins}_0 \times (PG_0 + PG_{60} \times 2 + PG_{120})/2 \times (\text{Ins}_0 + \text{Ins}_{60} \times 2 + \text{Ins}_{120}/2)\}, where PG_y and Ins_y represent plasma glucose (mg/dL) and insulin values (mU/L), respectively, at time y min during the OGTT. Insulin secretion was assessed by the ratio of the incremental insulin concentration to the incremental glucose concentration at the 30 min sample (the insulinogenic index: IGI). To evaluate beta cell function, we calculated the OGTT-derived disposition index using the following measures: Insulin Secretion- Sensitivity Index-2 (ISSI-2: the AUCins/glu multiplied by ISOGTT), where AUCins/glu represent the ratio of the total area under the insulin curve to the total area under the glucose curve during the OGTT [8].

In this study, maternal baseline characteristics (i.e. age and weight before pregnancy, gestational weight gain [GWG, calculated as the pre-pregnancy weight subtracted from the last clinically recorded weight within one week before delivery], prior GDM, a first-degree family history of diabetes mellitus [DM], and pre-pregnancy body mass index [BMI]), glycemic and metabolic features (i.e. gestational age at diagnosis, PG and Ins profile of the diagnostic OGTT, levels of HbA1c, IGI, ISOGTT, and ISSI-2), and insulin requirement during pregnancy (i.e. insulin requirement, gestational age at insulin treatment initiated, and dosage of insulin needed before delivery) were compared between the T-GDM and S-GDM groups.

Statistical analysis

Data were presented as median (interquartile range) or absolute numbers (percentage) in text and tables, where appropriate. Continuous data were compared between the groups by Wilcoxon signed-rank test. Categorical variables were analyzed by the chi-square test or Fisher exact test. Statistical analysis was performed using the JMP version 13 (SAS Institute, Cary, NC, USA) and p < 0.05 was considered statistically significant.

Results

After excluding women having medications known to affect glucose metabolism, 20 women with T-GDM and 451 with S-GDM were included in this analysis. The gestational age at delivery was less for T-GDM, but there was no significant difference in maternal age, pre-pregnancy BMI, GWG, a family history of DM, and prior GDM between the T-GDM and S-GDM groups (Table 1). The rate of GDM diagnosed before 20 weeks of pregnancy and one abnormal OGTT value in the T-GDM group were similar to that in the S-GDM group (Table 2). Women with T-GDM showed significantly lower levels of PG at fasting, compared with S-GDM. Additionally, levels of PG at 60 min after the load in T-GDM were significantly higher than those in S-GDM. The levels of IGI and ISSI-2 from the diagnostic OGTT were comparable between the two groups. Regarding the insulin requirement, there was no significant difference in the rate of insulin treatment, gestational age at insulin treatment initiated, and a dosage of insulin needed before delivery between the T-GDM and S-GDM groups (Table 3). The dosage of NPH insulin in T-GDM was comparable to that in S-GDM (7 [4–10] vs. 8 [4–14] units). Likewise, there was no significant difference in the dosage of regular or rapid acting insulin between T-GDM and S-GDM (14 [4–38] vs. 13 [6–21]). After adjustment for confounders (i.e. maternal age, pre-pregnancy BMI, GWG, a family history of DM, and prior GDM) by multivariate analysis, the risk of insulin treatment in T-GDM was not statistically higher than that in S-GDM (adjusted odds ratio 0.52; 95% confidence interval 0.20–1.38). Similarly, multivariate analysis showed gestational age
at insulin treatment initiated and a dosage of insulin requirement were still comparable between the two groups ($p = 0.24$ and $0.077$, respectively).

### Discussion

The present study demonstrated that maternal metabolic features (*i.e.* insulin sensitivity and beta cell function) based on the diagnostic OGTT were comparable
between women with the T-GDM and S-GDM. Additionally, the rate of insulin treatment and its dosage to achieve the glycemic goal in women with T-GDM were similar to those with S-GDM. Regarding GDM, there was a paucity of data on the degree of glucose intolerance in twin pregnancies, although much information is available on singleton pregnancies. To the best of our knowledge, this is the first report on the glycemic characteristics of twin pregnancies with GDM, especially in Japanese women.

In this study, there was no significant difference in antepartum insulin requirements between the T-GDM and S-GDM groups. Since maternal metabolic features at diagnosis were comparable between the two groups, our results suggested that the exacerbation of antepartum glucose intolerance in T-GDM was similar to that in S-GDM. Likewise, Schwartz et al. reported that insulin requirements in T-GDM were not different from those in S-GDM [1]. It was demonstrated that maternal resting energy expenditure increased in twin pregnancies, compared with singleton pregnancies [9]. Our observation that levels of fasting PG in T-GDM was lower than those in S-GDM might be associated with increased resting expenditure in twin pregnancies. Additionally, an increase in glucose consumption by fetuses might be related to the improvement of insulin resistance in twin pregnancy. These findings indicated that antepartum glucose intolerance in T-GDM was similar to that in S-GDM.

A major strength of our study was that the implementation of insulin treatment had little variation because it was based on daily glucose profile during the dietary management in our hospital. Additionally, women treated with ritodrine hydrochloride were excluded from analysis because it affects glucose tolerance. When analyzing maternal baseline characteristics, maternal age, pre-pregnancy BMI, and levels of IGI and ISSI-2 at the diagnosis of GDM in the study cohort were similar to those in women excluded, in both S-GDM and T-GDM groups (data not shown). Therefore, our study cohort was suitable to investigate glycemic characteristics in GDM, although the number of women with T-GDM was limited.

Weakness of the present study was its retrospective nature in a single institution. Additionally, twin pregnancy carries risk of preterm birth and elective cesarean section was performed near term because of maternal discomfort in our study cohort. In this study, there was a significant difference in gestational age at delivery between the two groups. Therefore, more dosage of insulin might be required if twins are delivered at term. In the real practice, however, the dosage of insulin administered did not change after late preterm period (i.e. 34–36 weeks of pregnancy) in most cases. Thus, the insulin requirement appears comparable between T-GDM and S-GDM. In the future, a larger multicenter collaborative study should be performed to replicate our findings regarding antepartum glucose intolerance in women with S-GDM and T-GDM.

In conclusion, our observation demonstrated that the severity of glucose intolerance of T-GDM was similar to that of S-GDM, although differences in insulin resistance, fetal glucose consumption, and maternal basal metabolic rate might exist between singleton and twin pregnancies. It was of importance that the rate of insulin treatment and its dosage to achieve the glycemic goal in GDM women with twins was comparable to those with singletons. Therefore, it is likely that twin pregnancy does not develop more profound hyperglycemia, compared with singleton pregnancy in GDM. Our data is retrospective in a single institution, but would be useful for pregnant women as well as clinical physicians in the antepartum management of GDM.

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Disclosure

There were no conflicts of interest with regard to this study.

Table 3  Insulin requirement before delivery in twin and singleton pregnancies with gestational diabetes

|                      | T-GDM (N = 20) | S-GDM (N = 451) | p    |
|----------------------|----------------|-----------------|------|
| Insulin treatment (%)| 9 (45%)        | 144 (32%)       | 0.22 |
| Gestational age at Insulin initiated (weeks) | 26 (14–29) | 27 (18–30) | 0.61 |
| Insulin dosage before delivery (unit/day) | 14 (4–45) | 13 (6–21) | 0.57 |

Data: median (interquartile range) or n (%).
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