Predictors of later insulin therapy for gestational diabetes diagnosed in early pregnancy

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Abstract. Interventions for gestational diabetes mellitus (GDM), diagnosed in early pregnancy, have been a topic of controversy. This study aimed to elucidate factors that predict patients with GDM diagnosed before 24 gestational weeks (early GDM: E-GDM) who require insulin therapy later during pregnancy. Furthermore, we identified patients whose impaired glucose tolerance should be strictly controlled from early gestation onward. Women diagnosed with GDM were categorized based on the gestational age at diagnosis into E-GDM (n = 388) or late GDM (L-GDM, diagnosed after 24 weeks, n = 340) groups. Clinical features were compared between the groups, and the predictors for insulin therapy was evaluated in the E-GDM group. There were no significant between-group differences in terms of perinatal outcomes (e.g., gestational weeks at delivery, fetal growth, hypertensive disorder of pregnancy), with the exception of the Apgar score at 5 min. Moreover, there was no significant difference in the frequency of insulin therapy during pregnancy between the two groups. Using multiple logistic regression analysis, pre-pregnancy body mass index (BMI) ≥25 kg/m2, a family history of diabetes, and higher fasting plasma glucose (FPG), 1 h-plasma glucose (PG), and 2 h-PG values increased insulin therapy risk during pregnancy in the E-GDM group. Furthermore, since E-GDM patients with abnormal levels of FPG, as well as 1 h-PG or 2 h-PG, and those with pre-pregnancy BMI ≥25 kg/m2 and a family history of diabetes had a higher risk of later insulin therapy during pregnancy, they may require more careful follow-up in the perinatal period.

Key words: Gestational diabetes, Insulin, Obesity, Oral glucose tolerance test, Pregnancy

GESTATIONAL DIABETES (GDM) is one of the most common perinatal diseases. It is associated with several perinatal complications, such as hypertensive disorder of pregnancy (HDP), cesarean section (CS), large-for-gestational age (LGA: birthweight >90th percentile), macrosomia (birthweight ≥4,000 g), neonatal hypoglycemia, and neonatal jaundice [1]. Furthermore, offspring born to GDM mothers are at a higher risk of obesity and abnormal glucose tolerance in the future [2, 3]. In Japan, GDM affects approximately 10% of all pregnancies (according to Japanese data) and is diagnosed using the Japan Society of Obstetrics and Gynecology criteria (JSOG), which is a modification of the International Association of Diabetes Pregnancy Study Groups (IADPSG) criteria formulated in 2010 [4]. The same cut-off values are used for diagnosing GDM before (early GDM [E-GDM]) and after (late GDM [L-GDM]) 24 gestational weeks [4]. Women with E-GDM have a higher frequency of preterm births than women with L-GDM, in addition to increased HDP, pre-eclampsia, CS, admission to neonatal intensive care units, macrosomia delivery, and babies who are LGA with neonatal jaundice [5-8]. Most patients with E-GDM and HbA1c >40 mmol/mol are at a higher risk of LGA, macrosomia, CS delivery, and maternal hypertensive disorders [9]. However, the treatment approach to GDM diagnosed in early pregnancy remains controversial. The benefits of treating L-GDM are that pre-eclampsia, shoulder dystocia, and macrosomia incidences can be reduced [10]. However, therapeutic interventions do not have the same effectiveness on E-GDM as they do on L-GDM [11]. Additionally, when women diagnosed with E-GDM were tested with OGTT at 24–28 gestational weeks, approximately half of them were found to have spontaneously resolved and did not have an abnormal oral glucose tolerance test (OGTT) result [12]. Hence, some women with E-GDM, who need therapeutic intervention, may be erroneously included with patients who do not need treatment. However, little is known about the clinical characteristics and management of...
E-GDM, including whether patients diagnosed with E-GDM should be treated more carefully.

Thus, this study aimed to elucidate factors that predict patients with GDM in early gestation who require insulin therapy later during pregnancy. Furthermore, we identified patients whose impaired glucose tolerance should be strictly controlled from early gestation onward.

Material and Methods

Our study was reviewed and approved by the Keio University Hospital Ethics Committee (Nos. 20150103 and 20150168). Since this was a retrospective study, we received a waiver for obtaining informed consent from patients.

Between April 2010 and December 2019, the number of deliveries was 5,833. Within this time period, we identified a cohort of 728 women diagnosed with GDM who received perinatal care at Keio University Hospital. Women who screened positive for GDM in the first trimester had at least one of the following criteria: random plasma glucose (RPG) level ≥5.3 mmol/L (95 mg/dL), HbA1c ≥41 mmol/mol (5.9%), glycoalbumin (GA) ≥15.8%, a personal history of GDM or macrosomia delivery, family history of type 2 diabetes (T2DM), or pre-pregnancy body mass index (BMI) ≥25 kg/m².

When patients were positive for E-GDM screening, they immediately underwent a 75-g OGTT to diagnose E-GDM. Since a two-step procedure to diagnose L-GDM is adopted in Japan, women who screened negative or had normal OGTT results in the first trimester were required to undergo a 50-g glucose challenge test (GCT) at 24–28 gestational weeks. If their GCT result was positive (≥7.8 mmol/L [140 mg/dL]), they immediately underwent diagnostic OGTT. According to the JSOG criteria based on IADPSG, E-GDM and L-GDM were diagnosed based on OGTT results if one or more values reached or exceeded the following thresholds: fasting plasma glucose (FPG) levels, 5.1 mmol/L (92 mg/dL); 1-h plasma glucose level during a 75-g OGTT (1 h-PG), 10.0 mmol/L (180 mg/dL); and 2-h plasma glucose level during a 75-g OGTT (2 h-PG), 8.5 mmol/L (153 mg/dL). We excluded women with multi-fetal pregnancies, congenital anomalies, overt diabetes during pregnancy, abnormality in the 75 g OGTT at postpartum period of previous pregnancy, and pre-existing diabetes (either type 1 diabetes or T2DM).

All women with GDM underwent dietary management, including three meals and three snacks after receiving counseling for diet. Capillary glucose profiles were obtained seven times a day under dietary management via self-monitored blood glucose (SMBG) measurements: upon waking up, one hour pre-prandial for all planned meals, two hours post-prandial, and bedtime. Our hospital’s dietary management is as follows: daily calorie intake: early pregnancy, 30 kcal × standard body weight (SBW: kg) + 150 kcal; late pregnancy, 30 kcal × SBW + 350 kcal; if obese, 30 kcal × SBW throughout pregnancy. SBW was calculated as maternal height (m) × maternal height (m) × 22. Insulin was administered when dietary treatment alone did not achieve the glycemic goal (i.e., FPG level <5.6 mmol/L [100 mg/dL] or 2 h PG <6.7 mmol/L [120 mg/dL]) [13]. In our hospital, GDM patients with two or three positive points of the diagnostic OGTT are hospitalized for one week for the purpose of education on GDM management, and then managed as outpatients, while GDM patients with one positive point are managed as outpatients. LGA and small-for-gestational age (SGA: birth weight <10th percentile) were calculated using the standard Japanese sex- and parity-specific birthweight percentile curves in this study [14]. We calculated the expected gestational weight gain (GWG) by subtracting maternal pre-pregnancy body weight from maternal body weight at delivery at 40 gestational weeks using a previously reported method, (gestational weight gain [kg] + 3.8)/(gestational weeks at delivery [weeks] – 2.6) × 37.4 – 3.8, which has been validated in a Japanese population [15, 16]. Maternal expected GWG was evaluated using the Institute of Medicine criteria [17].

Data are presented as the median (range) or number of cases (percentage). Continuous data (i.e., maternal age at delivery, pre-pregnancy BMI, GWG, gestational weeks at delivery, birth weight, OGTT during pregnancy, Apgar score 1/5 min, and umbilical pH) were compared between groups using the Mann-Whitney U test. Categorical variables (i.e., the incidence of nulliparity, family history of diabetes, CS delivery, preterm delivery, HDP, macrosomia, SGA, LGA, and Apgar score 5 min <8 points) were analyzed using the chi-squared test or Fisher’s exact test. The trend for the number of abnormal values during OGTT was analyzed using Cochran-Armitage trend analysis. Using logistic regression analysis to build a model, the following independent variables were included in the model based on clinical relevance and statistical significance of their association with insulin therapy to anticipate from early pregnancy screening and OGTT results: maternal age at delivery, pre-pregnancy BMI, RPG, family history of diabetes, history of prior GDM, fetal sex (male), and antepartum OGTT results. Additionally, predictive values of clinical characteristics for the risk of insulin therapy were obtained using logistic regression analysis and receiver operating characteristics (ROC) analysis. Odds ratios and their 95% confidence intervals were evaluated to assess the association between insulin therapy during pregnancy...
and the aforementioned clinical features. All tests were statistically analyzed by JMP software (ver. 15, SAS Inst. Inc, Cary, NC) and p values <0.05 were considered significant.

Results

The maternal and neonatal characteristics of women with E-GDM and L-GDM are shown in Table 1. There were no notable differences in maternal age at delivery and HbA1c at diagnostic OGTT between the E-GDM and L-GDM groups. However, the incidence of nulliparity was lower in E-GDM than in L-GDM (p = 0.0013). Furthermore, pre-pregnancy BMI was higher in E-GDM than in L-GDM (p = 0.0005). Regarding antepartum OGTT profiles, women with E-GDM had significantly higher FPG levels (≥5.1 mmol/L) compared to those with L-GDM (p = 0.0001). In contrast, women with E-GDM had significantly lower 1-h-PG and 2-h-PG levels during diagnostic OGTT than those with L-GDM (p < 0.0001). While the number of abnormal values in the diagnostic OGTT in E-GDM was significantly lower than that in L-GDM (p < 0.0001), 70% of women with E-GDM with one positive point had an abnormal FPG. There was no significant difference in GWG and other perinatal outcomes between the two groups, except for the Apgar score at 5 min that was significantly lower in E-GDM than in L-GDM. There was no difference between the two groups when the Apgar score at 5 min was <8 points; moreover, no significant between-group difference was observed in the frequency of insulin therapy during pregnancy (p = 0.13).

To evaluate who should be managed as GDM from early pregnancy, we analyzed the association between insulin therapy and clinical characteristics in E-GDM. Among 388 women with E-GDM, 249 were treated with diet therapy only (diet group) and 139 patients were treated with diet therapy and insulin treatment (diet + insulin group). The comparison of maternal and perinatal characteristics between the two groups is shown in Table 2. Pre-pregnancy BMI was significantly higher in the diet + insulin group than in the diet group (p = 0.011). There was no significant difference in other maternal and perinatal outcomes between the two groups except that the Apgar score at 5 min was significantly lower in the diet group than in the diet + insulin group. Furthermore, the incidence of an Apgar score at 5 min being <8 points in the diet + insulin group was higher than that in the diet group. According to antepartum OGTT results, 1-h-PG and 2-h-PG levels, but not FPG (p = 0.58), were significantly higher in the diet + insulin group than in the diet group (p < 0.0001). The number of abnormal values in the diagnostic OGTT in the insulin + diet group was significantly higher than that in the diet group (p < 0.0001).

The results of the logistic regression analysis in E-GDM are shown in Table 3. Pre-pregnancy BMI ≥25 kg/m², family history of diabetes, abnormal values in FPG (≥5.1 mmol/L), 1-h-PG (≥10.0 mmol/L), and 2-h-PG (≥8.5 mmol/L) increased the risk of insulin therapy during pregnancy in the multiple logistic regression models. In addition, the incidence of requiring insulin therapy later in pregnancy was 52.5% in women with E-GDM and a pre-pregnancy BMI ≥25 kg/m² and/or a family history of DM. The area under the ROC curve was used to evaluate the predictive power of these antepartum factors (Table 4). The 1-h PG showed the largest area under the ROC curve (AUC = 0.77) and the threshold of 1-PG to predict insulin therapy was 9.6 mmol/L. The comparison of maternal and perinatal characteristics between the diet + insulin group and the diet group in L-GDM is shown in Supplementary Table 2. While abnormal values in FPG (≥5.1 mmol/L), 1-h-PG (≥10.0 mmol/L), and 2-h-PG (≥8.5 mmol/L) increased the risk of insulin therapy during pregnancy in the multiple logistic regression models in L-GDM, pre-pregnancy BMI ≥25 kg/m² and a family history of diabetes were not associated with later insulin therapy.

Discussion

In this study, there was no difference in perinatal outcomes between E-GDM and L-GDM except Apgar score at 5 min, and there was no significant difference in the insulin required during pregnancy. In the analysis of risk of insulin therapy during pregnancy in women with E-GDM, 1-h-PG and 2-h-PG, but not FPG (p = 0.58) levels, were significantly higher in the diet + insulin group than in the diet group (p < 0.0001). However, among the patients with E-GDM pre-pregnancy BMI ≥25 kg/m², a family history of diabetes, and abnormal values in FPG, 1-h-PG and 2-h-PG during antepartum OGTT increased the risk of insulin therapy during pregnancy in the multiple logistic regression models.

It was previously reported that E-GDM had poor prognosis [5-9], and the therapeutic interventions for E-GDM were not found to be as effective as those for L-GDM [11]. Furthermore, when patients were diagnosed with GDM in early pregnancy, since their GWG would be limited, it was expected that SGA might be increased. However, in the present study, there were no differences in perinatal outcomes, including SGA, and the frequency of insulin therapy during pregnancy between women with E-GDM and L-GDM. The reasons for the lack of difference in perinatal outcomes between the two groups...
were considered as follows. First, we changed the diet therapy of GDM women between early pregnancy (30 kcal × SBW + 150 kcal) and late pregnancy (30 kcal × SBW + 350 kcal), and the women were managed with care to avoid excessive nutritional intake in our hospital. Since Horie et al. reported that appropriate diet therapy would be effective for managing glucose tolerance in E-GDM women [18], we believe that our diet therapy might have helped manage E-GDM better. Second, because data related to PG at fasting, 2 h-post-breakfast, before lunch, 2 h post-lunch, before dinner, 2 h post-dinner, and bedtime were collected from all women with GDM via SMBG measurements, it was considered that they could have avoided unnecessary excessive

| Table 1 | Comparison of maternal and perinatal characteristics between early GDM and late GDM |
|---------------------------------|------------------|------------------|------------------|
| | Early GDM (n = 388) | Late GDM (n = 340) | p-value |
| Maternal age at delivery (years) | 37 (24–57) | 37 (23–59) | 0.14 |
| Nulliparity (%) | 222 (57%) | 234 (69%) | 0.0013 |
| Pre-pregnancy BMI (kg/m²) | 21.4 (16.0–41.1) | 20.7 (16.4–36.3) | 0.0005 |
| Pre-pregnancy BMI ≥25 kg/m² (%) | 73 (19%) | 28 (8%) | <0.0001 |
| Pre-pregnancy BMI ≥30 kg/m² (%) | 17 (4%) | 9 (3%) | 0.23 |
| Gestational weight gain (kg/40 weeks) | 8.7 (–8.6–24.4) | 8.8 (–7.3–20.8) | 0.66 |
| Family history of diabetes (%) | 95 (24%) | 35 (10%) | <0.0001 |
| HbA1c at diagnostic OGTT (mmol/mol) | 34.0 (13.0–42.0) | 33.0 (23.0–57.0) | 0.66 |
| Gestational age at diagnosis (weeks) | 14 (8–23) | 27 (24–35) | <0.0001 |
| Antepartum 75-g OGTT | | | |
| Fasting glucose level (mmol/L) | 5.2 (3.7–6.4) | 4.8 (3.0–7.7) | <0.0001 |
| 1-h glucose level (mmol/L) | 9.1 (3.9–15.1) | 9.9 (5.1–14.1) | <0.0001 |
| 2-h glucose level (mmol/L) | 7.8 (4.7–14.2) | 8.7 (3.8–16.2) | <0.0001 |
| Abnormal values of diagnostic OGTT | | | |
| Fasting glucose level (≥5.1 mmol/L) (%) | 253 (65%) | 111 (33%) | <0.0001 |
| 1-h glucose level (≥10.0 mmol/L) (%) | 136 (35%) | 168 (49%) | 0.0001 |
| 2-h glucose level (≥8.5 mmol/L) (%) | 156 (40%) | 243 (71%) | <0.0001 |
| Number of abnormal values in diagnostic OGTT | | | |
| 1 point (%) | 266 (69%) | 184 (54%) | <0.0001 |
| 2 points (%) | 87 (22%) | 130 (38%) | |
| 3 points (%) | 35 (9%) | 26 (8%) | |
| Insulin requirement during pregnancy (%) | 139 (36%) | 141 (41%) | 0.13 |
| Gestational weeks at delivery (week) | 38 (23–41) | 38 (24–41) | 0.52 |
| Preterm delivery (%) | 65 (17%) | 73 (21%) | 0.11 |
| Cesarean section delivery (%) | 197 (51%) | 179 (53%) | 0.71 |
| Emergency cesarean delivery (%) | 88 (23%) | 77 (23%) | 1.00 |
| Hypertensive disorder of pregnancy (%) | 19 (5%) | 12 (4%) | 0.46 |
| Birth weight (g) | 2,899 (438–4,526) | 2,882 (333–3,974) | 0.53 |
| Small for gestational age (%) | 31 (8%) | 32 (9%) | 0.51 |
| Large for gestational age (%) | 47 (12%) | 48 (14%) | 0.44 |
| Macrosomia (%) | 4 (1%) | 0 (0%) | 0.13 |
| Neonatal sex (female) (%) | 190 (49%) | 170 (50%) | 0.71 |
| Apgar score 1 min | 8 (1–10) | 8 (1–10) | 0.078 |
| Apgar score 5 min | 9 (2–10) | 9 (2–10) | 0.012 |
| Apgar score 5 min <8 (%) | 23 (6%) | 26 (8%) | 0.38 |
| Umbilical artery pH | 7.31 (6.92–7.53) | 7.32 (7.07–7.49) | 0.51 |

BMI, Body mass index; OGTT, Oral glucose tolerance test.
Data are presented as median (range) or n (%). Continuous data were compared between groups using Mann-Whitney U test. Categorical variables were analyzed using Fisher’s exact test. In all tests, p < 0.05 was considered significant.
### Table 2  Comparison of maternal and perinatal characteristics between diet and insulin group and diet group in early GDM

|                                      | Diet and insulin \( n = 139 \) | Diet \( n = 249 \) | \( p \)-value |
|--------------------------------------|----------------------------------|--------------------|---------------|
| Maternal age at delivery (years)     | 38 (26–57)                       | 37 (24–51)         | 0.05          |
| over 35 years                        | 88 (81%)                         | 137 (70%)          | 0.06          |
| Nulliparity                          | 61 (56%)                         | 111 (57%)          | 0.90          |
| Pre-pregnancy BMI (kg/m\(^2\))       | 22.2 (17.0–41.1)                 | 21.3 (16.0–36.3)   | 0.011         |
| Pre-pregnancy BMI ≥25 kg/m\(^2\)     | 22 (20%)                         | 37 (19%)           | 0.88          |
| Pre-pregnancy BMI ≥30 kg/m\(^2\)     | 10 (7%)                          | 7 (3%)             | 0.07          |
| Gestational weight gain (kg/40 weeks)| 8.6 (–6.4–19.1)                  | 8.7 (–8.6–21.3)    | 0.57          |
| Screening for early GDM              |                                  |                    |               |
| Random glucose level ≥5.3 mmol/L     | 86 (79%)                         | 153 (78%)          | 1.00          |
| Family history of diabetes           | 33 (30%)                         | 40 (21%)           | 0.07          |
| Personal history of GDM              | 17 (16%)                         | 18 (9%)            | 0.13          |
| History of macroamnia delivery       | 0 (0%)                           | 3 (2%)             | 0.56          |
| HbA1c ≥40.0 mmol/mol                 | 1 (1%)                           | 0 (0%)             | 0.36          |
| Glycoalbumin ≥15.8%                  | 11 (10%)                         | 15 (8%)            | 0.52          |
| Antepartum 75-g OGTT                 |                                  |                    |               |
| Fasting glucose level (mmol/L)       | 5.2 (4.2–6.4)                    | 5.2 (3.9–6.1)      | 0.58          |
| 1-h glucose level (mmol/L)           | 10.3 (5.2–15.2)                  | 8.3 (3.9–13.4)     | <0.0001       |
| 2-h glucose level (mmol/L)           | 8.7 (4.8–14.2)                   | 7.1 (4.7–12.7)     | <0.0001       |
| Abnormal values of diagnostic OGTT   |                                  |                    |               |
| Fasting glucose level (≥5.1 mmol/L)  | 65 (59%)                         | 131 (67%)          | 0.21          |
| 1-h glucose level (≥10.0 mmol/L)     | 70 (64%)                         | 42 (22%)           | <0.0001       |
| 2-h glucose level (≥8.5 mmol/L)      | 64 (59%)                         | 47 (24%)           | <0.0001       |
| Number of abnormal values in diagnostic OGTT | <0.0001                         |                   |               |
| 1 point                              | 40 (37%)                         | 173 (89%)          |               |
| 2 points                             | 48 (44%)                         | 19 (10%)           |               |
| 3 points                             | 21 (19%)                         | 3 (2%)             |               |
| Gestational weeks at delivery (week) | 38 (30–41)                       | 38 (23–41)         | 0.35          |
| Preterm delivery                     | 25 (23%)                         | 27 (14%)           | 0.06          |
| Cesarean section delivery            | 62 (57%)                         | 95 (49%)           | 0.19          |
| Emergency cesarean delivery          | 29 (27%)                         | 43 (22%)           | 0.40          |
| Hypertensive disorder of pregnancy   | 8 (7%)                           | 8 (4%)             | 0.28          |
| Neonatal sex (male)                  | 54 (50%)                         | 102 (52%)          | 0.72          |
| Birth weight (g)                     | 2,860 (854–4,272)                | 2,910 (438–4,526)  | 0.19          |
| Small for gestational age            | 12 (11%)                         | 12 (6%)            | 0.18          |
| Large for gestational age            | 13 (12%)                         | 12 (12%)           | 1.00          |
| Macrosomia                           | 2 (2%)                           | 1 (1%)             | 0.29          |
| Apgar score 1 min                    | 8 (1–10)                         | 8 (0–10)           | 0.13          |
| Apgar score 5 min                    | 9 (6–10)                         | 9 (0–10)           | 0.015         |
| Apgar score 5 min <8                 | 14 (10%)                         | 9 (4%)             | 0.013         |
| Umbilical artery pH                  | 7.32 (7.13–7.45)                 | 7.31 (6.92–7.53)   | 0.31          |

BMI, Body mass index; OGTT, Oral glucose tolerance test.

Data are presented as median (range) or \( n \) (%). Continuous data were compared between groups using Mann-Whitney \( U \) test. Categorical variables were analyzed using Fisher’s exact test. In all tests, \( p < 0.05 \) was considered significant.
treatment. The management of GDM, including SMBG, reduced serious perinatal complications (e.g., CS, shoulder dystocia) [19, 20]. The American Diabetes Association recommends that fasting and postprandial blood glucose levels be measured using SMBG in women with GDM to achieve glycemic control [21]. Nakanishi et al. reported that the incidence of preterm birth in women with E-GDM who were followed up without treatment and had abnormal OGTT results at 24–28 gestational weeks was significantly higher than that in women with low-risk GDM who were followed up without treatment and had normal OGTT results at 24–28 gestational weeks (p = 0.01) [12]. Given that there was no difference in perinatal outcomes and the frequency of insulin therapy during pregnancy between the two groups, the therapeutic interventions might have similar effects in both E-GDM and L-GDM.

Table 3  Clinical risk factors of insulin therapy during pregnancy based on logistic regression analysis in early GDM

| Variable                      | Univariate            |                      |                      | Multiple              |                      |
|-------------------------------|-----------------------|----------------------|----------------------|-----------------------|----------------------|
|                               | Odds ratio            | 95%CI                | p-value              | Odds ratio            | 95%CI                | p-value              |
| Maternal age at delivery      |                       |                      |                      |                       |                      |
| <35 years                     | 1 (reference)         |                      |                      | 1 (reference)         |                      |                      |
| over 35 years                 | 1.57 (0.96–2.55)      | 0.07                 | 1.63 (0.90–2.96)     | 0.10                  |
| Pre-pregnancy BMI             |                       |                      |                      |                       |                      |
| ≤25 kg/m²                     | 1 (reference)         |                      |                      | 1 (reference)         |                      |                      |
| >25 kg/m²                     | 1.87 (1.12–3.13)      | 0.018                | 1.90 (1.01–2.91)     | 0.03                  |
| Random glucose level ≥5.3 mmol/L | 1 (reference) |                      |                      | 1 (reference)         |                      |                      |
| no                            | 1.09 (0.65–1.82)      | 0.74                 | 1.82 (0.92–3.60)     | 0.08                  |
| yes                           | 2.39 (0.87–6.57)      | 0.09                 | 1.30 (0.31–5.51)     | 0.72                  |
| HbA1c ≥40.0 mmol/mol          |                       |                      |                      |                       |                      |
| no                            | 1 (reference)         |                      |                      | 1 (reference)         |                      |                      |
| yes                           | 2.39 (0.87–6.57)      | 0.09                 | 1.30 (0.31–5.51)     | 0.72                  |
| Family history of diabetes   |                       |                      |                      |                       |                      |
| no                            | 1 (reference)         |                      |                      | 1 (reference)         |                      |                      |
| yes                           | 1.8 (1.12–2.88)       | 0.015                | 2.03 (1.09–3.79)     | 0.025                 |
| Personal history of GDM      |                       |                      |                      |                       |                      |
| no                            | 1 (reference)         |                      |                      | 1 (reference)         |                      |                      |
| yes                           | 1.92 (0.98–3.76)      | 0.06                 | 1.23 (0.53–2.85)     | 0.62                  |
| Fetal sex                     |                       |                      |                      |                       |                      |
| male                          | 1 (reference)         |                      |                      | 1 (reference)         |                      |                      |
| female                        | 1.05 (0.69–1.59)      | 0.82                 | 1.15 (0.69–1.92)     | 0.60                  |

BMI, body mass index; GDM, gestational diabetes; OGTT, oral glucose tolerance test; CI, confidence interval.

Table 4  Predictive values of characteristics for the risk of insulin therapy in early GDM

|                      | AUC    | p value  | Cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|----------------------|--------|----------|---------|-----------------|-----------------|---------|---------|
| Pre-pregnancy BMI    | 0.62   | <0.0001  | 21.5    | 63.3            | 57.8            | 54.4    | 73.8    |
| FPG                  | 0.52   | 0.094    | 5.5     | 20.1            | 92.0            | 58.3    | 67.4    |
| 1 h PG               | 0.77   | <0.0001  | 9.6     | 71.2            | 74.7            | 61.1    | 82.3    |
| 2 h PG               | 0.75   | <0.0001  | 7.7     | 78.4            | 64.7            | 55.3    | 84.3    |

AUC, area under the receiver operating characteristics curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; FPG, fasting plasma glucose; 1-h, 2-h PG, plasma glucose at 1 hour and 2 hour in the antepartum oral glucose tolerance test, respectively.
group was higher than that in the diet group. Since, in the insulin + diet group, the frequency of preterm delivery tended to be higher than that in the diet group. We considered that preterm delivery may have contributed to a lower Apgar score at 5 min. Thus, in this study, we analyzed the need of insulin therapy in women with E-GDM and attempted to categorize them into those who should be treated more carefully from the first trimester, and who do not require strict treatment from the first trimester. Because FPG tends to decrease as pregnancy advances [22], the need for therapeutic intervention in E-GDM with abnormal FPG but normal 1 h-PG and 2 h-PG has been questioned. Accordingly, 70% of women with E-GDM with one positive point in the present study had abnormal FPG, but the incidence of insulin therapy among those patients was only 18%. In contrast, women with E-GDM with two or three positive points had abnormal FPG as well as abnormal 1 and/or 2-h PG, suggesting that impaired insulin secretion might be associated with the development of glucose intolerance in Japanese mothers [23-25]. Therefore, these patients may have developed GDM due to insufficient endogenous insulin secretion and the added insulin resistance of pregnancy. We considered that these women required insulin therapy. This is supported by a report that an increasing number of abnormal values was significantly associated with the requirement for insulin therapy in women with GDM diagnosed using a 100-g/3-h OGTT [26]. McIntyre et al. suggested that it was not considered reasonable to diagnose women who had FPG ≥5.1 mmol/L (92 mg/dL) in the first trimester as E-GDM based on some current evidence [27]. However, our findings indicate that an abnormal value in FPG is one of the most important predictors of insulin therapy during pregnancy in patients with E-GDM. Additionally, in the present study, pre-pregnancy BMI ≥25 kg/m² and a family history of diabetes were good predictors of insulin therapy in E-GDM but not in L-GDM. In this study, the incidence of requiring insulin therapy later in pregnancy was 52.5% in women with E-GDM and a pre-pregnancy BMI ≥25 kg/m² and/or a family history of DM. Previously, it was reported that higher pre-pregnancy BMI and a family history of T2DM were associated with later insulin therapy in GDM diagnosed using the IADPSG criteria (diagnosed after 24 gestational weeks) [28, 29]. According to our criteria, women with a pre-pregnancy BMI ≥25 kg/m² and a family history of diabetes were assigned to the first trimester screening positive group and received an OGTT in the first trimester, resulting in most women with these risk factors being diagnosed with GDM before 24 weeks of gestation. Therefore, E-GDM patients with pre-pregnancy BMI ≥25 kg/m² as well as those with a family history of diabetes may need a more careful treatment approach in the perinatal period.

This study had several limitations. First, this was a single institutional retrospective analysis. However, the sample size of this study was more extensive than that of previous reports. The diagnostic criteria and management for E-GDM were consistent with no variation. Second, the incidence of obesity was low in this study. Therefore, compared with the general GDM patients, it is possible that a higher proportion of patients with impaired insulin secretion developed GDM. To confirm our results, a randomized controlled study in a larger sample is warranted.

In conclusion, there was no difference in the perinatal outcomes or the probability of requiring insulin therapy between patients with E-GDM and L-GDM. Furthermore, as women with E-GDM, a pre-pregnancy BMI ≥25 kg/m², and a family history of diabetes are more likely to require insulin therapy later during pregnancy, they may require more careful follow-up during the perinatal period.

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Author Contribution

MT and YK collected data, performed statistical analyses, wrote the manuscript, contributed to the discussion, and reviewed/edited manuscript. YS, YT, KH, MO, TE, YS, SI, MT, and DO contributed to the discussion, and reviewed and edited the manuscript.

Conflict of Interest

The authors report no conflict of interest.

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