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Non-efficacy of early intervention strategy for non-obese patients with early-onset gestational diabetes mellitus: solely based on the short-term outcomes

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ABSTRACT

Introduction To verify the effectiveness of intervention in early pregnancy for women with early-onset gestational diabetes mellitus (GDM).

Research design and methods This study included women with a singleton pregnancy who were diagnosed with early-onset GDM by 20 weeks of gestation according to the International Association of Diabetes and Pregnancy Study Group (IADPSG) threshold. We retrospectively evaluated the pregnancy outcomes in pregnant women with early-onset GDM. In the treatment from early pregnancy group (n=286), patients were diagnosed with early-onset GDM at the Yokohama City University Medical Center (YCU-MC) in 2015–2017 and were treated for GDM from early pregnancy. Concerning the treatment from mid-pregnancy group (n=248), participants were diagnosed with early-onset GDM at five sites, including the YCU-MC in 2018–2019, and were followed up without treatment until the second 75 g oral glucose tolerance test (OGTT) at 24–28 weeks of gestation. Treatment for GDM was given only if the GDM pattern was still present in the second OGTT.

Results There were no significant differences in maternal backgrounds, including GDM risk factors and gestational weight gain, between the groups. Among the treatment from mid-pregnancy group, the false-positive early GDM was 124/248 (50%). Regarding pregnancy outcome, the rate of large for gestational age (LGA) was 8.8% in the treatment from early pregnancy group and 10% in the treatment from mid-pregnancy group, with no significant difference, whereas small for gestational age (SGA) was significantly higher in the treatment from early pregnancy group (9.4%) than in the treatment from mid-pregnancy group (4.8%) (p=0.046). There were no significant differences in maternal adverse events and neonatal outcomes between the groups. In a subanalysis limited to body mass index >25 kg/m^2, LGA was significantly lower in the treatment from early pregnancy group than in the treatment from mid-pregnancy group.

Conclusions The strategy for diagnosing GDM by IADPSG thresholds in early pregnancy and providing treatment to all patients from early pregnancy did not improve the pregnancy outcomes, but rather increased the SGA rate.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ No definitive evidence that intervention from early pregnancy improves the pregnancy outcomes for patients with early-onset gestational diabetes mellitus (GDM) diagnosed in early pregnancy, and when early-onset GDM diagnosed by International Association of Diabetes and Pregnancy Study Group (IADPSG) thresholds was followed up without treatment until mid-pregnancy, approximately half of the cases were false positive for early GDM with a normal pattern of 75 g oral glucose tolerance test at mid-pregnancy.

WHAT THIS STUDY ADDS

⇒ Diagnosing GDM by IADPSG thresholds in early pregnancy and providing therapeutic intervention to all patients with early-onset GDM did not improve the pregnancy outcomes, but rather increased the small for gestational age rate.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The Japanese treatment strategy, which recommends that all pregnant women with impaired glucose tolerance by IADPSG thresholds in early pregnancy should be treated from early pregnancy, needs to be revisited.

INTRODUCTION

The diagnosis and treatment of gestational diabetes mellitus (GDM) aim to avoid maternal and neonatal adverse outcomes.[1 2] It is clear that the optimal diagnosis and treatment of GDM improve pregnancy outcomes, although there is no definitive evidence that intervention from early pregnancy improves the pregnancy outcomes for patients with early-onset GDM diagnosed in early pregnancy.[3–5] The International Association of Diabetes and Pregnancy Study Group

(IADPSG) currently advocates that GDM should be diagnosed at 24–28 weeks of gestation using the 75 g oral glucose tolerance test (OGTT).[6 7] Although there are variations in diagnostic methods and criteria for GDM,[8] 24–28 weeks of gestation is the gold standard period for diagnosis of GDM worldwide.[9 10] For the diagnosis of GDM in Japan, the IADPSG thresholds are not limited to 24–28 weeks of gestation, but rather include the entire pregnancy, including the early pregnancy period. Further, therapeutic intervention is recommended from the time of diagnosis.[11] However, the validity of using 75 g OGTT to diagnose GDM from early pregnancy and intervening in all such early-onset GDM cases from early pregnancy has not been verified, and this treatment strategy for GDM is controversial in some reports.[12 13] As a nested case–control study in the TTIGDM study (a study to investigate the optimal Timing of Therapeutic Intervention for Gestational Diabetes Mellitus diagnosed in early pregnancy), we reported that when early-onset GDM diagnosed by IADPSG thresholds was followed up without treatment until mid-pregnancy, approximately half of the cases were false positive for early GDM with a normal pattern of 75 g OGTT at mid-pregnancy. Therefore, using IADPSG thresholds to diagnose GDM in early pregnancy may lead to overdiagnosis.[14] Meanwhile, early treatment of false-positive early GDM, even if overdiagnosed, may also ameliorate the condition, which may result in improved pregnancy outcomes for all women with early-onset GDM. Therefore, this study aimed to investigate the effectiveness of early intervention in women with early-onset GDM diagnosed by IADPSG thresholds in early pregnancy by comparing the pregnancy outcome between the group of early-onset GDM, in which all cases were intervened from early pregnancy, and in which only pregnant women diagnosed with GDM by retesting 75 g OGTT were treated after the reconfirmation of GDM.

METHODS

Subjects

This study included pregnant women with a singleton pregnancy who were diagnosed with early-onset GDM by 20 weeks of gestation by IADPSG thresholds. We retrospectively evaluated the pregnancy outcomes in pregnant women with early-onset GDM, who were divided into two groups: treatment from mid-pregnancy group (n=248) and treatment from early pregnancy group (n=286) (figure 1). We performed the subgroup analysis with only obese pregnant women.

Definition of early-onset GDM

Early-onset GDM in this study was defined as pregnant women who underwent a 75 g OGTT at <20 weeks of gestation because of risk factors for GDM and were diagnosed with GDM by IADPSG thresholds. IADPSG thresholds are 75 g OGTT with preload, 1-hour, and 2-hour values of at least one of 92 mg/dL (5.1 mmol/L), 180 mg/dL (10 mmol/L), and 153 mg/dL (8.5 mmol/L), respectively. The risk factors for GDM were defined as at least one of the following: random blood glucose level of ≥95 mg/dL (5.3 mmol/L) in early pregnancy, pre-pregnancy body mass index (BMI) of ≥25 kg/m^2, maternal age of ≥35 years, family history of diabetes in the second degree, history of large for gestational age (LGA) delivery, positive urinary glucose, and history of gestational diabetes. Pregnant women complicated by or with a history of overt diabetes mellitus and type 2 diabetes mellitus were excluded from the study.

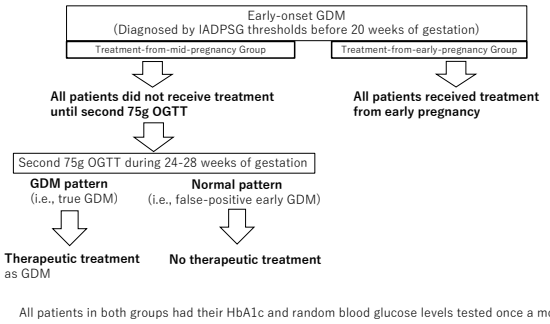

Figure 1 Flow chart of this study. GDM, gestational diabetes mellitus; IADPSG, International Association of Diabetes and Pregnancy Study Group; OGTT, oral glucose tolerance test.

Definition of the groups

Figure 1 shows the flow chart of the study. The patients were divided into the treatment from mid-pregnancy and the treatment from early pregnancy groups. The treatment from mid-pregnancy group included 248 pregnant women with early-onset GDM who participated in the TTIGDM study at five sites in Japan, including the Perinatal Center for Maternity and Neonate Yokohama City University Medical Center from 2018 to 2019. In the study, pregnant women diagnosed with early-onset GDM by IADPSG thresholds by 20 weeks of gestation underwent a second 75 g OGTT at 24–28 weeks of gestation. All the study participants were informed about their positive first 75 g OGTT results, and they provided consent to participate in this study. During the period between the diagnosis of early-onset GDM and the second 75 g OGTT, only HbA1c and random blood glucose were measured once a month as a follow-up, and no therapeutic intervention was performed. During the follow-up period, there were no cases that presented with blood glucose level ≥200 mg/dL (11.1 mmol/L) or HbA1c ≥6.5% (≥47 mmol/mol). Pregnant women with a normal second 75 g OGTT at 24–28 weeks of gestation were diagnosed with 'false-positive early GDM', and no therapeutic intervention was given until delivery. On the other hand, pregnant women who were confirmed to have GDM on the second 75 g OGTT at 24–28 weeks of gestation were treated as 'true GDM'.

Table 1 Maternal characteristics

	Treatment from early pregnancy group, n=286	Treatment from mid-pregnancy group, n=248	P value
Maternal age (years)	36 (32–39)	36 (33–39)	0.70
Pre-pregnancy BMI	22.6 (20.0–26.7)	22.8 (20.1–27.2)	0.53
Nullipara	137 (48%)	99 (40.0%)	0.067
Smoking	0 (0%)	2 (0.8%)	0.22
Chronic hypertension	14 (4.9%)	10 (4.0%)	0.68
False-positive early GDM	Not applicable	124 (50%)	
Risk factors of GDM (multiple responses included)			
Pre-pregnancy BMI ≥25 kg/m^2	88 (31%)	77 (31%)	1.00
High random blood glucose	87 (30%)	68 (27%)	0.50
Positive urinary glucose	7 (2.5%)	7 (2.8%)	0.79
History of LGA	1 (0.4%)	4 (1.6%)	0.19
Family history of type 2 DM	65 (23%)	50 (20%)	0.53
History of GDM	38 (13%)	33 (13%)	1.00
Maternal age ≥35 years	187 (65%)	176 (71%)	0.19
First OGTT fasting value (mg/dL, mmol/L)	92 (87–96), 5.1 (4.8–5.3)	92 (85–95), 5.1 (4.7–5.3)	0.26
First OGTT 1-hour value (mg/dL, mmol/L)	160 (132–184), 8.9 (7.3–10.2)	167 (139–187), 9.3 (7.7–10.4)	0.038
First OGTT 2-hour value (mg/dL, mmol/L)	136 (116–160), 7.6 (6.4–8.9)	145 (119–164), 8.1 (6.6–9.1)	0.11
Second OGTT fasting value (mg/dL, mmol/L)	–	87 (82–92), 4.8 (4.6–4.7)	
Second OGTT 1-hour value (mg/dL, mmol/L)	–	159 (135–182), 8.8 (7.5–10.1)	
Second OGTT 2-hour value (mg/dL, mmol/L)	–	137 (114–154), 7.6 (6.3–8.6)	

Values are expressed as median (IQR) or n (%).
All cases in the treatment from early pregnancy group were treated as GDM from early pregnancy. In the treatment from mid-pregnancy group, those with early GDM diagnosed by International Association of Diabetes and Pregnancy Study Group (IADPSG) thresholds were rediagnosed at mid-pregnancy, and only those with GDM in mid-pregnancy underwent treatment.
BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; LGA, large for gestational age; OGTT, oral glucose tolerance test.

The treatment from early pregnancy group included 286 pregnant women with early-onset GDM, who delivered between 2015 and 2017 at the Perinatal Center for Maternity and Neonate Yokohama City University Medical Center. All cases in the treatment from early pregnancy group were treated as GDM from early pregnancy (ie, the time of diagnosis of early-onset GDM) until delivery. The 75 g OGTT was not retested during pregnancy in this group.

Treatment for GDM

In both groups, HbA1c and random blood glucose were measured once a month after the diagnosis of early-onset GDM as an indicator of glycemic control during pregnancy. The treatment for GDM was similar in both groups. As therapeutic interventions, diet therapy was initiated primarily, and insulin therapy was added if the target blood glucose level was not achieved. The target blood glucose level was set at <100 mg/dL (5.6 mmol/L) before meals and <120 mg/dL (6.7 mmol/L) 2 hours after meals. The target HbA1c level was set at <5.8% (<39 mmol/mol). In patients receiving insulin therapy in whom the cervical ripening was favorable after 37 weeks of gestation, labor was induced; even if the cervical ripening was not favorable, labor was induced before 40 weeks of gestation.

Measures of pregnancy outcomes

Maternal age, pre-pregnancy BMI, primiparity, and GDM risk factors were obtained for the maternal characteristics. Pregnancy outcomes included gestational weight gain (GWG), insulin therapy, gestational age, preterm labor, birth weight, LGA, small for gestational age (SGA), macrosomia, Apgar score, umbilical cord artery pH, pre-eclampsia, method of delivery, neonatal intensive care unit admission, neonatal hypoglycemia, neonatal hyperbilirubinemia, and respiratory distress syndrome (RDS). LGA infants were defined as those with birth weight >90th percentile. SGA infants were defined as those with birth weight <10th percentile. Macrosomia was defined as an infant with a birth weight of ≥4000 g. Neonatal hypoglycemia was defined as a blood glucose level <40 mg/dL (2.2 mmol/L), and hyperbilirubinemia was defined as requiring phototherapy. All neonates were checked for these parameters using the same method. RDS was defined by characteristic findings on the chest

Table 2 Pregnancy outcomes

	Treatment from early pregnancy group, n=286	Treatment from mid-pregnancy group, n=248	P value
Gestational weight gain (kg)	7.5 (4.1–11.2)	8.2 (4.8–11.5)	0.19
Insulin therapy	54 (19%)	37 (15%)	0.25
Gestational age (weeks)	38.7 (38.1–39.8)	38.7 (38.0–40.0)	0.71
Preterm labor	22 (7.7%)	18 (7.3%)	0.87
Preterm labor before 28 weeks of gestation	4 (1.4%)	0 (0.0%)	0.13
Birth weight (g)	2965 (2666–3183)	3028 (2753–3270)	0.062
LGA	25 (8.8%)	25 (10%)	0.66
SGA	27 (9.4%)	12 (4.8%)	0.046
Macrosomia	1 (0.4%)	1 (0.4%)	1.000
Apgar score at 5 min <7	5 (1.8%)	2 (0.8%)	0.46
Umbilical artery pH<7.10	8 (2.8%)	3 (1.2%)	0.24
Pre-eclampsia	15 (5.2%)	11 (4.4%)	0.69
Vaginal delivery	179 (63%)	153 (62%)	0.86
Emergency cesarean delivery	32 (11%)	32 (13%)	0.59
Operative delivery	21 (7.3%)	17 (6.9%)	0.87
NICU admission	54 (19%)	46 (19%)	1.00
Neonatal hypoglycemia	16 (5.6%)	14 (5.7%)	1.00
Neonatal hyperbilirubinemia	44 (15%)	28 (11%)	0.20
RDS	4 (1.4%)	2 (0.8%)	0.69

Values are expressed as median (IQR) or n (%).
All cases in the treatment from early pregnancy group were treated as gestational diabetes mellitus (GDM) from early pregnancy. In the treatment from mid-pregnancy group, those with early GDM diagnosed by International Association of Diabetes and Pregnancy Study Group (IADPSG) thresholds were rediagnosed at mid-pregnancy, and only those with GDM in mid-pregnancy underwent treatment. Calculations of the centile of the birth weight were based on fetal growth curves based on a report by the Neonatal Committee of the Japan Pediatric Society published in 2011.
LGA, large for gestational age; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; SGA, small for gestational age.

radiographic examination and oxygen requirement within 24 hours after birth.

Presentation of data and statistical analysis

Statistical analysis was performed using JMP Pro V.15 (SAS Institute, Cary, North Carolina, USA). All the continuous data were presented as medians (IQR). All the categorical data are presented as proportions. Medians and proportions were compared using Mann-Whitney U test and Fisher's exact test, respectively. The level of statistical significance was set at $p<0.05$.

RESULTS

Table 1 shows the maternal characteristics. The pregnant women in the treatment from early pregnancy group showed no significant difference in the maternal background, such as maternal age, pre-pregnancy BMI, and GDM risk factors, compared with those in the treatment from mid-pregnancy group. In the treatment from mid-pregnancy group, there were 124 (50%) women with untreated early GDM who had a normal second OGTT. These women were classified as having false-positive early GDM and remained untreated for GDM through all of their pregnancies.

Table 2 shows the pregnancy outcomes of the treatment from early pregnancy and treatment from mid-pregnancy groups. The pregnant women in the treatment from early pregnancy group showed no significant difference in LGA (8.8% vs 10%), birth weight, macrosomia, insulin therapy, method of delivery, and neonatal outcomes compared with those in the treatment from mid-pregnancy group.

The pregnant women in the treatment from early pregnancy group showed no significant difference in GWG, compared with the treatment from mid-pregnancy group (7.5 kg vs 8.2 kg, respectively). However, in the treatment from mid-pregnancy group, the women with true GDM showed significantly lower GWG, compared with those with false-positive early GDM. (7.0 kg vs 8.9 kg, respectively; p=0.017).

In contrast, concerning SGA, the pregnant women in the treatment from early pregnancy group showed a higher SGA rate, compared with those in the treatment from mid-pregnancy group (9.4% vs 4.8%, respectively;

Table 3 Maternal characteristics and pregnancy outcomes of pregnant women with BMI ≥25 kg/m^2

	Treatment from early pregnancy group, n=88	Treatment from mid-pregnancy group, n=86	P value
Maternal age (years)	36 (32–39)	36 (32–39)	0.87
Pre-pregnancy BMI (kg/m^2)	29.7 (27.1–32.9)	28.8 (26.8–32.6)	0.30
Nullipara	44 (50%)	36 (42%)	0.29
Smoking during pregnancy	0 (0%)	1 (1.2%)	0.49
Chronic hypertension	9 (10%)	7 (8.1%)	0.79
False-positive early GDM	Not applicable	30 (35%)	
Gestational weight gain (kg)	4.4 (–0.4 to 8.5)	5.2 (1.8–9.5)	0.16
Insulin therapy	23 (26%)	18 (21%)	0.47
Gestational age (weeks)	38.9 (38.2–40.0)	38.7 (38.2–40.1)	0.52
Preterm labor	6 (6.8%)	9 (10%)	0.43
Birth weight (g)	2993 (2791–3195)	3080 (2730–3393)	0.32
LGA	6 (6.8%)	16 (19%)	0.023
SGA	6 (6.8%)	3 (3.5%)	0.50
Macrosomia	1 (1.1%)	1 (1.2%)	1.00
Apgar score at 5 min <7	1 (1.1%)	2 (2.3%)	0.62
Umbilical artery pH<7.10	1 (1.1%)	3 (3.5%)	0.36
Pre-eclampsia	5 (5.7%)	8 (9.3%)	0.40
Vaginal delivery	59 (67%)	52 (60%)	0.43
Emergency cesarean delivery	8 (9.1%)	16 (19%)	0.081
NICU admission	15 (17%)	23 (27%)	0.14
Neonatal hypoglycemia	4 (4.6%)	5 (5.8%)	0.75
Neonatal hyperbilirubinemia	14 (16%)	14 (16%)	1.00
RDS	1 (1.1%)	0 (0%)	1.00

Values are expressed as median (IQR) or n (%).
All cases in the treatment from early pregnancy group were treated as GDM from early pregnancy. In the treatment from mid-pregnancy group, those with early GDM diagnosed by International Association of Diabetes and Pregnancy Study Group (IADPSG) thresholds were rediagnosed at mid-pregnancy, and only those with GDM in mid-pregnancy underwent treatment. Calculations of the centile of the birth weight were based on fetal growth curves based on a report by the Neonatal Committee of the Japan Pediatric Society published in 2011.
BMI, body mass index; GDM, gestational diabetes mellitus; LGA, large for gestational age; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; SGA, small for gestational age.

p=0.046). In the treatment from early pregnancy group, the pregnant women with SGA showed significantly lesser weight gain, compared with those without SGA (4.7 kg vs 7.7 kg, respectively; p=0.006). In the treatment from mid-pregnancy group, the pregnant women with SGA showed no significant difference in GWG, compared with those without SGA (8.9 kg vs 8.1 kg, respectively; p=0.31).

In addition, subgroup analyses were performed. Table 3 shows the maternal background and delivery outcomes limited to pre-pregnancy obese pregnant women (pre-pregnancy BMI >25 kg/m^2) only. In the analysis limited to pre-pregnancy obesity pregnant women only, there were no significant differences between the two groups with regard to maternal background, including GDM risk factors. In the treatment from mid-pregnancy group with pre-pregnancy obesity, there were 30 (35%) cases of false-positive early GDM. The pregnant women in the treatment from early pregnancy group with pre-pregnancy obesity showed no significant difference in SGA rate but had significantly lower LGA rate as compared with those in the treatment from mid-pregnancy group (SGA: 6.8% vs 3.5%, respectively, p=0.50; LGA: 6.8% vs 19%, respectively, p=0.023).

DISCUSSION

There was no significant difference in LGA rate and adverse neonatal outcomes, such as neonatal hypoglycemia or hyperbilirubinemia, between the treatment from early pregnancy group and the treatment from mid-pregnancy group. On the other hand, although there was no significant difference in birth weight, the SGA rate was higher in the group where all cases were intervened from early pregnancy.

Between the treatment from early pregnancy group and the treatment from mid-pregnancy group, there

was no difference in the LGA rate and adverse neonatal outcome, such as neonatal hypoglycemia and hyperbilirubinemia. Liu *et al*[15] conducted a prospective cohort study of low-risk pregnant women in China, where 75 g OGTT was performed in early pregnancy and mid-pregnancy, and the therapeutic intervention for GDM was based on the mid-pregnancy 75 g OGTT results. They stated that, even in low-risk pregnant women, GDM diagnosed at 18–20 weeks of gestation is associated with a poor outcome, and that diagnosing and managing GDM from early pregnancy may improve the outcomes. On the other hand, Harper *et al*[16] reported that there was no significant difference in the LGA rate and neonatal outcome between obese American pregnant women who were diagnosed with early-onset GDM and started treatment in early pregnancy and those who were only followed up during early pregnancy and diagnosed with GDM in mid-pregnancy and started treatment from mid-pregnancy. Even in the obese population, the authors reported that they did not find any differences in pregnancy outcomes by screening and treating GDM from early pregnancy, which contradicts the findings of Liu *et al*.[15] Our findings in Japanese pregnant women at a high risk for GDM showed no improvement in pregnancy outcomes with therapeutic intervention from early pregnancy for those diagnosed with GDM in early pregnancy by IADPSG thresholds. However, in a subanalysis limited to BMI >25 kg/m^2, LGA was significantly reduced in the intervention group that was treated from early pregnancy as compared with the follow-up group until second 75 g OGTT, suggesting that intervention from early pregnancy may be beneficial only for obese pregnant women. The differences between our results and those of Harper *et al* may be due to differences in the diagnostic criteria for GDM.

Although there was no significant difference in birth weight, the SGA rate was higher in the group receiving interventions from early pregnancy. The rate of SGA in women with GDM is 4.4%–11.6%,[17–21] and in Japanese women with GDM, the rate of SGA is reported to be almost 7%,[17 18] which is lower than that of the general population of pregnant women. However, even in GDM cases, it is reported that strict glycemic control leads to SGA.[22–24] Among the early-onset GDM group receiving interventions from early pregnancy as GDM, the median weight gain of pregnant women with SGA was 4.7 kg, whereas that of pregnant women without SGA was 7.7 kg. Thus, the lesser weight gain in the group with higher SGA rate suggests that excessive interventions for GDM may have resulted in an increase in SGA births. The increase in the number of low birthweight babies is a concern in Japan, and it is reported that a nationwide effort to raise awareness of this issue and an immediate response to the matter in question are needed, as a decrease in birth weight may pose a risk of long-term health problems, such as diabetes and hypertension.[25] Therefore, in this context, it is necessary to reconsider the diagnosis and therapeutic intervention of GDM from early pregnancy.

This study has some limitations. First, this is not a prospective randomized controlled trial, but a retrospective study comparing a prospective cohort of one arm with historical controls. Second, in this study, there was no significant difference in pregnancy outcomes between the two groups, but we were not able to verify equivalence. Third, although the women in the treated from mid-pregnancy group did not receive active GDM treatment until after a mid-pregnancy OGTT, and only if the second test was positive, they were aware of the early diagnosis of GDM and some may have modified lifestyle from early pregnancy as a result. In addition, it has been reported that maternal hyperglycemia during pregnancy can affect future pediatric health,[26] but in this study, we were only able to examine the short-term outcomes. As it is known that the profile of 75 g OGTT and subsequent pregnancy outcomes vary according to ethnicity,[27] the advantage of this study is that it is the first to report whether therapeutic intervention from early pregnancy for early-onset GDM is effective for pregnant women in Japan.

In conclusion, diagnosing GDM by IADPSG thresholds in early pregnancy and providing therapeutic intervention to all patients with early-onset GDM did not improve the pregnancy outcomes, but rather increased the SGA rate. The Japanese treatment strategy, which recommends that all pregnant women with impaired glucose tolerance by IADPSG thresholds in early pregnancy should be treated from early pregnancy, needs to be revisited.

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Contributors SN researched the data and wrote the manuscript. SA was guarantor. SA and JK contributed to study design and wrote the manuscript. RS, SO, YH, AM and KK researched the data. EM finalized the manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the protocol for this research project was approved by a suitably constituted Ethics Committee of the Yokohama City University Medical Center (Approval No F220100009), and it conforms to the provisions of the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

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