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High probability of false-positive gestational diabetes mellitus diagnosis during early pregnancy

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ABSTRACT

Introduction This study aimed to assess the validity of applying the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria for the diagnosis of gestational diabetes mellitus (GDM) at any time during pregnancy.

Research design and methods This multicenter cohort study was conducted at five Japanese facilities from January 2018 to April 2019. The study cohort included women at a high risk of GDM who met one or more of the following IADPSG criteria during early pregnancy: fasting plasma glucose (FPG) ≥92 mg/dL and 75 g oral glucose tolerance test (OGTT) value of ≥180 mg/dL at 1 hour, or ≥153 mg/dL at 2 hour (hereafter early-onset GDM). Women diagnosed with early-onset GDM were followed up without therapeutic intervention and underwent the 75 g OGTT again during 24–28 weeks of gestation. Those exhibiting the GDM patterns on the second 75 g OGTT were diagnosed with true GDM and treated, whereas those exhibiting the normal patterns were diagnosed with false positive early GDM and received no therapeutic intervention.

Results Of the 146 women diagnosed with early-onset GDM, 69 (47%) had normal 75 g OGTT values at 24–28 weeks of gestation, indicating a false-positive result. FPG levels were significantly higher in the first 75 g-OGTT test than in the second 75 g-OGTT test (93 mg/dL and 87.5 mg/dL, respectively; p<0.001). FPG levels were high in 86 (59%) women with early-onset GDM during early pregnancy but in only 39 (27%) women during mid-pregnancy. Compared with false positive early GDM, true GDM was more frequently associated with adverse pregnancy outcomes.

Conclusions Although women with early-onset GDM were followed up without treatment, the results of repeated 75 g OGTT during mid-pregnancy were normal in about 50%. Our data did not support the adoption of IADPSG thresholds for the diagnosis of GDM prior to 20 weeks of gestation.

Significance of this study

What is already known about this subject?

- The efficacy of therapeutic interventions for gestational diabetes mellitus (GDM) diagnosed during early pregnancy remains unclear. However, in 2013, the WHO recommended a diagnosis of GDM if the 75 g oral glucose tolerance test (OGTT) results at any time during pregnancy are equal to or exceed any of the following values (International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria): fasting plasma glucose (FPG) level of 92 mg/dL, 1-hour value of 180 mg/dL, and/or 2-hour value of 153 mg/dL.

What are the new findings?

- About half of women who were diagnosed with GDM during early pregnancy according to IADPSG criteria had normal 75 g OGTT values at 24–28 weeks of gestation, without therapeutic intervention.
- In women with early-onset GDM, FPG levels significantly decreased from early pregnancy to 24–28 weeks of gestation, whereas the 1-hour and 2-hour values remained virtually unchanged.

How might these results change the focus of research or clinical practice?

- IADPSG criteria for diagnosing GDM should not be adopted to the entire pregnancy period, including early pregnancy.

INTRODUCTION

Detection of gestational diabetes mellitus (GDM) is important for reducing the risks associated with maternal glucose intolerance.[1 2] Although there is clear evidence that the diagnosis and treatment of GDM improve pregnancy outcomes,[3] the efficacy of therapeutic interventions for GDM diagnosed during early pregnancy remains unclear.

In 2010, the International Association of Diabetes and Pregnancy Study Group (IADPSG) proposed the following criteria based on the Hyperglycemia and Adverse Pregnancy Outcome study:[4] (a) GDM should be diagnosed if the results of the 75 g oral glucose tolerance test (OGTT) at 24–28 weeks of gestation are equal to or exceed any of the following values: fasting plasma glucose (FPG) level of 92 mg/dL, 1-hour value of 180 mg/dL, and/or 2-hour value of 153 mg/dL and (b) an FPG level of 92–125 mg/dL during early pregnancy

should be classified as GDM. However, in response to reports from Italy[5] and China,[6] since 2016, the IADPSG does not recommend a diagnosis of GDM on the basis of an FPG level of 92–125 mg/dL during early pregnancy and issued a statement that the development of diagnostic criteria for abnormal glucose tolerance during early pregnancy is urgently needed.[7]

On the other hand, in 2013, the WHO recommended a diagnosis of GDM if the 75 g OGTT results are equal to or exceed any of the following values at any time during pregnancy: FPG level of 92–125 mg/dL, 1-hour value of ≥180 mg/dL, and/or 2-hour value of 153–199 mg/dL.[3] In Japan, the diagnostic criteria were changed in 2010 to those similar to the WHO criteria preceding the WHO's publication. Moreover, once GDM was diagnosed, therapeutic interventions were recommended, without the requirement of any further re-examinations.[8] This change led to a dramatic increase in the number of women diagnosed with GDM,[9 10] as well as the burden on such women and healthcare professionals in Japan. Nevertheless, the validity of diagnosing and treating GDM according to WHO 2013 criteria has not been evaluated.

Therefore, we are currently conducting a study to investigate the optimal Timing of Therapeutic Intervention for Gestational Diabetes Mellitus diagnosed in early pregnancy (TTIGDM study). In the present study, as a nested case-control study within the TTIGDM study, we examined the reproducibility of the OGTT results during early pregnancy and 24–28 weeks of gestation to evaluate the validity of the 2013 WHO criteria, which states that GDM should be diagnosed if the OGTT results are equal to or exceed any of the following values at any time during pregnancy: FPG level of 92 mg/dL, 1-hour value of 180 mg/dL, and/or 2-hour value of 153 mg/dL.

RESEARCH DESIGN AND METHODS

The multicenter prospective cohort study was conducted at five secondary and tertiary medical facilities in Japan. As stated above, the TTIGDM study was initiated with the aim of determining the optimal timing of therapeutic intervention for gestational diabetes diagnosed in early pregnancy, and the present study is an interim report focusing on changes in blood glucose levels. The participating facilities and investigators are listed in the online supplementary appendix. We recruited 151 women with singleton pregnancies who were at a high risk of GDM between January 2018 and April 2019 at the participating facilities who underwent the 75 g OGTT before 20 weeks of gestation and exhibited signs of GDM patterns (meeting any of the following values: FPG level of ≥92 mg/dL, 1-hour value of ≥180 mg/dL, and/or 2-hour value of ≥153 mg/dL), which confirms the definitive diagnosis of early-onset GDM. Women with a random blood glucose level of ≥200 mg/dL, FPG level of ≥126 mg/L, or a hemoglobin A1c (HbA1c) level of ≥6.5% (48 mmol/mol) and those with a prior or current diagnosis of diabetes mellitus were excluded. The enrolled early-onset GDM women were followed up without therapeutic intervention, and they underwent the 75 g OGTT again (second 75 g OGTT) at 24–28 weeks of gestation (mid-pregnancy). All the study participants were fully informed about the possible disadvantages of not receiving any therapeutic intervention during the follow-up period, and they provided consent to participate in this study. Meanwhile, they received lifestyle instructions that are generally provided to pregnant women by maternity nurses and other healthcare professionals. Specifically, the study participants were instructed to follow a balanced diet. According to the guidelines issued by the Japanese Ministry of Health, Labour and Welfare, the following instructions on weight gain were provided: the optimal weight gain during pregnancy should be 9–12 kg for pregnant women with a prepregnancy body mass index (BMI) of <18.5 kg/m^2 and 7–12 kg for those with prepregnancy BMIs of ≥18.5 and <25 kg/m^2. Those with a prepregnancy BMI of ≥25 kg/m^2 were instructed on a case-by-case basis, with an overall instruction to keep the weight gain around 5 kg.[11] Pregnant women exhibiting the GDM patterns on the second 75 g OGTT were diagnosed with true GDM and received nutrition therapy and insulin therapy, if needed. On the other hand, pregnant women not exhibiting the GDM patterns on the second 75 g OGTT were diagnosed with false GDM and received no therapeutic intervention.

In addition, during the follow-up observation before the second 75 g OGTT, all the study participants underwent clinical examinations and had HbA1c and a random blood glucose samples collected once per month. In case an HbA1c of ≥6.5% (48 mmol/mol) or a random blood glucose level of ≥200 mg/dL was detected, they were excluded from the study and received treatment for GDM.

Pregnant women at a high risk of GDM were defined as those meeting any of the following conditions: random blood glucose level of ≥95 mg/dL; prepregnancy body mass index (BMI) of ≥25 kg/m^2; positive urinary glucose; advanced maternal age at pregnancy (≥35 years); family history of first or second-degree relatives with diabetes mellitus; previous history of large for gestational age (LGA) delivery, macrosomic delivery, or shoulder-dystocia delivery; previous history of perinatal loss or malformation of unknown causes; or previous history of GDM.

The maternal characteristics examined were maternal age, prepregnancy BMI, nulliparous rate (%), smoking during pregnancy, reasons for OGTT, and gestational age at the time of the 75 g OGTT during early and mid-pregnancy. The primary outcome was the reproducibility rate of the diagnosis of GDM by the second 75 g OGTT at mid-pregnancy. The secondary outcomes were changes in the results of the 75 g OGTT between early and mid-pregnancies. In addition, the maternal characteristics and pregnancy outcomes were compared between women who did not meet the diagnostic criteria for GDM based on the second 75 g OGTT results (ie, false GDM; early+/late−) and women who met the diagnostic criteria for GDM (ie, true GDM; early+/late+). The comparison of

the maternal characteristics included overall gestational weight gain, weight gain up to the second 75 g OGTT, fluctuations in HbA1c levels, and therapeutic strategies for GDM. The compared pregnancy outcomes included birth weight (g); gestational age (weeks); and rates (%) of cesarean delivery, emergency cesarean delivery, hypertensive disorders of pregnancy (HDP), preterm birth, macrosomia, shoulder dystocia, LGA, admission to the neonatal intensive care unit (NICU), neonatal hypoglycemia, hyperbilirubinemia, and respiratory distress syndrome (RDS). A diagnosis of HDP was established in pregnant women with a blood pressure of ≥140/90 during pregnancy, according to the definition stipulated by the Japan Society for the Study of Hypertension in Pregnancy.[12] Macrosomia was defined as birth weight >4000 g. LGA infants were defined as those with birth weight exceeding the 90th percentile based on the report from Neonate Committee of the Japan Pediatric Society. Neonatal hypoglycemia was defined as a blood glucose level of <40 mg/dL. Preterm birth was defined as birth before 37 weeks of gestation. Hyperbilirubinemia was defined as the requirement of phototherapy in an infant. Furthermore, RDS was defined as the presence of RDS-specific chest radiographic findings and requirement of oxygen administration within 24 hours of birth.

All data are presented as medians and were compared using the Wilcoxon signed-rank test, Mann-Whitney U test, and Fisher's exact test. A probability (p) value of <0.05 was considered statistically significant. Statistical analyses were performed using JMP Pro12 software (SAS Institute, Cary, North Carolina, USA).

RESULTS

In total, 151 women were enrolled in the study. Before the 75 g OGTT was repeated at 24–28 weeks of gestation, one woman experienced a miscarriage, two were transferred to another hospital, and two withdrew their consent. Thus, 146 women underwent a repeated 75 g OGTT. During the follow-up period, no woman exhibited poor glycemic control, as defined by a random blood glucose level of ≥200 mg/dL or HbA1c level of ≥6.5% (48 mmol/mol).

Table 1 lists the characteristics of the study participants during pregnancy. The median maternal age was 36 years, and the median prepregnancy BMI was 22.8 kg/m^2. The most common risk factor for GDM as the reason for performing the 75 g OGTT in early pregnancy was older age (≥35 years; 60.3%), followed by high BMI (≥25 kg/m^2; 34.9%) and a high random blood glucose level (24%).

Of the 146 women diagnosed with GDM in early pregnancy (early-onset GDM), 69 (47.3%) had normal results of the second 75 g OGTT performed at 24–28 weeks of gestation. In other words, the results of the second 75 g OGTT in about half of the women with early-onset GDM were false positive (ie, false positive early GDM).

Table 2 and figure 1 show changes in plasma glucose levels between the first and second 75 g OGTTs. In women with early-onset GDM, the median FPG level during the first 75 g OGTT was 93 mg/dL, which was significantly higher than the median FPG level of 87.5 mg/dL of the second 75 g OGTT performed in mid-pregnancy (p<0.001). Compared with FPG levels in early pregnancy, that in mid-pregnancy decreased in 95/146 women (65%). There was no significant difference in either the 1-hour or 2-hour values.

Table 3 shows the proportions of women with abnormal values of each 75 g OGTT parameter, namely, FPG, 1-hour value, and 2-hour value. In the first 75 g OGTT, 86/146 women (59%) had an elevated FPG level, which was the most common reason for a diagnosis of GDM. In 51/146 women (35%), GDM was diagnosed by an abnormally

Table 1 Maternal characteristics (n=146)

Median maternal age (years) (IQR)		36 (33.8–39)
Median prepregnancy BMI (kg/m^2) (IQR)		22.8 (20.0–26.8)
Gestational age at the time of the first 75 g OGTT before 20 weeks (weeks) (IQR)		14.7 (13.9–17.1)
Gestational age at the time of the second 75 g OGTT at 24–28 weeks (weeks) (IQR)		26.1 (25.3–27.1)
Nullipara, n (%)		62 (43%)
Smoking during pregnancy, n (%)		1 (0.7%)
Risk factors of GDM	Advanced maternal age	94 (60%)
(Multiple responses included)	BMI>25 kg/m^2	51 (35%)
	High value of random blood glucose	35 (24%)
	Family history of type 2 DM	34 (23%)
	Previous history of GDM	15 (10%)
	Positive urinary glucose	5 (3.4%)
	Previous history of macrosomic delivery, LGA delivery, and shoulder-dystocia delivery	3 (2.1%)

BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; LGA, large for gestational age; OGTT, oral glucose tolerance test.

Table 2 Comparison of median glucose levels (mg/dL) as determined with the 75 g OGTT (IQR) between before 20 weeks of gestation and 24–28 weeks of gestation

	75 g OGTT before 20 weeks	75 g OGTT at 24–28 weeks	P value
FPG	93 (88–95)	87.5 (82–92)	<0.001
1-hour value	162 (129–185)	159 (131–180)	0.98
2-hour value	149 (116–167)	136.5 (113–157)	0.21

The study participants were instructed to fast for 10 hours before the 75 g OGTT.
FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.

high FPG level alone. On the other hand, 37/146 women (27%) had an abnormally high FPG levels on the second 75 g OGTT.

Table 4 shows the pregnancy outcomes of the women with false positive early GDM and true GDM. Compared with the women false positive early GDM, those with true GDM had significantly higher prepregnancy BMIs and higher HbA1c levels at all time points including baseline, second OGTT, and delivery. In particular, there were significantly more women with true GDM among those with a prepregnancy BMI of ≥25 kg/m^2 (p=0.016). The degree of weight gain up to the second OGTT was equivalent between the women with false positive early GDM and true GDM (4 kg vs 4.5 kg); furthermore, the degree of weight gain up to delivery was non-significantly larger in the women with false positive early GDM (8.9 kg vs 7.7 kg). Regarding the pregnancy outcomes, the rates of preterm birth and NICU admission were significantly higher in the women with true GDM. Although not significantly different, the rate of LGA infants was higher in the women with true GDM. Overall, the pregnancy outcomes were poor in the women with true GDM.

DISCUSSION

When standard IADPSG thresholds are applied to the 75 g OGTT performed at <20 weeks of gestation in women at risk of developing GDM, nearly half of those with at least one abnormal value in early pregnancy, will have normal test results when repeated at 24–28 weeks of gestation.

In 2010, IADPSG stated that during early pregnancy, GDM is diagnosed if FPG is 92–125 mg/dL. However, in previous reports, 60% of pregnant women with an FPG level of ≥92 mg/dL during early pregnancy did not have high FPG levels, as determined with the 75 g OGTT, at 24–28 weeks of gestation,[6] and 55% of those with high FPG levels during early pregnancy were not diagnosed as having GDM at 24–28 weeks of gestation.[5] In response to

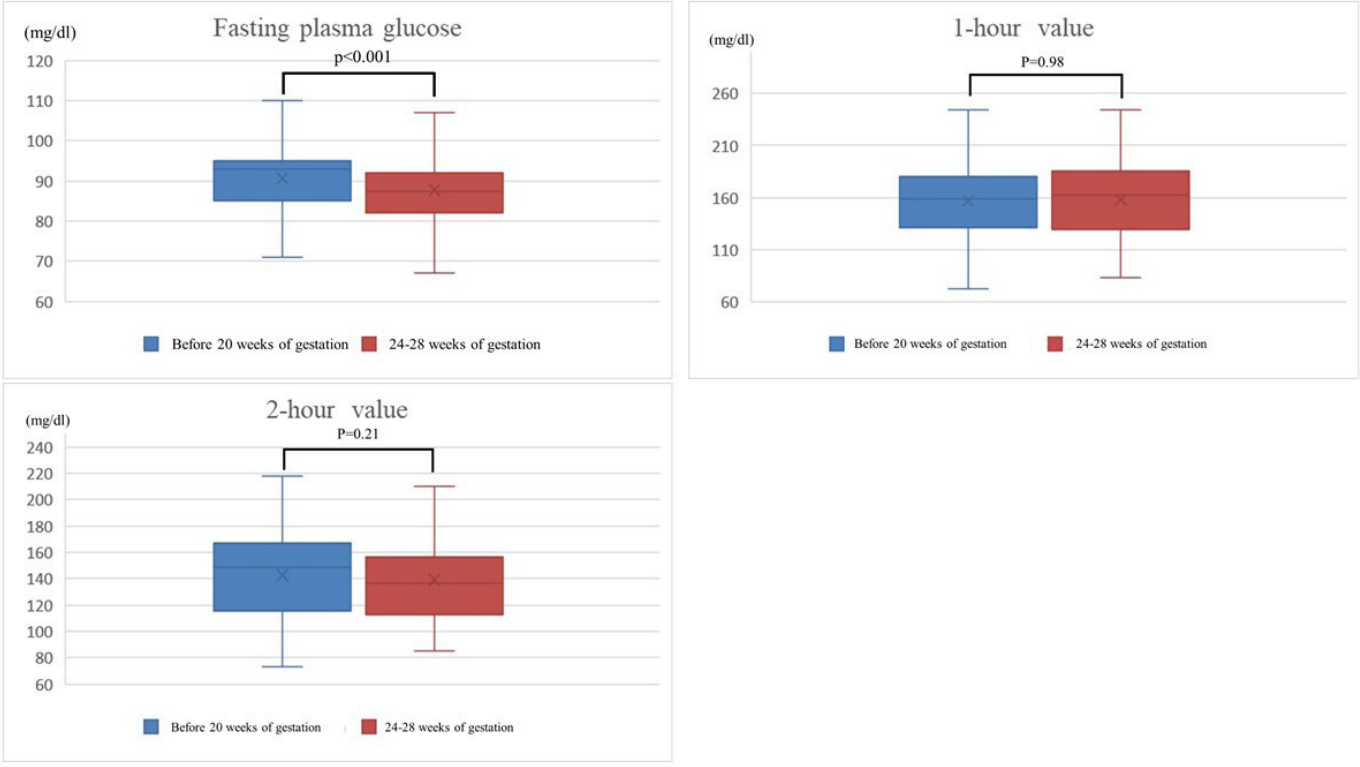

Figure 1 Comparison of glucose levels (mg/dL) as determined with the 75 g OGTT between before 20 weeks of gestation and 24–28 weeks of gestation. OGTT, oral glucose tolerance test.

Table 3 The number of subjects with individual glucose measures≥threshold

	75 g OGTT before 20 weeks of gestation	75 g OGTT at 24–28 weeks of gestation
FPG	86 (59%)	39 (27%)
1-hour value	47 (32%)	38 (26%)
2-hour value	67 (46%)	42 (29%)

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.

these reports, the IADPSG withdrew the criteria for FPG levels in respect to early-onset GDM in 2016. Mills *et al*[13] reported that FPG levels decrease physiologically as pregnancy progresses. The results of the present study, which was limited to Japanese pregnant women, were consistent with these results. In Japan, the same criteria as the WHO criteria are adopted. However, given that about half of women with early-onset GDM have false positive early GDM, which is diagnosed based on normal blood glucose patterns during re-examination at 24–28 weeks of gestation, the WHO diagnostic criteria should be reviewed.

The clinical significance of early-onset GDM still remains unknown. Sweeting *et al*[14] reported that in women at a high risk of GDM, early-onset GDM was associated with poor pregnancy outcomes that were more comparable with those of women with type 2 diabetes mellitus rather than those with late-onset GDM diagnosed at or after 24–28 weeks of gestation. On the other hand, Hong *et al*[15] found no benefit of a diagnosis of early-onset GDM in pregnant women at a high risk of GDM. In Japan, Hagiwara *et al*[16] reported no differences in the pregnancy outcomes between women with early-onset GDM treated from early pregnancy and those with late-onset GDM diagnosed and treated during or after 24–28 weeks

Table 4 Maternal characteristics and pregnancy outcomes of women with false positive early GDM (early+/late–) and true GDM (early+/late+)

	False positive early GDM (early+/late–) n=69	True GDM (early+/late+) n=77	P value	OR (95% CI)
Maternal age (years)	37 (19–47)	36 (23–45)	0.62	
Prepregnancy BMI (kg/m^2)	21.8 (16.4–43.1)	24.0 (17.3–41.8)	0.001	
Prepregnancy BMI:<18.5 kg/m^2	8 (11.6%)	5 (6.5%)	0.39	
Prepregnancy BMI: 18.5–25 kg/m^2	44 (63.8%)	38 (49.4%)	0.096	
Prepregnancy BMI:≥25 kg/m^2	17 (24.6%)	34 (44.2%)	0.016	
Primipara	29 (42%)	33 (43%)	1.00	
Smoking during pregnancy	1 (1.4%)	0 (0%)		
Weight gain until second OGTT (kg)	4 (–9.3–15)	4.5 (–4.8–15.8)	0.75	
Weight gain until delivery (kg)	8.9 (–11–19.2)	7.7 (–5.0–18.0)	0.25	
HbA1c on baseline (%)	5.2 (4.6–5.9)	5.4 (4.6–6.3)	<0.001	
HbA1c at second OGTT (%)	5.1 (4.6–6.0)	5.4 (4.8–6.1)	<0.001	
HbA1c at delivery (%)	5.5 (4.8–6.1)	5.7 (5.0–7.5)	<0.001	
Nutrition therapy (%)	Not applicable	56 (73%)		
Insulin therapy (%)	Not applicable	21 (27%)		
Hypertensive disorders of pregnancy (%)	12 (17%)	13 (17%)	1.00	
Birth weight (g)	3002 (1896–3786)	2976 (1552–4058)	0.66	
Gestational age (weeks)	39.3 (34.0–42.1)	38.7 (33.8–41.7)	0.009	
Preterm birth	1 (1.4%)	10 (12%)	0.010	0.0985 (0.0122 to 0.791)
Macrosomia	0 (0%)	1 (1.3%)		
Shoulder dystocia	0 (0%)	1 (1.3%)		
Large for gestational age	6 (8.7%)	15 (20%)	0.10	0.394 (0.143 to 1.080)
Cesarean delivery	29 (42%)	25 (32%)	0.30	1.508 (0.767 to 2.963)
Emergency cesarean delivery	12 (17%)	10 (13%)	0.49	1.411 (0.567 to 3.506)
Admission to NICU	6 (8.7%)	18 (23%)	0.024	0.312 (0.116 to 0.840)
Neonatal hypoglycemia	4 (5.8%)	3 (3.9%)	0.71	1.497 (0.323 to 6.942)
Neonatal hyperbilirubinemia	7 (10%)	11 (14%)	0.46	0.667 (0.243 to 1.831)
Respiratory distress syndrome	0 (0%)	0 (0%)		

The values are expressed as mean (range) or number (%).
BMI, body mass index; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; NICU, neonatal intensive care unit; OGTT, oral glucose tolerance test.

of gestation and concluded that the diagnostic criteria for GDM should probably be applied only at 24–28 weeks of gestation, rather than throughout pregnancy. A systematic review and meta-analysis of the screening and treatment for early-onset GDM[17] also concluded that the therapeutic effects on early-onset GDM are dubious and that randomized controlled trials investigating the therapeutic effects on early-onset GDM are urgently required.

In response to the findings of a large-scale cohort study conducted on the association between HbA1c levels during early pregnancy and pregnancy outcomes in New Zealand,[18] the IADPSG stated that early-onset GDM may be defined as a HbA1c level of ≥5.9% (41 mmol/mol) in early pregnancy instead of an FPG level of 92–125 mg/dL.[7] In the present study, HbA1c levels had been significantly higher since the baseline in the women with true GDM than in those with false positive early GDM. This may support the validity of the new IADPSG proposal. Given the finding of this study that the 1-hour and 2-hour values of the 75 g OGTT were almost comparable between early pregnancy and 24–28 weeks of gestation, it seems that a 1-hour value of ≥180 mg/dL or 2-hour value of ≥153 mg/dL should be regarded as a high risk of a diagnosis of GDM at 24–28 weeks of gestation, or in other words, booking GDM. Because there were significantly more women with true GDM among those with a prepregnancy BMI of ≥25 kg/m^2, the presence of obesity in combination with the above conditions should be regarded as being linked to a higher risk of diagnosis of GDM during 24–28 weeks of gestation.

The pregnancy outcomes were overall poorer in the women with true GDM who exhibited the GDM patterns during early pregnancy and during 24–28 weeks of gestation than in those with false positive early GDM who exhibited the GDM patterns only during early pregnancy. Because false positive early GDM was not regarded as GDM during pregnancy, the women with false positive early GDM did not receive any therapeutic intervention. On the other hand, true GDM had been treated as GDM since mid-pregnancy, and the women with true GDM received therapeutic interventions including nutrition therapy and insulin therapy. Nevertheless, the rate of LGA infants was higher (20%) in the women with true GDM, although the difference was not significant. Conversely, the delivery rate of LGA infants in the women with false positive early GDM was 8.7%, which is comparable with the rate expected in the general population. These results suggest that no therapeutic interventions are necessary for women with false positive early GDM who exhibit GDM patterns only during early pregnancy.

There were some limitations to this study that should be addressed. First, all of the study participants were Japanese. Because GDM prevalence and glucose tolerance vary among different populations,[19] the results of the present study will not necessarily be applicable to other populations. Second, certain selection bias was noted in this study. This study included pregnant women at a high risk of GDM who were diagnosed with GDM based on 75 g OGTT during early pregnancy; therefore, the study participants were not selected via universal screening. Because there are pregnant women without any risk factors who are diagnosed with GDM,[20 21] the present study results may not be applicable to all pregnant women with GDM. Third, because this was a prospective study, the participating women themselves were aware that they would be diagnosed as having GDM under usual circumstances in Japan. Hence, it is possible that the women unconsciously improved some lifestyle factors. However, because the degree of weight gain during follow-up without treatment up to 24–28 weeks of gestation was almost similar between the women with true and false positive early GDM, it can be assumed that there was almost no impact on weight gain; this could imply that both groups implemented similar lifestyle. Finally, the results of the glucose tolerance test are known to be imprecise because of poor reproducibility in itself.[22] However, to the best of our knowledge, this is the first prospective study in pregnant women with early-onset GDM to investigate whether the results of the 75 g OGTT in early pregnancy were reproducible at 24–28 weeks of gestation, when GDM should be diagnosed according to the recommendation of the IADPSG.

In conclusion, although women with early-onset GDM were followed up without treatment, the results of repeated 75 g OGTT during mid-pregnancy were normal in about 50%. Our data did not support the adoption of IADPSG thresholds for the diagnosis of GDM prior to 20 weeks of gestation.

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Contributors SN researched data and wrote the manuscript. SA contributed to study design and wrote the manuscript. JK contributed to study design and researched data. RS and SO researched data. YH and AM researched data and recruited the subjects. EM finalized the manuscript.

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Patient consent for publication Not required.

Ethics approval The study protocol was approved by the Ethics Committee of the Yokohama City University Medical Center (approval no. B171102004).

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