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Adverse obstetric outcomes in early-diagnosed gestational diabetes mellitus: The Japan Environment and Children's Study

Hyo Kyozuka[1,2]*, Shun Yasuda[1,2], Tsuyoshi Murata[1,2], Toma Fukuda[1,2], Akiko Yamaguchi[1,2], Aya Kanno[1,2], Akiko Sato[2], Yuka Ogata[2], Mitsuaki Hosoya[2,3], Seiji Yasumura[2,4], Koichi Hashimoto[2,3], Hidekazu Nishigori[2,5], Keiya Fujimori[1,2], The Japan Environment and Children's Study (JECS) Group†

[1]Department of Obstetrics and Gynecology, Fukushima Medical University School of Medicine, Fukushima, Japan, [2]Fukushima Regional Center for the Japan Environmental and Children's Study, Fukushima, Japan, [3]Department of Pediatrics, Fukushima Medical University School of Medicine, Fukushima, Japan, [4]Department of Public Health, Fukushima Medical University School of Medicine, Fukushima, Japan, and [5]Fukushima Medical Center for Children and Women, Fukushima Medical University, Fukushima, Japan

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***Correspondence**
Hyo Kyozuka
Tel.: +81-24-547-1288
Fax: +81-24-548-3878
E-mail address:
kyozuka@fmu.ac.jp

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ABSTRACT

Aims/Introduction: To examine adverse outcomes in women with early-diagnosed gestational diabetes mellitus using data from a large birth cohort study in Japan.

Materials and Methods: This study analyzed data from singleton pregnancies in the Japan Environment and Children's Study including births during 2011–2014. Mothers with an HbA1c level ≥6.5% in the first trimester, a history of diabetes mellitus, or steroid use during pregnancy were excluded. The participants were divided into three groups: control (without gestational diabetes mellitus), early-diagnosed gestational diabetes mellitus (diagnosed before gestational week 24), and late-diagnosed gestational diabetes mellitus (diagnosed after gestational week 24). Multiple logistic regression analysis was performed to calculate the risk of early-diagnosed and late-diagnosed gestational diabetes mellitus for adverse obstetrics outcomes.

Results: In total, 100,376 eligible participants were included in this study. The number of individuals in control cases, early-diagnosed gestational diabetes mellitus cases, and late-diagnosed gestational diabetes mellitus cases was 98,090 (97.7%), 751 (0.7%), and 1,535 (1.5%), respectively. When control cases were used as reference, multiple logistic regression analysis revealed that early-diagnosed gestational diabetes mellitus increased the risk of hypertensive disorders of pregnancy (adjusted odds ratio: 2.08, 95% confidence interval: 1.51–2.86), early-onset hypertensive disorders of pregnancy (adjusted odds ratio: 1.91, 95% confidence interval: 1.01–3.65), and late-onset hypertensive disorders of pregnancy (adjusted odds ratio: 1.92, 95% confidence interval: 1.29–2.86).

Conclusion: Early-diagnosed gestational diabetes mellitus is associated with serious obstetric complications. Our findings indicate the necessity of further investigations to validate the benefit of early screening for gestational diabetes mellitus in pregnant women.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a condition wherein glucose intolerance occurs during pregnancy [1]. GDM causes long-term health problems for both the affected mothers and their offspring. Approximately 70% of women with GDM develop diabetes mellitus within 22–28 years after pregnancy [2]. GDM also increases the risk of developing obesity, impaired glucose tolerance, and diabetes in the offspring [3,4]. Moreover, poorly controlled maternal diabetes during pregnancy may cause adverse neurodevelopmental outcomes [5]. Despite strong evidence of the association between maternal age and these adverse outcomes [6], the gestational age at GDM diagnosis has not always been reported [7].

†The Japan Environment and Children's Study (JECS) Group: Michihiro Kamijima, Shin Yamazaki, Yukihiro Ohya, Reiko Kishi, Nobuo Yaegashi, Koichi Hashimoto, Chisato Mori, Shuichi Ito, Zentaro Yamagata, Hidekuni Inadera, Takeo Nakayama, Hiroyasu Iso, Masayuki Shima, Youichi Kurozawa, Narufumi Suganuma, Koichi Kusuhara, Takahiko Katoh

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Routine screening for GDM is recommended in pregnancy [8] because treatment reduces the risk of adverse outcomes [9,10]; however, the best screening approach remains unclear. The Japan Society of Obstetrics and Gynecology (JSOG) and the Japan Association of Obstetricians and Gynecologists (JAOG) recommend GDM screening at two time points, i.e., in the first trimester (at approximately 12 weeks) and the second trimester (between approximately 24–28 weeks) [11].

Therefore, women diagnosed with GDM have either early-diagnosed (Ed)-GDM identified during early pregnancy or late-diagnosed (Ld)-GDM identified later than Ed-GDM (around gestational weeks 24–28). However, it remains unclear whether pregnancy outcomes can be improved by detecting GDM early in pregnancy versus screening women for GDM in late pregnancy. Thus far, only a few studies have compared obstetrics outcomes between women with GDM diagnosis in the first half of their pregnancy and those with a GDM diagnosis in the second half [12,13]. The results of these studies suggested that women diagnosed with GDM during early pregnancy have a potential risk of adverse pregnancy outcomes such as large-for-gestational-age newborns, hypertensive disorders of pregnancy (HDP), and cesarean sections. However, these studies were limited due to the small number of Ed-GDM cases or retrospective study designs.

Therefore, the present study evaluated the risk of adverse pregnancy complications in the Ed- and Ld-GDM groups using the largest Japanese birth cohort database.

METHODS

The Japan Environment and Children's Study (JECS)

In this study, we used the data from JECS, a government-funded birth cohort study [14]. JECS was started in January 2011 to investigate the effects of several environmental factors on the future health of children. This study was conducted in 15 regional centers across Japan, and the protocol has been reported elsewhere [14]. The eligibility criteria for the JECS participants were as follows: (i) living in one of the study areas at the time of recruitment and expected to reside in Japan, (ii) an expected delivery date between August 1, 2011, and mid-2014, and (iii) the ability to participate in the study without difficulty in writing and reading Japanese. The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the ethics committees of all participating institutions. The JECS was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all participating women.

Data collection

The current study utilized the JECS dataset released in June 2016 (dataset: jecs-ag-20160424). We used three types of data: (i) T1: data obtained at a time around the first trimester (first questionnaire), including a self-reported questionnaire related to the maternal medical background, as well as data for blood parameters such as HbA1c levels; (ii) T2: data collected around the second/third trimester (second questionnaire), including information regarding maternal socioeconomic status and background; and (iii) M0: obstetric outcomes retrieved from the medical records provided by the co-operating health care providers. The exclusion criteria were multiple pregnancies, incomplete data, presence of diabetes mellitus (either insulin-dependent diabetes mellitus or non-insulin-dependent diabetes mellitus) at the time of pregnancy, HbA1c ≥6.5% in the first trimester, and/or any steroid use during pregnancy.

Diagnosis of GDM in Japan

All pregnant women participating in JECS underwent the screening procedure for GDM in both early and late pregnancy. In Japan, glucose tolerance screening and testing for GDM is performed for every pregnant woman, according to the protocols recommended by the Obstetrics Society and Diabetes Society of Japan, and, depending on the local obstetrics institution, it is a two-step protocol during both first and second/third trimesters [11,15,16]. Briefly, the first step is the screening of random blood glucose (RBG) levels or 1-h fasting 50-g oral glucose challenge test (GCT) levels during the first trimester. If the screening result is positive, the pregnant women undergo the 75-g oral glucose tolerance test (OGTT) and are confirmed to have GDM. If the first-trimester screening is negative, the women undergo the second screening using either RBG or a 1-h fasting 50-g GCT in the second/third trimester. An RBG level of ≥95 mg/dL or a GCT level of >140 mg/dL is considered a positive screening result. In case of a positive screening result, a 75-g OGTT is conducted with cutoff values of ≥92 mg/dL for fasting plasma glucose, ≥180 mg/dL for plasma glucose at 1 h, and ≥153 mg/dL for plasma glucose at 2 h. GDM is confirmed if at least one of the three aforementioned glycemic levels is above the recommended threshold during OGTT (fasting plasma glucose, plasma glucose at 1 h, and plasma glucose at 2 h). The M0 data included the gestational age at the time of GDM diagnosis.

Maternal medical background

Information on the medical background of participants was retrieved from the M0 data (maternal age, body mass index [BMI] before pregnancy, presence of maternal chronic hypertension, and parity), T1 data (manner of conception and presence of polycystic ovary syndrome [PCOS]), and T2 data (maternal education and annual household income).

The maternal age before pregnancy was categorized into six age groups: <20, 20–24, 25–29, 30–34, 35–39, and ≥40 years. The BMIs before pregnancy were calculated according to the World Health Organization standard as body weight divided by height squared (kg/m^2), and the participants were divided into three groups according to their BMIs: <18.5, 18.5–25.0, and ≥25.0 kg/m^2. The mothers were also categorized into primipara or multipara based on the number of deliveries: 0 (primipara) and more than 1 (multipara). The method of conception was

categorized as natural pregnancy or pregnancy after assisted reproductive technology (ART), with ART being defined as a conception after in vitro fertilization and/or intracytoplasmic sperm injection, or a cryopreserved, blastocyst, or frozen embryo transfer [17]. Maternal participants were also asked to answer the question: "Have you ever been diagnosed with PCOS in a medical institution?" Maternal participants who answered "yes" were classified as having PCOS. The information on maternal chronic hypertension was derived from the M0 data and was defined as the presence of hypertension before conception. Maternal education was categorized into four groups: junior high school, <10 years of education; high school, 10–12 years; technical/vocational college, 13–16 years; and graduate school, ≥17 years. The annual household income was categorized into four levels: <2,000,000 Japanese yen (JPY); 2,000,000–5,999,999 JPY; 6,000,000–9,999,999 JPY; and ≥10,000,000 JPY [18]. In this analysis, information on the pre-pregnancy gynecological condition, PCOS, was obtained from the self-reported questionnaire [19].

Intermediate information during pregnancy

Intermediate information, such as smoking during pregnancy and the K6 score, was obtained in both the first and second/third trimesters. We used the Japanese version of the K6 to screen for psychological distress in the first and second/third trimesters. The K6 is a self-administered questionnaire that consists of six questions evaluating depression and anxiety on a scale from 0 (little to no depression or anxiety) to 4 (high levels of depression or anxiety). The K6 score is a continuous variable determined by the sum of six sub-scores with the total possible score ranging from 0 to 24. In the present study, a patient with a K6 score of ≥13 was defined as having psychological stress [18,20].

A self-reported questionnaire in both the first and second/third trimesters provided information on the smoking history based on the following answers: "Never," "Previously did, but quit before realizing current pregnancy," "Previously did, but quit after realizing current pregnancy," and "Currently smoking." Women who chose "Currently smoking" as the answer were considered smokers (smoking category); otherwise, they were considered non-smokers (non-smoking category).

Obstetric outcomes

Obstetric outcomes obtained from the M0 data included the following: preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA) and large for gestational age (LGA), HDP, placenta accreta spectrum and placental abruption, mode of delivery, umbilical artery (UmA) pH, and maternal transfusion. PTB was categorized as <37 weeks and <34 weeks. LBW was classified as <2,500 g and <1,500 g. SGA and LGA were defined as a birth weight below 1.5 and above 1.5 standard deviations, respectively, corrected for gestational age and sex according to the "New Japanese neonatal anthropometric charts for gestational age at birth" [21,22]. HDP in the present analysis was defined as new onset of hypertension (≥140/90 mmHg) after the confirmation of pregnancy [23]. HDP was further classified into three categories: Eo-HDP (early-onset HDP, occurring before 34 weeks of gestation), Lo-HDP (late-onset HDP, occurring after 34 weeks of gestation), and HDP with SGA, suggesting a severe HDP phenotype [24]. The mode of delivery was categorized into vaginal delivery or cesarean section (CS). The definition of a placental complication (abruption or accreta) was dependent on the obstetrician in charge and was diagnosed clinically. Histological confirmation was not mandatory for the diagnosis of a placental complication in the present study [17]. Fetal arterial blood was obtained at the site of delivery, and the UmA-pH was measured immediately after delivery. Fetal acidosis was defined as an UmA-pH <7.20, <7.10, or <7.00, according to the results of a previous study that showed that an UmA-pH threshold of 7.20 is associated with an increased risk of adverse short-term outcomes [25]. An UmA-pH threshold of 7.10 is associated with an increased risk of adverse neurological sequelae [26]. Cerebral palsy is thought to occur more frequently with an UmA-pH <7.00 [27].

Statistical analysis

After applying the inclusion criteria, 100,376 participants were enrolled in the present analysis (Figure 1). The frequency of GDM by gestational age was also examined (Figure 2). Based on the frequency of GDM by gestational age, we defined GDM diagnoses before and after 24 weeks as Ed-GDM and Ld-GDM, respectively. The maternal background data, intermediate events during pregnancy, and obstetric outcomes were analyzed with respect to three groups: without GDM (control), with Ed-GDM, and with Ld-GDM. The chi-square test was used to compare categorical variables, whereas the one-way analysis of variance or the Kruskal–Wallis test was used to compare continuous variables. If there was a significant difference regarding obstetric outcomes among the three groups, we further examined the risk of Ed-GDM and Ld-GDM for obstetric outcomes, and the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for each obstetric outcome were calculated using a univariate regression model. Maternal BMI before pregnancy, maternal age, maternal smoking habit, parity, ART pregnancy, maternal education, and presence of hypertension at the time of pregnancy were used as confounding factors. Logistic regression analysis was performed using dummy variables for categorical variables comprising more than three categories (e.g., BMI could be categorized as <18.5, 18.5 − 25.0, and >25 kg/m^2). The confounding factors in this study were determined based on previously identified risk factors for the occurrence of PTB, LBW, and HDP [22,23,24]. We excluded women with hypertension at the time of pregnancy to calculate the risk of HDP, which indicates new-onset hypertension during pregnancy. SPSS version 26 (IBM Corp., Armonk, NY, USA) was used for conducting statistical analyses. The level of statistical significance was set at $P < 0.05$.

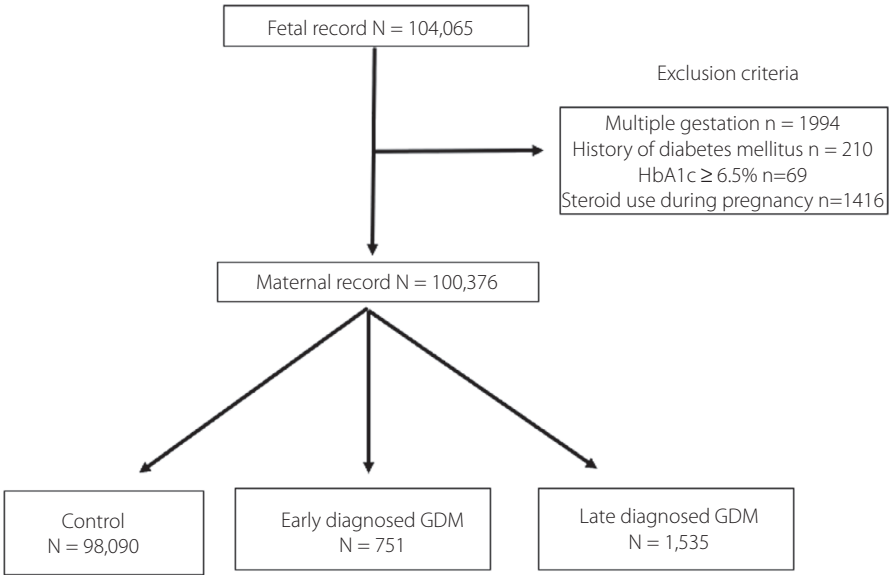

Figure 1 | Flowchart of the study selection process.

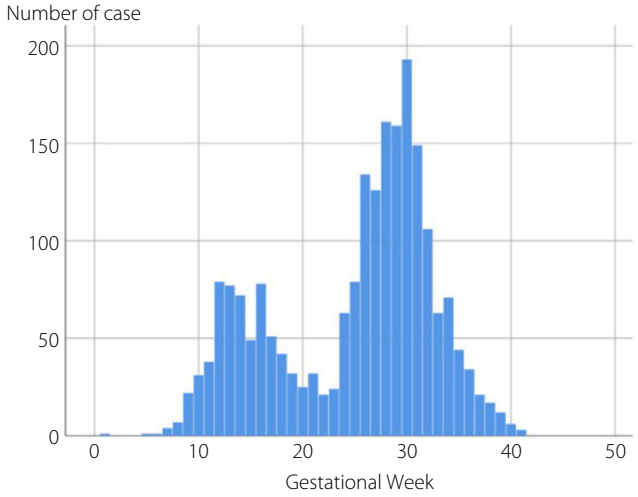

Figure 2 | Occurrence of gestational diabetes mellitus (GDM) by gestational week. The two distinct peaks for the occurrence of GDM reflect the screening procedures in the first and second/third trimesters. After gestational week 24, the prevalence of GDM is remarkably increased. Thus, we propose the definition of early-diagnosed (Ed) and late-diagnosed (Ld)-GDM based on the threshold of 24 weeks and categorize the study population into three groups: control, Ed-GDM, and Ld-GDM.

RESULTS

The total number of participants was 100,376, comprising 98,090 control cases and 2,560 (2.6%) GDM cases (751 (0.7%) Ed-GDM cases and 1,535 (1.5%) Ld-GDM cases). For 274 GDM cases, the gestational age at the time of GDM diagnosis was unknown.

Table 1 summarizes the maternal background of the three defined study groups. There were significant differences in the categories of maternal age and BMI before pregnancy ($P < 0.001$). In the Ed-GDM group, the percentages of women with maternal age over 40 years and BMI more than 25 kg/m^2 were 12.4% and 36.4%, respectively, which were the highest values of the three groups. The rates of chronic hypertension, PCOS, and ART pregnancy were significantly different among the three groups ($P < 0.001$ for all three groups), and again, the highest percentages were observed in the Ed-GDM group (5.9%). There were no significant differences regarding the ratios of primipara, maternal education, and annual household income among the three groups ($P = 0.087$, $P = 0.895$, and $P = 0.127$, respectively).

Table 2 shows the intermediate events during pregnancy of the three defined study groups. There was no significant difference in the K6 scores ≥13 of the first and second trimesters ($P = 0.999$ and $P = 0.127$, respectively). Although a significantly higher rate of smokers in the first trimester was observed for the Ld-GDM group (6.2%, $P = 0.036$), there was no significant difference in the rate of smokers in the second trimester among the three study groups ($P = 0.082$).

Table 3 summarizes the obstetric outcomes of the three defined study groups. The highest occurrence rates of PTB <37 weeks (7.7%, $P = 0.003$), PTB <34 weeks (3.1%, $P = 0.015$), LBW <2,500 g (11.3%, $P = 0.021$), LBW <1,500 g (2.4%, $P < 0.001$), HDP (9.6%, $P < 0.001$), Eo-HDP (4.0%, $P < 0.001$), Lo-HDP (4.3%, $P < 0.001$), HDP with SGA (1.1%, $P = 0.032$), and CS (30.5%, $P < 0.001$) were observed in the Ed-GDM group.

Table 4 shows the risk of obstetric outcomes posed by both Ed-GDM and Ld-GDM using a multiple logistic regression

Table 1 | Maternal background data based on the GDM phenotype

Variable	Participants			*P*-value
	Control *n* = 98,090	Ed-GDM *n* = 751	Ld-GDM *n* = 1,535	
Maternal age (years), mean (SD)	31.1 (5.1)	33.7 (5.0)	33.2 (5.0)	<0.001†
Maternal age category (years), %				
≤19	0.9	0.3	0.5	<0.001‡
20–29	37.2	19.7	23.9	
30–39	57.5	67.6	65.3	
≥40	4.5	12.4	10.2	
BMI before pregnancy, mean (SD)	21.2 (18.2)	24.2 (5.5)	23.1 (4.7)	<0.001†
BMI before pregnancy (kg/m^2), %				
<18.5	17.6	8.0	11.5	<0.001‡
18.5–25.0	73.2	55.9	61.5	
>25.0	9.2	36.1	27.0	
Primipara, %	40.4	36.4	40.4	0.087‡
Hypertension before pregnancy, %	1.1	5.9	2.5	<0.001‡
PCOS, %	2.1	4.9	3.6	<0.001‡
ART, %	2.9	5.2	4.6	<0.001‡
Maternal education (years), %				
<10	4.8	5.5	5.1	0.895‡
10–12	31.5	32.6	31.7	
13–16	42.0	41.9	42.0	
>17	21.7	20.0	21.2	
Annual household income (JPY), %				
<2,000,000	5.7	5.2	6.7	0.127‡
2,000,000–5,999,999	67.6	67.0	65.2	
6,000,000–9,999,999	22.4	23.6	22.5	
>10,000,000	4.3	4.2	5.6	

†One-way analysis of variance. ‡Chi-square test. ART, assisted reproductive technology; BMI, body mass index; Ed, early diagnosed; GDM, gestational diabetes mellitus; JPY, Japanese yen; Ld, late diagnosed; PCOS, polycystic ovary syndrome; SD, standard deviation.

Table 2 | Intermediate factors based on the GDM phenotype

Variable	Participants			*P*-value†
	Control *n* = 98,090	Ed-GDM *n* = 751	Ld-GDM *n* = 1,535	
K6 score ≥13 in the 1st trimester, %	3.5	3.5	3.5	0.999
K6 score ≥13 in the 2nd trimester, %	3.2	3.3	4.2	0.127
Smoking during the 1st trimester, %	4.8	5.4	6.2	0.036
Smoking during the 2nd trimester, %	4.6	4.6	5.8	0.082

†Chi-square test. Ed, early diagnosed; GDM, gestational diabetes mellitus; Ld, late diagnosed.

model, with the control group as reference. Ld-GDM was a risk factor for both PTB <37 weeks and LGA (aOR: 1.49, 95% CI: 1.00–1.72 and aOR: 1.57, 95% CI: 1.32–1.85, respectively). Both Ed-GDM and Ld-GDM increased the risk of HDP (aOR: 2.08, 95% CI: 1.51–2.86 and aOR: 1.73, 95% CI: 1.36–2.22, respectively). Both Ed-GDM and Ld-GDM also increased the risk of Eo-HDP (aOR: 1.91, 95% CI: 1.01–3.65 and aOR: 1.99, 95% CI: 1.24–3.19, respectively) and Lo-HDP (aOR: 1.92, 95% CI: 1.29–2.86 and aOR: 1.71, 95% CI: 1.27–2.30, respectively). Moreover, both Ed-GDM and Ld-GDM increased the possibility of CS (aOR: 1.34, 95% CI: 1.13–1.59 and aOR: 1.40, 95% CI: 1.24–1.58, respectively).

DISCUSSION

In this study, gestational week 24 was defined as the cutoff value to categorize GDM into Ed and Ld types based on the

Table 3 | Obstetric outcomes based on the GDM phenotype

Variable	Participants			*P*-value†
	Control *n* = 98,090	Ed-GDM *n* = 751	Ld-GDM *n* = 1,535	
PTB <37 weeks, %	6	7.7	7.7	0.003
PTB <34 weeks, %	2.4	3.1	1.4	0.015
LBW <2,500 g, %	8.7	11.3	9.6	0.021
LBW <1,500 g, %	1.3	2.4	0.5	<0.001
SGA, %	5.2	5.7	4.7	0.598
LGA, %	6.8	10.2	12.1	<0.001
HDP, %	2.9	9.6	6.7	<0.001
Eo-HDP, %	0.7	4	2.4	<0.001
Lo-HDP, %	2.0	4.3	4.1	<0.001
HDP with SGA	0.5	1.1	0.3	0.032
Placenta abruption, %	0.4	0.1	0.7	0.115
Placenta accreta spectrum, %	0.2	0.1	0.3	0.829
Cesarean delivery, %	18.4	30.5	28.1	<0.001
UmA pH <7.20, %	6.4	7.1	6.5	0.723
UmA pH <7.10, %	1.2	1.3	1.3	0.923
UmA pH <7.00, %	0.3	0.1	0.1	0.606

†Chi-square test. Ed, early diagnosed; Eo, early onset; GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; LBW, low birth weight; LGA, large for gestational age; Ld, late diagnosed; Lo, late onset; PTB, preterm birth; SGA, small for gestational age; UmA, umbilical artery.

Table 4 | Risk posed by Ed-GDM and Ld-GDM for each obstetric outcome

	Ed-GDM				Ld-GDM			
	OR	95% CI	aOR	95% CI	OR	95% CI	aOR	95% CI
PTB <37 weeks	1.31	1.00–1.72	1.02	0.73–1.42	1.31	1.08–1.58	1.49	1.21–1.83
PTB <34 weeks	1.28	0.85–1.95	1.04	0.55–1.98	0.56	0.37–0.87	1.02	0.63–1.67
LBW <2,500 g	1.34	1.07–1.68	1.18	0.91–1.53	1.11	0.93–1.32	1.18	0.98–1.41
LBW <1,500 g	1.91	1.19–3.06	1.16	0.54–2.51	0.36	0.17–0.75	0.48	0.20–1.17
LGA	1.58	1.24–2.00	1.09	0.84–1.42	1.90	1.62–2.22	1.57	1.32–1.85
HDP†	3.51	2.75–4.49	2.08	1.51–2.86	2.38	1.94–2.92	1.73	1.36–2.22
Eo-HDP†	6.05	4.17–8.79	1.91	1.01–3.65	3.46	2.46–4.85	1.99	1.24–3.19
Lo-HDP†	2.27	1.59–3.24	1.92	1.29–2.86	2.12	1.64–2.75	1.71	1.27–2.30
HDP with SGA†	2.40	1.19–4.84	1.10	0.35–3.47	0.73	0.30–1.76	0.70	0.26–1.89
Cesarean delivery	1.95	1.66–2.28	1.34	1.13–1.59	1.73	1.55–1.94	1.40	1.24–1.58

The aOR was calculated by logistic regression analysis, after adjusting for maternal age (20–29 years as reference), body mass index before pregnancy (18.5–25.0 kg/m^2 as reference), maternal smoking habit, hypertension at the time of pregnancy, parity (primipara or multipara), maternal education, and use of assisted reproductive technology. †For logistic regression analysis of HDP, we excluded 1168 cases of maternal hypertension at the time of pregnancy, and aOR was calculated by logistic regression analysis, after adjusting for maternal age (20–29 years as reference), body mass index before pregnancy (18.5–25.0 kg/m^2 as reference), maternal smoking habit, parity (primipara or multipara), maternal education, and use of assisted reproductive technology. Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; Ed, early diagnosed; Eo, early onset; GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; LBW, low birth weight; LGA, large for gestational age; Ld, late diagnosed; Lo, late onset; PTB, preterm birth; SGA, small for gestational age.

time of the diagnosis of GDM. As a result, we found clear differences for maternal background before pregnancy and obstetric outcomes among the cases without GDM, with Ed-GDM, and with Ld-GDM. Regarding the maternal background among the three groups, patients who developed Ed-GDM tended to have a higher maternal age, a higher BMI before pregnancy, a higher probability of the pregnancy being conceived using ART, and an increased rate of medical conditions, such as hypertension and PCOS, before pregnancy. Conventional GDM, which corresponds to Ld-GDM in this study, is known to be associated with adverse obstetric outcomes, such as HDP, shoulder dystocia, and macrosomia—defined as birthweight

>4000 g [9]. Ed-GDM, which is diagnosed by the Japanese unique system, is also known to increase the risk of pregnancy-related maternal life-threatening conditions, such as Eo-HDP and Lo-HDP [17,28].

Consensus regarding the appropriate time for a GDM diagnosis during pregnancy has not been reached yet. In women with diabetes risk factors, the American Diabetes Association recommends screening for undiagnosed type 2 diabetes at the first prenatal visit. In pregnant women without a known diabetes diagnosis, it recommends performing GDM testing at 24–28 weeks of gestation [29]. Based on the Hyperglycemia Adverse Pregnancy Outcome Study, new GDM criteria have been proposed by the International Association of Diabetes in Pregnancy Group [30]. These criteria are based on the premise that an early GDM diagnosis before gestational week 24 increases the occurrence of adverse obstetric outcomes, such as the delivery of LGA infants and CS [30]. Early detection of GDM aims to identify women with overt diabetes, which poses a similar risk as undetected preexisting diabetes mellitus because, compared to GDM, overt diabetes increases the risk of adverse obstetric outcomes, such as HDP [31]. The American Diabetes Association clearly states that the International Association of Diabetes in the Pregnancy Group criteria, as well as the diagnostic criteria used in the JSOG and JAOG two-step approach, were not derived from women enrolled in the first half of their pregnancy. Considering this observation, the rationale behind extending the diagnostic criteria to the entire second trimester (13–28 weeks) and selectively excluding the first trimester (<13 weeks) remains elusive. Our findings provide validation for the early screening for GDM among the general population because it could be a potential biomarker for HDP.

In Japan, pregnant women usually undergo a universal screening process for GDM in both early and late pregnancy. As a result, GDM cases in Japan can be divided into two groups: Ed-GDM, diagnosed in early pregnancy, and Ld-GDM, diagnosed in late pregnancy. Using 600 Ed-GDM cases and 881 Ld-GDM cases from 40 institutions, Usami et al. reported that the rates of maternal complications, including HDP (9.3% vs 4.8%, $P < 0.001$) and CS delivery (34.2% versus 32.0%, $P < 0.001$), were higher in the Ed-GDM group than in the Ld-GDM group [13]. However, their retrospective study did not include control subjects and was conducted in large-scale institutions that mainly treat high-risk populations. Therefore, the study conducted by Usami et al. was potentially limited by its participant selection bias and difficulty in identifying control cases. Using a prospective study design, we could include a large number of control cases and calculate the ORs of both Ed-GDM and Ld-GDM for each obstetric outcome. Considering the adverse outcomes among women with Ed-GDM, our findings suggest that GDM screening should be carried out during early pregnancy. The identified differences in the maternal background, such as maternal age, BMI before pregnancy, presence of chronic hypertension or PCOS, and ART pregnancy, among the control, Ed-GDM, and Ld-GDM groups indicated that the Ed-GDM group had cases requiring the greatest attention due to the high risk of adverse obstetric outcomes such as placenta accreta, PTB, and HDP [17,22,23,24].

A strength of the present study is the utilization of data from the first large-scale Japanese birth cohort study conducted by the Japanese government. Thus, the present study can be considered to be representative of the general pregnant population in Japan [17]. Additionally, it included a large number of women without GDM, enabling us to calculate the ORs for various obstetric outcomes. Nevertheless, the present study has potential limitations. First, the data did not include the glycemic conditions, such as the results of the RBG, fasting GCT, and OGTT, that may have affected the obstetric outcomes [32]. Second, we are not aware of any medical interventions in the GDM cases, which might also have affected the obstetric outcomes [33]. Third, although Japanese obstetricians tend to strictly follow the guidelines recommended by the JSOG or JAOG, there was a substantial number of Ld-GDM cases after 30 weeks of gestation, as shown in Figure 2. We considered that the timing of GDM diagnosis depends on the pregnant women's compliance, policy of each hospital or clinic, and clinical symptoms. For example, initially, some cases could be diagnosed as Ld-GDM (screening around 28 weeks of gestation) because of the presence of polyhydramnios or macrosomia. Therefore, further screening should be performed at 30–32 weeks for confirming Ld-GDM. Finally, we could not ascertain whether the glycemic control for GDM was appropriate or comparable between the two GDM groups at the time of delivery.

Japan has a unique and universal screening procedure for the diagnosis of GDM. Consequently, GDM cases were identified as Ed-GDM and Ld-GDM. Using the largest birth cohort study, we identified distinct characteristics with regard to the maternal background and obstetric outcomes, distinguishing the Ed-GDM and Ld-GDM cases. Furthermore, the cases with Ed-GDM, which were diagnosed by the Japanese unique system, had a higher risk of HDP, Eo-HDP, and Lo-HDP. To date, several studies have been conducted to examine the validity of diagnostic criteria, treatment of GDM, preconception care for GDM, and/or short- and long-term prognosis for both the mother and the offspring. The findings of our study provide validation for early screening for GDM because Ed-GDM was found to be associated with adverse obstetric outcomes. Further studies considering the time of GDM onset are warranted.

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DISCLOSURE

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