

Screening methods for gestational diabetes mellitus in Japan in 2018: a retrospective cohort study using a national surveillance questionnaire

Mamoru Morikawa¹⁾, Takashi Sugiyama²⁾, Yuji Hiramatsu³⁾ and Norimasa Sagawa⁴⁾

¹⁾ Department of Obstetrics and Gynecology, Kansai Medical University, Osaka, Japan

²⁾ Department of Obstetrics and Gynecology, Ehime University Graduate School of Medicine, Ehime, Japan

³⁾ Department of Obstetrics and Gynecology, Okayama City Hospital, Okayama, Japan

⁴⁾ Department of Obstetrics and Gynecology, Rakuwakai Otowa Hospital, Kyoto, Japan

Abstract. This study aimed to investigate the relationship between gestational diabetes mellitus (GDM) screening methods and GDM incidences. In 2018, a national questionnaire was administered at 231 institutions (56.6%) of all 408 perinatal medical centers in Japan. Of 100,485 women, 2,982 (3.0%) were diagnosed with GDM during their first pregnancy period (FPP) and 7,289 (7.3%) were diagnosed with GDM during their middle pregnancy period (MPP). The proportion of women diagnosed with GDM during FPP and MPP using 95 mg/dL as the cutoff value (CV) for random plasma glucose (PG) at FPP (4.3% and 9.2%) was significantly higher than that of women diagnosed with GDM using 100 mg/dL as the CV for random PG (2.7% and 6.9%, $p < 0.0001$, respectively). Compared with women screened for GDM using “random PG and random PG,” women who were screened for GDM using “random PG and 50-g glucose challenge test (GCT)” had a significantly higher incidence of GDM (6.6% versus 8.9%, $p < 0.0001$). Using random PG and 50-g GCT, the incidence of GDM among women diagnosed at MPP using a CV of 95 mg/dL at FPP was significantly higher than that of women diagnosed using a CV of 100 mg/dL (16.5% versus 7.8%: $p < 0.0001$). While, using “random PG and random PG,” the incidences of GDM among women were similar between institutions using a CV of 100 mg/dL and those using a CV of 95 mg/dL at FPP (6.7% versus 6.9%: $p = 0.3581$). This study showed random PG as a first-step screening method in MPP may overlook women with GDM.

Key words: Gestational diabetes mellitus, Glucose challenge test, Random plasma glucose level, Cutoff value, Two-step method

THE CURRENT JAPANESE CRITERIA for diagnosing gestational diabetes mellitus (GDM) were established in 2010. These criteria modified those of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) with the goal of developing universal diagnosis criteria [1]. The IADPSG criteria [2] were created from the results of the HAPO study [3] and have been recommended by the World Health

Organization [4]. However, the HAPO study did not include Japanese pregnant women. Thus, whether IADPSG criteria are in fact applicable to Japanese pregnant women has not been clarified.

Since the introduction of the IADPSG criteria, in Japan, the top priority for GDM screening is to screen for GDM in both the early pregnancy period (EPP) and middle pregnancy period (MPP) [1]. The policy of screening for GDM early in the pregnancy period in Japan is unique in the international obstetrical practice. Thus, in this study, we evaluate whether the current Japanese methods for diagnosing GDM is ideal for Japanese pregnant women. We investigated all problems involved in the present Japanese screening method for GDM during EPP and MPP by using a national surveillance questionnaire.

Submitted Feb. 15, 2022; Accepted May 16, 2022 as EJ22-0072

Released online in J-STAGE as advance publication Jul. 1, 2022

Correspondence to: Mamoru Morikawa, Department of Obstetrics and Gynecology, Kansai Medical University, Shinmachi 2-5-1, Hirakata City, Osaka 573-1010, Japan.

E-mail: mmamoru@hirakata.kmu.ac.jp

Abbreviations: DM, diabetes mellitus; EPP, early pregnancy period; GCT, glucose challenge test; GDM, gestational diabetes mellitus; GWs, gestational weeks; HFD, heavy-for-dates; IADPSG, International Association of Diabetes and Pregnancy Study Groups; JSOG, Japan Society of Obstetrics and Gynecology; MPP, middle pregnancy period; OGTT, oral glucose tolerance test; PG, plasma glucose; PMCs, perinatal maternal centers.

Methods

Study design

We conducted this study in 2019 to collect detailed data on GDM in 2018. Questionnaires were sent to all 408 perinatal maternal centers (PMCs) with neonatal intensive care units certified by the Japanese Ministry of Health and Labor as of December 31, 2018. The questionnaires were constructed according to the recommendations for the management of GDM in Japan.

Furthermore, the questionnaires were administered to determine the relationship between the number of Japanese pregnant women with GDM in 2018 and the protocols for managing GDM at each institution.

The questionnaires comprised the following items: (1) presence/absence of full-time diabetologist(s), internist(s), and pediatrician(s) in the institutions, (2) the types of items used to screen for GDM during EPP and MPP (random PG, fasting PG, 50-g GCT, and others), (3) the incidence of low- and high-risk GDM, (4) the types of items used in treating GDM (self-measurements of blood glucose + dietetic therapy, insulin therapy, referral to a diabetologist(s) or internist(s), (5) the incidence of heavy-for-dates infants or intra-uterine fetal deaths.

Screening of GDM

According to the Japanese recommendation, the screening for GDM should be performed using two-step testing twice in the first and second trimesters. The clinical sequences are as follows: (1) for all pregnant women in the first trimester, a value greater than the threshold of the random plasma glucose (PG) level of ≥ 95 mg/dL (5.3 mmol/L) or ≥ 100 mg/dL (5.55 mmol/L), which is allowed to be determined in each institution, is regarded as a positive screening test result, and a 75-g oral glucose tolerance test (OGTT) should then be performed, and (2) for all pregnant women excluding those diagnosed with GDM in the first trimester at 24–28 gestational weeks (GWs), a PG level of ≥ 140 mg/dL (7.8 mmol/L) 1 h after a 50-g glucose challenge test (GCT) or a value greater than the threshold of the random PG level of ≥ 95 mg/dL (5.3 mmol/L) or ≥ 100 mg/dL (5.55 mmol/L), which is allowed to be determined in each institution, is regarded as a positive screening test result, and a 75-g OGTT should then be performed at 24–28 GWs (two-step strategy) [1]. In this study, two institutions had answered that their method of screening for GDM consisted of either random PG or fasting PG, and we classified these as random PG.

In this study, the women with GDM were divided into two groups: (1) low risk, including women with values of 1 positive point on the 75-g OGTT, and (2) high risk, including women with values of 2 or 3 positive points on

the 75-g OGTT. According to the recommendation in Japan, pregnant women are diagnosed with “overt diabetes in pregnancy” if any of the following four criteria is met: (1) fasting PG level ≥ 126 mg/dL (7.0 mmol/L); (2) HbA1c level $\geq 6.5\%$, expressed as the National Glycohemoglobin Standardization Program value; (3) definite diabetic retinopathy; and (4) random PG level ≥ 200 mg/dL (11.1 mmol/L) with any of the first three criteria or 2-h PG level ≥ 200 mg/dL with any of the first three criteria [1]. In Japan, pregnant women diagnosed with overt diabetes in pregnancy are managed similarly to pregnant women with diabetes mellitus (DM).

In Japan, the 75-g OGTT at 6–12 weeks postpartum is recommended to all women with GDM as well as those diagnosed with overt diabetes in pregnancy to assess the degree of glucose intolerance under the nonpregnant condition [1].

Treatment for GDM

In the dietetic therapy of GDM, the PG target levels are <95 mg/dL (5.3 mmol/L) in the early morning after fasting, <100 mg/dL (5.6 mmol/L) before meals, and <120 mg/dL (6.7 mmol/L) at 2 h after meals [1]. In Japan, no medications except for insulin are recommended for treating pregnant women whose PG level measured through the self-monitoring of blood glucose (SMBG) is greater than the target PG levels [1].

Statistical analysis

We used JMP Pro (version 16.0; SAS Institute Inc., Cary, NC, USA) to perform the statistical analyses. Fisher's exact test was used to compare categorical data. In all analyses, $p < 0.05$ indicated statistical significance.

Ethical approval

This study was conducted with the approval of the Institutional Review Board of Hokkaido University Hospital (No. 018-0336).

Results

Participants

We received responses from 231 PMCs (56.6% of the total questionnaires mailed). Of the 231 PMCs, 180 institutions (77.9%) employed full-time diabetologist(s). A total of 181 institutions (78.4%) responded with the case numbers of the incidence, treatment, and neonatal outcomes of GDM. We received results of 101,949 women who gave birth in 2018.

GDM screening method

Of 231 PMCs, 219 (94.8%) had selected random PG, 10 (4.3%) had selected fasting PG, and 2 (0.9%) had

selected 50-g GCT as the screening items of GDM during the EPP at 8 to 13 GWs. In particular, of 231 PMCs, 169 (73.2%) selected 100 mg/dL, 36 (15.6%) selected 95 mg/dL, and 14 (6.1%) selected “others” as the cutoff value for random PG.

During the MMP at 24–28 GWs, 131 (56.7%) institutions selected random PG, 98 (42.4%) selected 50-g GCT, and 9 (3.9%) selected fasting PG as the GDM screening items. Especially, of the 131 institutions that selected random PG, 113 (86.3%) used 100 mg/dL, 6 (4.6%) 95 mg/dL, and 12 (9.2%) “others” as the cutoff value for random PG.

Of the 231 PMCs, the main patterns of the screening items selected during EPP and MMP were “random PG and random PG” (56.3%) or “random PG and 50-g GCT” (38.1%). Among the institutions selecting “others” (5.6%), five institutions selected “fasting PG and fasting PG” two institutions selected “50-g GCT and 50-g GCT,” and two institutions selected “fasting PG and random PG” or “random PG and fasting.”

The frequencies of the institutions selecting “random PG and random PG” were similar between the 75 general PMCs and 156 local PMCs (49.3% versus 59.6%, $p = 0.1578$). Furthermore, the frequencies of the institutions selecting “random PG and random PG” and “random PG and 50-g GCT” were similar between the 180 PMCs with full-time diabetologist(s) and 51 PMCs without them (53.9% versus 64.7%, $p = 0.2106$; 41.1% versus

27.5%, $p = 0.1018$).

Proportion of women with GDM according to the pattern of GDM screening

Fig. 1 shows the incidences of women with GDM by patterns of GDM screening.

In the present study, the incidence of GDM was 10.2% (10,730/105,022).

Of all 105,022 pregnant women screened for GDM at MPP, 100,485 (95.7%) were treated at institutions using random PG at FPP.

Table 1 shows the incidences of women with GDM according to the cutoff values of random PG at FPP (100 mg/dL, 95 mg/dL, and others). Of 100,485 women, 2,982 (3.0%) women were diagnosed with GDM at FPP, whereas 7,289 (7.3%) women were diagnosed with GDM at MPP. Thus, of the pregnant women screened for GDM with random PG at FPP and diagnosed with GDM at FPP or MPP, 29.0% (2,982/10,271) were diagnosed with GDM at FPP. The proportion of women diagnosed with GDM at FPP and MPP with a cutoff value of 95 mg/dL for random PG at FPP (767/17,707; 4.3%, 1,624/17,707; 9.2%) was significantly higher than that of women diagnosed with GDM with a cutoff value of 100 mg/dL (2,168/78,895 (2.7%, $p < 0.0001$) and 5,466/78,895 (6.9%, $p < 0.0001$), respectively).

Table 2 shows the differences in women with GDM according to three main patterns of the screening items.

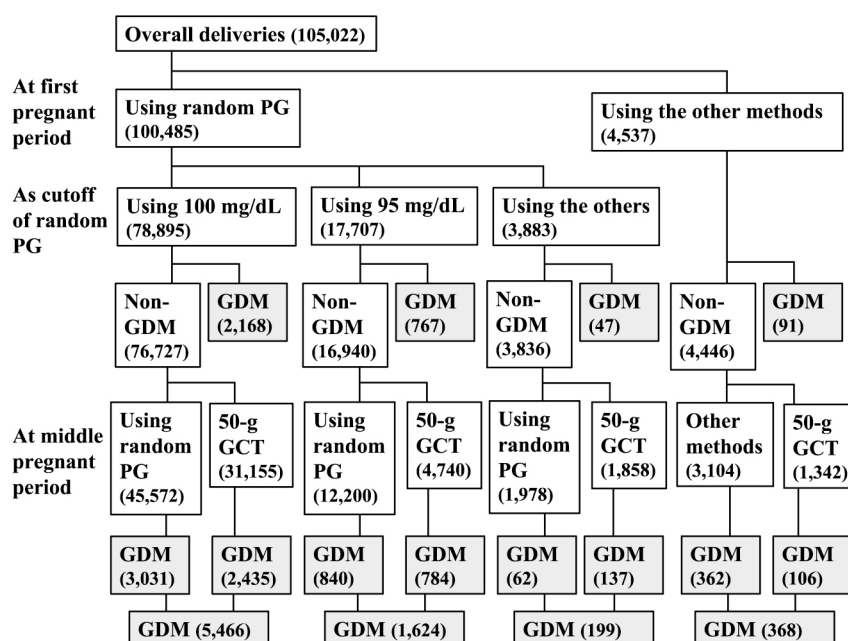


Fig. 1 The incidences of women with GDM by patterns of GDM screening.

GDM, gestational diabetes mellitus; PG, plasma glucose; GCT, glucose challenge test, GWs, gestational weeks.

At FPP, 8–13 GWs and at MPP, 24–28 GWs.

Table 1 Proportion of women with gestational diabetes mellitus (GDM) according to the cutoff values of random PG at first pregnancy period

	Random PG at first pregnancy period				Other methods (<i>n</i> = 4,537)	<i>p</i> value
	Cutoff of random PG at first pregnancy period					
	Overall (<i>n</i> = 100,485)	100 mg/dL (a) (<i>n</i> = 78,895)	95 mg/dL (b) (<i>n</i> = 17,707)	Others (c) (<i>n</i> = 3,883)		
GDM diagnosed at first pregnancy period	2,982 (3.0%)	2,168 (2.7%)	767 (4.3%)	47 (1.2%)	91 (2.0%)	<0.0001 <0.0001 <0.0001
GDM diagnosed at middle pregnancy period	7,289 (7.3%)	5,466 (6.9%)	1,624 (9.2%)	199 (5.1%)	468 (10.3%)	<0.0001 <0.0001 <0.0001
Overall	10,271 (10.2%)	7,634 (9.7%)	2,391 (13.5%)	246 (6.3%)	451 (9.9%)	<0.0001 <0.0001 <0.0001

(a) measured random PG at 8–13 and 24–28 GWs; (b) measured random PG at 8–13 GWs and performed 50-g GCT at 24–28 GWs; (c) everything except a and b, included “fasting PG” and “50-g GCT” at first pregnancy period.

GDM, gestational diabetes mellitus; PG, plasma glucose; GCT, glucose challenge test; GWs, gestational weeks.

Table 2 Proportion of women with gestational diabetes mellitus (GDM) according to the pattern of GDM screening at middle pregnancy period

	Overall (<i>n</i> = 101,949)	Random PG and random PG (a) (<i>n</i> = 59,750)	Random PG and 50-g GCT (b) (<i>n</i> = 37,753)	Others (c) (<i>n</i> = 4,446)	<i>p</i> value a versus b a versus c b versus c
GDM diagnosed at middle pregnancy period					
Overall	7,657 (7.5%)	3,933 (6.6%)	3,356 (8.9%)	368 (8.3%)	<0.0001 <0.0001 0.1734
Low risk	4,696 (4.6%)	2,423 (4.1%)	2,060 (5.5%)	213 (4.8%)	0.3720 [†]
High risk	2,961 (2.9%)	1,510 (2.5%)	1,296 (3.4%)	155 (3.5%)	<0.0001 <0.0001 0.8533

* excluded women with GDM diagnosed at first pregnancy period, [†] analyzed by Fisher’s exact test (3 × 2).

(a) measured random PG at 8–13 and 24–28 GWs; (b) measured random PG at 8–13 GWs and performed 50-g GCT at 24–28 GWs; (c) everything except a and b, included “fasting PG and fasting PG,” “fasting PG and random PG,” “fasting PG and 50-g GCT,” and “50-g GCT and 50-g GCT.”

GDM, gestational diabetes mellitus; PG, plasma glucose; GCT, glucose challenge test; GWs, gestational weeks; OGTT, oral glucose tolerance test; Low-risk GDM, women with values of 1 positive point on 75-g OGTT; High-risk GDM, women with values of 2 or 3 positive points on 75-g OGTT.

Of all 101,949 pregnant women, the incidences of women with GDM treated at institutions using “random PG and random PG” (3,933/59,750; 6.6%) was significantly lower than those in the “random PG and 50-g GCT” (3,356/37,753; 8.9%, $p < 0.0001$) and “others” (368/4,446; 8.3%, $p < 0.0001$). In particular, the incidences of women with high-risk GDM treated at institutions using the “random PG and random PG” method (1,510/59,750; 2.5%) was significantly lower those at institutions using “random PG and 50-g GCT”

(1,296/37,753; 3.4%, $p < 0.0001$) and “others” (156/4,446; 3.5%, $p < 0.0001$).

Table 3 shows the proportion of women diagnosed with GDM according to the cutoff values of random PG at FPP and MPP in the institutions using “random PG and random PG” (2,865/3,933; 72.8%, $p < 0.0001$) and “others” (253/368; 68.8%, $p < 0.0001$). On the other hand, the frequencies of women treated. Of 47,572 women using 100 mg/dL as the cutoff value for random PG at FPP in “random PG and random PG,” all women

Table 3 Proportion of women with gestational diabetes mellitus according to the cutoff values of random PG at first and middle pregnancy periods at the institutions using “random PG and random PG”

	Cutoff of random PG at first pregnancy period				a versus b p value
	Overall (n = 59,750)	100 mg/dL (a) (n = 45,572)	95 mg/dL (b) (n = 12,200)	Others (c) (n = 1,978)	
Cutoff of random PG at middle pregnancy period					
100 mg/dL (d)	6.6% (3,717/56,118)	6.7% (3,031/45,572)	6.5% (686/10,546)	No case	0.5865
95 mg/dL (e)	9.3% (154/1,654)	No case	9.3% (154/1,654)	No case	—
Others (f)	3.1% (62/1,978)	No case	No case	3.1% (62/1,978)	—
d versus e p value	<0.0001	—	<0.0001	—	

(c) Others included 90, 92, and 110 mg/dL; (f) Others included 90, 92, and 110 mg/dL.

Random PG was measured in all women at 8–13 and 24–28 GWs.

GDM, gestational diabetes mellitus; PG, glucose challenge test; GWs, gestational weeks.

Table 4 Proportion of women with gestational diabetes mellitus according to the cutoff values of random PG at first pregnancy period at the institutions using “random PG and random PG”

	Cutoff of random PG at first pregnancy period				p value
	Overall (n = 59,750)	100 mg/dL (a) (n = 45,572)	95 mg/dL (b) (n = 12,200)	Others (c) (n = 1,978)	a versus b a versus c b versus c
GDM diagnosed at middle pregnancy period					
Overall	3,933 (6.6 %)	3,031 (6.7%)	840 (6.9%)	62 (3.1%)	0.3581 <0.0001 <0.0001
Low risk	2,423 (4.1%)	1,875 (4.1%)	520 (4.3%)	28 (1.4%)	0.4666 <0.0001 <0.0001
High risk	1,510 (2.5%)	1,156 (2.5%)	320 (2.6%)	34 (1.7%)	0.5915 0.0017 0.0168

* excluded women with GDM diagnosed at first pregnancy period; (c) Others included 90, 92, and 110 mg/dL.

Random PG was measured in all women at 8–13 and 24–28 GWs.

GDM, gestational diabetes mellitus; PG, plasma glucose; GWs, gestational weeks; OGTT, oral glucose tolerance test; Low-risk GDM, women with values of 1 positive point on 75-g OGTT; High-risk GDM, women with values of 2 or 3 positive points on 75-g OGTT.

used 100 mg/dL as the cutoff values for random PG at MPP. On the other hand, of 12,200 women using 95 mg/dL as the cutoff value for random PG at FPP in “random PG and random PG,” 10,546 women (86.4%) used 100 mg/dL as the cutoff value for random PG at MPP. Among the women at institutions using 95 mg/dL as the cutoff value for random PG at FPP, the incidence of GDM at MPP at institutions a cutoff value of 95 mg/dL at MPP (154/1,654; 9.3%) was significantly higher than that at institutions using a cutoff value of 100 mg/dL (686/10,546; 6.5%, $p < 0.0001$). Moreover, among the women at institutions using a cutoff value of

100 mg/dL for random PG at FPP, the incidence of GDM was similar to that at institutions using a cutoff value of 95 mg/dL (3,031/45,572, 6.7% versus 686/10,546; 6.5%, $p = 0.5865$).

Table 4 shows the differences in the proportion of women with GDM diagnosed at MPP according to the cutoff values of random PG at FPP (100 mg/dL, 95 mg/dL, and others) at institutions using “random PG and random PG.” Among the women at institutions using “random PG and random PG,” the proportion of women diagnosed with GDM was similar between the institutions using 100 mg/dL and 95 mg/dL as the cutoff

values for random PG at FPP, respectively (3,031/45,572; 6.7% *versus* 840/12,200; 6.9%; $p = 0.3581$).

Table 5 shows the differences in the proportion of women with GDM diagnosed at MPP according to the cutoff values of random PG at FPP (100 mg/dL, 95 mg/dL, and others) at institutions using “random PG and 50-g GCT.” Among the women at institutions using “random PG and 50-g GCT,” the proportion of women with GDM diagnosed at MPP at institutions using a cutoff value of 95 mg/dL for random PG at FPP was significantly higher than that of women with GDM diagnosed at MPP at institutions using a cutoff value of 100 mg/dL (784/4,740; 16.5% *versus* 2,435/31,155; 7.8%; $p < 0.0001$).

Discussion

The results of the present study emphasize four points: (1) At FPP, a cutoff value of 95 mg/dL for random PG might be a more sensitive method to screen GDM than a value of 100 mg/dL (Table 1); (2) “Random PG and 50-g GCT” might be a more sensitive method for screening GDM than “random PG and random PG” (Table 2); (3) Among the women screened for GDM using “random PG and random PG,” a cutoff value of 95 mg/dL for random PG at FPP and MPP, respectively, might be a more sensitive method for screening GDM (Tables 3 and 4); and (4) Among the women screened for GDM using “random PG and 50-g GCT,” the women without GDM

who were screened with a cutoff value of 95 mg/dL for random PG at FPP might include more women with hyperglycemia than those screened with a cutoff value of 100 mg/dL for random PG at FPP (Table 5).

To the best of our knowledge, this is the first Japanese study to analyze the difference in the present screening methods of institutions for GDM preferred in PMCs between women suspected of having GDM using random PG during the EPP plus random PG during the MPP and women suspected of having GDM using random PG during the EPP plus 50-g GCT during the MPP.

In the present study, among women with GDM in PMCs selecting “random PG and random PG,” the incidence of GDM was significantly lower than those in PMCs selecting “random PG and 50-g GCT” (Table 2). The levels of PG using “random PG” would change by the intervals from the last meal to the blood examination of PG level. Some levels of PG using “random PG” would be fasting PG with the lower than the cutoff value of “random PG” to screen GDM. On the other hand, all levels of PG determined using “50-g GCT” were measured at 1 h after the tolerance of 50-g glucose. “Random PG and random PG” has more data dispersion than “random PG and 50-g GCT.” Thus, some pregnant women with GDM might be missed in PMCs selecting “random PG and random PG.” In particular, the proportion of women at a high risk for GDM in PMCs selecting “random PG and random PG” was significantly lower than that in PMCs selecting “random PG and 50-g GCT

Table 5 Proportion of women with gestational diabetes mellitus according to the cutoff values of random PG at first pregnant period in the institutions using “Random PG and 50-g GCT”

	Cutoff of random PG at first pregnant period				<i>p</i> value
	Overall (<i>n</i> = 37,753)	100 mg/dL (a) (<i>n</i> = 31,155)	95 mg/dL (b) (<i>n</i> = 4,740)	Others (c) (<i>n</i> = 1,858)	a <i>versus</i> b a <i>versus</i> c b <i>versus</i> c
GDM diagnosed at middle pregnant period					
Overall	3,356 (8.9 %)	2,435 (7.8%)	784 (16.5%)	137 (7.4%)	<0.0001 0.4896 <0.0001
Low risk	2,060 (5.5%)	1,491 (4.8%)	484 (10.2%)	85 (4.6%)	<0.0001 0.6787 <0.0001
High risk	1,296 (3.4%)	944 (3.0%)	300 (6.3%)	52 (2.8%)	<0.0001 0.5712 <0.0001

* excluded women with GDM diagnosed at first pregnant period; (c), Others included 90 mg/dL, 92 mg/dL, and 110 mg/dL.

All women were measured random PG at 8–13 GWs and measured random PG at 24–28 GWs. GDM, gestational diabetes mellitus; PG, plasma glucose; GCT, glucose challenge test. GWs, gestational weeks; OGTT, oral glucose tolerance test. Low-risk GDM, women with values of 1 positive point on the 75-g OGTT. High-risk GDM, women with values of 2 or 3 positive points on the 75-g OGTT.

(Table 2). It is important to determine the best screening methods for detecting women with high-risk GDM because these women have a high risk of recurrent GDM during a subsequent pregnancy [5]. The guidelines for obstetrical practice in Japan published by Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) state that “random PG and 50-g GCT” has been the best method to screen GDM according to the cost performance and the efficacy to diagnose GDM [1]. Based the results of this study, we regard “random PG and 50-g GCT” as the more sensitive selecting method for screening women with GDM considering the high proportion of women with GDM. However, from an economic perspective, as the cost performance per pregnant woman is higher, “random PG and random PG” would be a better option to screen women with GDM. Furthermore, 50-g GCT needs the cost of oral 50-g glucose (test agent) and time/effort to administer the test agent to a pregnant woman (examinee) and perform blood examination at 1 h after administering the test agent.

In the present study, between the institutions with or without full-time diabetologists, the frequencies of “random PG and random PG” and “random PG and 50-g GCT” did not vary. Thus, the full-time diabetologists appear to be not involved in the selection of patterns of the screening items of GDM during EPP and MPP.

Almost all of the institutions selecting random PG as the screening method for GDM selected 100 mg/dL as the cutoff value for random PG. However, according to the worldwide criteria for diagnosing DM or overt diabetes in pregnancy, a cutoff value of 100 mg/dL for random PG might not be appropriate in screening women with GDM because the cutoff values to diagnose GDM using 75-g OGTT include 92 mg/dL for fasting PG but not 100 mg/dL for random PG [1, 2]. According to this hypothesis, the use of random PG could possibly miss some women with GDM. Thus, the 50-g GCT test might be better than random PG as a first-step screening method for GDM at MPP. However, women undergoing screening for GDM with the 50-g GCT are required to remain in the institution for 1 h.

Table 6 shows the methods for GDM screening in the main guidelines. There has been no unified view in Europe or the United States regarding the methods for diagnosing GDM. Currently, the best method of GDM screening has not remained delineated by some systematic review or meta-analysis [6, 7]. In United States, some guidelines provide different criteria for diagnosing GDM, such as using the one-step method or two-step method and positive cutoff values of 50-g GCT or/and 75-g OGTT. Using the criteria of the American Diabetes Association for the one-step method of the 75-g OGTT,

the incidence rate of GDM was 18% [8]. In a previous report, the incidence of GDM using the one-step method was significantly higher than that using the two-step method, but there was no difference in maternal and neonatal outcomes between the methods [9]. However, in another previous report, the incidence rate of preeclampsia or infants with macrosomia in women without GDM assessed with the two-step method was significantly higher than in those assessed with the one-step method [10]. In the United Kingdom, the National Institute for Health and Care Excellence proposed its own criteria in its guideline due to a significant increase in GDM in countries in which the IADPSG criteria were introduced and the low cost-effectiveness of GDM screening using the IADPSG criteria [11]. However, using the new criteria outlined by the NICE guideline, 3,000 to 4,000 women with GDM are overlooked (decreased) every year in the United Kingdom [12]. The guideline of the Society of Obstetricians and Gynaecologists Canada used both the original cutoff value of the 75-g OGTT in the two-step method and the cutoff value of the 75-g OGTT in the one-step method from the IADPSG criteria [13]. The guideline of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists uses the original cutoff value of the 75-g OGTT in the two-step method [14]. A study in northern India, which used the World Health Organization criteria defined in 1999 to classify women as having hyperglycemia per the modified IADPSG criteria, reported that the proportion of women with GDM increased from 9% to 35% [15]. In Japan, in our previous cohort study that used the Japan Society of Obstetrics and Gynecology (JSOG) criteria to classify women as having hyperglycemia per the modified IADPSG criteria (“random PG and 50-g GCT” in the two-step method by the JSOG), there was a 2.7-fold increase (from 2.4% to 6.6%) in women with GDM [16]. In another previous cohort study in Japan, the researchers reported a 4.5-fold increase in women with GDM: from 2.9% using the JSOG criteria to 13% at institutions using “random PG and 50-g GCT” in the two-step method by the JSOG [17]. In the present study, the incidence of GDM was 10.2% in the institutions selecting “random PG and 50-g GCT” in the two-step method by the JSOG (Table 1).

In 2010, the methods of screening GDM in Japan were recommended by the Japanese Society of Diabetes and Pregnancy and JSOG. The methods were determined according to the data reported in a previous study based on the data of Japan Assessment of GDM Screening, which was modified to the IADPSG criteria of GDM using 75-g OGTT [18, 19]. All 2,839 pregnant women with DM underwent one of four methods as follows: (1) PG at 1 h using random 50-g GCT, (2) random PG, (3)

Table 6 Screening criteria for gestational diabetes mellitus in the main guidelines

	First-step test	Cutoff of GCT (mg/dL)	Second-step test	Plasma glucose levels (mg/dL)				Criteria for GDM	Approximately rate of detecting (%)
				Fasting	60 min	120 min	180 min		
IADPSG criteria [2]	75-g OGTT	—	—	≥92	≥180	≥153	—	≥1 point	
WHO recommendation [4]	50-g GCT	≥140	75-g OGTT	≥92	≥180	≥153	—	≥1 point	
United States (ACOG, ADA)									
One-step strategy (revised IADPSG)	75-g OGTT	—	—	≥92	≥180	≥153	—	≥1 point	20–30
Two-step strategy									
ADA [8]	50-g GCT	≥140	75-g OGTT	≥92	≥180	≥153	—	≥1 point	18
Carpenter and Coustan criteria	50-g GCT	≥130 ≥135 ≥140	100-g OGTT	≥95	≥180	≥155	≥140	≥2 points	10–20
National Diabetes Data Group criteria	50-g GCT	≥130 ≥135 ≥140	100-g OGTT	≥105	≥190	≥165	≥145	≥2 points	5–10
United Kingdom (NICE guideline) [12]	75-g OGTT	—	—	≥101	—	≥140	—	Either	4–10
Canada (CDA) [13]									
One-step strategy	75-g OGTT	—	—	≥92	≥180	≥153	—	≥1 point	18
Two-step strategy	50-g GCT [†]	≥140	75-g OGTT	≥95	≥191	≥162	—	≥1 point	10
Australia and New Zealand (ADIPS, RANZCOG) [14]	50-g GCT	≥140	75-g OGTT	≥99	—	≥144	—	≥1 point	15
Japan (JSOG) [1]	50-g GCT [‡]	≥140	75-g OGTT	≥92	≥180	≥153	—	≥1 point	7–10

[†] Plasma glucose levels of ≥200 mg/dL are diagnosed as GDM without 75-g OGTT.

[‡] Either of 50-g GCT or random plasma glucose levels of ≥95 mg/dL or ≥100 mg/dL.

GDM, gestational diabetes mellitus; GCT, glucose challenge test; OGTT, oral glucose tolerance test; IADPSG, International Association of Diabetes and Pregnancy Study Group; WHO, World Health Organization; NICE, National Institute for Health and Care Excellence; ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; NIH, National Institute of Health; CDA, Canadian Diabetes Association; ADIPS, Australasian Diabetes in Pregnancy Society; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; JSOG, Japan Society of Obstetrics and Gynecology.

PG at 2 h after meal, and (4) fasting PG as the first step during the first trimester and the MPP (at 24–28 GW). Furthermore, all pregnant women without GDM diagnosed in the first trimester underwent 75-g OGTT as the second step during the first trimester and the MPP (at 24–28 GW). Based on the results of this study, a random PG level of ≥95 mg/dL in the first trimester and a PG level of ≥140 mg/dL at 1 h using random 50-g GCT during the MPP were the more sensitive screening methods for detecting GDM considering the high proportion of women with GDM and are clinically acceptable for detecting a pregnant woman with GDM. However, eventually, from the viewpoints of primary institutes, a random PG level of ≥95 mg/dL or ≥100 mg/dL in the first

trimester, a PG level of ≥140 mg/dL at 1 h using random 50-g GCT, or a random PG level of ≥100 mg/dL during the MPP are recommended as the standard methods/cutoffs for screening women with GDM in Japan.

As described in the guidelines for obstetrical practice in Japan, the Japanese two-step method to screen GDM (“random PG and 50-g GCT” or “random PG and random PG”) represent the cost-effective method used in GDM screening [1]. According to the Japanese criteria for diagnosing GDM, which were modified according to the IADPSG criteria, the incidence of GDM in Japan is approximately 10%. Some Japanese obstetricians might consider this ratio to be too high. The SMBG and insulin therapy might lead to a significant economic stress

among pregnant women diagnosed with GDM. The increase in the incidence of pregnant women diagnosed with GDM might burden the Japanese Medicaid (public medical insurance system) in the short term. However, women who experience GDM during pregnancy reportedly have a higher tendency to exhibit glucose intolerance with advancing age. Thus, early detection of the risk of later development of DM prevents the onset of DM and its further development to metabolic syndrome. Thus, in the long term, the detection of GDM during pregnancy serves as a pre-emptive measure to reduce medical and economic expense. In pregnant women with mild glucose intolerance during their pregnancy, lifestyle changes might prevent the onset of DM and metabolic syndrome. If they develop DM and require insulin therapy in the future, they would have to pay approximately 15 million JPY (120,000–150,000 USD) for it in their lifetime, but this can be avoided by providing sufficient care for pregnant women with mild glucose intolerance during their pregnancy. This would financially benefit both the medical institution and patients.

This study has some limitations. The number of patients was small. As of December 31, 2018, Japan had 406 PMCs, and only 56.6% (231/408) participated in the present study. Furthermore, we were able to obtain the results of the case numbers with GDM from only 44.3% (181/408) of PMCs. In addition, because the present study was based on a survey questionnaire, detailed data could not be obtained. We had simplified the questionnaire items to achieve high recovery rates. Furthermore, we could not perform a secondary collection of data to obtain detailed information regarding women with GDM because of the ethical rules of each institution. Thus, we could not obtain any data on women with GDM aged ≥ 35 years with a history of previous GDM and obesity (BMI ≥ 25). In particular, we could not determine the incidence of maternal and neonatal complications among women with GDM, respectively. Thus, a future multicenter cohort study with detailed data is needed to improve the maternal and fetal outcomes of women with GDM. Furthermore, further research with future prospective case–control studies (women with GDM *versus* women without GDM or prospective randomized studies might be therefore required.

Conclusion

The women screened for GDM using “random PG and 50-g GCT” had significantly higher incidences of GDM than women screened for GDM using “random PG and random PG.” The first step of the Japanese two-step screening for GDM in MPPs, either random PG or 50g-GCT, might not be sufficient to screen for GDM in

Japanese pregnant women. Multi-central randomized prospective cohort studies are needed to propose a modification of the diagnostic criteria based on scientific evidences.

Funding

The study (first author) was supported by a grant from Manpei Suzuki Diabetes Foundation.

Acknowledgments

The authors thank Enago (www.enago.jp) for the English language review. The authors thank the 231 institutions who responded to the questionnaires in this study.

Disclosure

Authors declare no Conflict of Interests for this article.

Contributors

MM conceived and designed the study. TS, YH, and NS evaluated and revised the study. MM conducted the data analysis and drafted the initial version of the manuscript. All authors contributed to data interpretation, critically revised the manuscript, had full access to the data in the study, and took responsibility for data integrity and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that persons who did not meet the criteria have been omitted.

Availability of Data and Materials

The data analyzed in the current study are not publicly available to protect the privacy and anonymity of the participants.

Ethics Approval and Consent to Participate

The institutional review board of Hokkaido University Hospital (No. 019-0336) approved the present study.

Competing Interests

The authors declare no conflict of interest regarding the publication of this study.

Consent for Publication

The authors had shown the information of this study to

the patients and controls for the publication of this study in the website of Hokkaido University Hospital.

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