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Predictive factors for postpartum glucose intolerance in women with gestational diabetes mellitus

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24 Running title: Postpartum glucose intolerance in GDM

25

Abstract

Aim:

The aim of this prospective cohort study was to evaluate the risk factors for postpartum glucose intolerance (GI) in women with gestational diabetes mellitus (GDM).

Method:

A total of 140 women with GDM were enrolled. Of these, 115 underwent a 75-g oral glucose tolerance test (OGTT) at 12 weeks after delivery. Clinical factors and parameters in the antepartum 75-g OGTT associated with postpartum GI were evaluated by logistic regression analyses.

Results:

Twenty-two (19.1%) of the 115 women with GDM developed postpartum GI. The univariate and multivariable logistic regression analyses revealed that low oral disposition index (DI) was a risk factor for postpartum GI (OR, 0.2; 95% CI, 0.04–0.7; $p<0.05$), and that no clinical factors were associated with postpartum GI.

Conclusions:

41 Lower oral DI on the antepartum 75-g OGTT may be a useful marker for identifying
42 GDM women who are at high risk for postpartum GI.

43

44 **Key Words:**

45 Gestational diabetes mellitus, glucose intolerance, oral disposition index, postpartum,
46 75-g oral glucose tolerance test

47

Introduction

Pregnant women with gestational diabetes mellitus (GDM) have an increased risk of glucose intolerance (GI). A systematic review and meta-analysis has demonstrated that women with GDM have a 7.4-fold increased risk of developing type 2 diabetes mellitus (DM) after delivery compared with those without GDM [1]. Prenatal prediction of postpartum GI may allow clinicians to identify pregnant women who required long-term follow-up to assess the development of type 2 DM. The American Diabetes Association (ADA) recommend screening for GI, including type 2 DM, in women with GDM at 4–12 weeks after delivery, using 75-g oral glucose tolerance test (OGTT) [2].

We have reported that, in women with GDM, the low insulinogenic index (II) levels on the antepartum 75-g OGTT is a risk factor for developing GI during the early postpartum period [3]. However, the previous study evaluated only parameters of the antepartum 75-g OGTT, and did not evaluate any clinical factors, such as body mass index (BMI) prior to pregnancy, weight gain during pregnancy, and family history of DM, etc.

This prospective cohort study aimed to assess predictive clinical factors and laboratory parameters in the antepartum 75-g OGTT for GI during the early postpartum

65 period among women with GDM.

66

67 **Material and Methods**

68 ***Study design and participants***

69 This prospective cohort study enrolled women with singleton pregnancies who were
70 diagnosed with GDM by the 75-g OGTT during pregnancy and delivered at the Kobe
71 University Hospital from January 2011 to December 2018. The study followed the
72 principles of the Declaration of Helsinki, and it was approved by the Institutional
73 Review Board of the Kobe University Hospital (reference number B200228). Written
74 informed consent was obtained from all participants.

75 ***Procedures***

76 All pregnant women who visited or were referred to the Kobe University Hospital
77 underwent screening for GDM both at 10–14 and 24–28 gestational weeks (GW).
78 Pregnant women who had casual blood glucose (BG) levels of ≥100 mg/dL
79 (5.5 mmol/L) at 10–14 or 24–28 GW, or those who had 1-hr BG levels of ≥140 mg/dL
80 (7.8 mmol/L) on 50-g glucose challenge tests (GCT) at 24–28 GW, or those with risk

81 factors for GDM, including obesity, family history of DM, past history of macrosomia,
82 presence of persistent glycosuria, polyhydramnios, and suspected heavy for date (HFD)
83 underwent the 75-g OGTT. According to the International Association of Diabetes and
84 Pregnancy Study Groups (IADPSG) criteria [4], the diagnosis of GDM is made when any
85 of the following are met: fasting BG (FBG) ≥92 mg/dL (5.1 mmol/L), 1-hr BG
86 ≥180 mg/dL (10.0 mmol/L), or 2-hr BG ≥153 mg/dL (8.5 mmol/L). BG and
87 immunoreactive insulin (IRI) levels at fasting, 0.5, 1, 1.5, and 2 hr after the oral
88 ingestion of 75-g glucose were also measured, and the total area under the curve (AUC)
89 of glucose and insulin were calculated by the trapezoid method [5].

90 As an insulin resistance parameter, the homeostasis model assessment-insulin
91 resistance (HOMA-IR) (=FBG (mg/dL) × fasting IRI (FIRI) (μU/mL) / 405) was used.
92 HOMA-β (=360 × FIRI (μU/mL) / [FBG (mg/dL) - 63]) and insulinogenic index (II) (=
93 [0.5-hr IRI (μU/mL) - FIRI (μU/mL)] / [0.5-hr BG (mg/dL) - FBG (mg/dL)]) were
94 calculated for evaluating the insulin secretory capacity of pancreatic β cells. The oral
95 disposition index (DI), which represents the compensation of pancreatic β cells for
96 insulin resistance, was calculated as the product of the Matsuda index of insulin
97 sensitivity and the ratio of the AUC of insulin to the AUC of glucose during the OGTT [6].

The Matsuda index was calculated using the following formula: $10^4/\sqrt{}$ (FGB × FIRI × mean BG during 75-g OGTT × mean IRI during 75-g OGTT) [7].

All pregnant women diagnosed with GDM were referred to diabetologists in the Kobe University Hospital and underwent self-monitoring of blood glucose (SMBG) and diet therapy. If FBG levels exceeded 100 mg/dL, or 2-hr BG levels exceeded 120 mg/dL in SMBG regardless of diet therapy, an insulin therapy was started. Insulin doses were adjusted to achieve both FBG levels of <100 mg/dL and 2-hr BG levels of <120 mg/dL.

All pregnant women with GDM were instructed to undergo a 75-g OGTT at 12 weeks after delivery. Using the WHO's 1999 criteria [8], DM was diagnosed by either FBG levels of ≥126 mg/dL (7.0 mmol/L) or 2-hr BG levels of ≥200 mg/dL (11.1 mmol/L). IFG was diagnosed by FBG levels of ≥110 mg/dL (6.1 mmol/L), and IGT was diagnosed by 2-hr BG levels of ≥140 mg/dL (7.8 mmol/L). GI was defined by the presence of DM, impaired fasting glucose (IFG), or impaired glucose tolerance (IGT). FBG levels of <110 mg/dL (6.1 mmol/L) and 2-hr BG levels of <140 mg/dL (7.8 mmol/L) were identified as normal.

Statistical analysis

Clinical characteristics were compared between pregnancies with GI during the early postpartum period and pregnancies without them. Differences between the two groups were analyzed using the Mann-Whitney *U* test, Fisher exact test, and $\chi 2$ test. *P* values <0.05 were considered statistically significant. The stepwise approach was used to evaluate clinical factors and parameters in the antepartum 75-g OGTT associated with GI during the early postpartum period. To avoid overfitting in multivariable logistic regression analyses, the number of variables in the final model of multivariable analyses was restricted to a maximum of 10% of the case number. Variables with the lowest and the second-lowest *P* values in univariate logistic regression analyses were subjected to the final model of multivariable logistic regression analyses, and variables with *P* values <0.05 in the final model of multivariable logistic regression analyses were determined as clinical factors and parameters in the antepartum 75-g OGTT associated with GI during the early postpartum period in women with GDM. All statistical analyses were performed using the SPSS software, version 19 (SPSS Inc., Chicago, Illinois).

Results

A flowchart of the subjects in this prospective cohort study is shown in **Figure 1.** Of

2,370 pregnant women with singleton pregnancies who underwent screening for GDM at the Kobe University Hospital, 140 (5.9%) were diagnosed with GDM from January 2011 to December 2018. The indications for the antepartum 75-g OGTT in the 140 pregnant women with GDM were as follows: casual BG level ≥100 mg/dL and/or 1-hr BG level on a 50-g glucose challenge tests ≥140 mg/dL (n=99); casual BG level ≥100 mg/dL (n=13); suspicion of polyhydramnios and/or HFD on ultrasound examinations during pregnancy (n=10); and presence of other risk factors of GDM, including a history of GDM, obesity, and persistent glycosuria (n=18). Twenty-five of the 140 women with GDM refused to receive a 75-g OGTT at 12 weeks after delivery. Therefore, 115 women with GDM were included in the analyses of risks for GI during the early postpartum period.

Twenty-two of the 115 (19.1%) pregnant women with GDM had GI at 12 weeks after delivery, including one, two, and 19 women with DM, IFG and IGT, respectively.

Table 1 shows the clinical characteristics and laboratory data in antepartum 75-g OGTT of the subjects. The group of GDM women with postpartum GI (GI group) had a significantly higher 0.5-hr BG ($p<0.05$) and lower oral DI ($p<0.01$) than the group

without postpartum GI (non-GI group).

Univariate logistic regression analyses demonstrated that FBG (OR, 1.0; 95% CI, 1.0–1.1; p=0.04), 0.5-hr BG (OR, 1.0; 95% CI, 1.0–1.1; p=0.02) and oral DI (OR, 0.1; 95% CI, 0.03–0.5; p<0.01) were associated with the occurrence of GI during the early postpartum period in women with GDM (**Table2**). The final model of multivariable logistic regression analyses of the 2 factors with the lowest P value in univariate analyses revealed that oral DI (OR, 0.2; 95% CI, 0.04–0.7; p<0.05) was an independent factor associated with GI during the early postpartum period (**Table2**).

Discussion

This study used IADPSG criteria for diagnosing GDM [4], and 140 of the 2,370 (5.9%) pregnant women were diagnosed with GDM. Because medians of the prevalence of GDM in Japan were reported to be 2.8%–13.0% [9], the prevalence of GDM in this study was thought to be valid. In addition, the incidence of GI during the early postpartum period in women with GDM (19.1%) was also comparable to those (16.7%–36.6%) in previous studies [3,10,11].

To the best of our knowledge, this prospective cohort study of pregnant women with GDM, for the first time, assessed both the clinical factors and parameters in the antepartum 75-g OGTT associated with GI during the early postpartum period by logistic regression analyses using a stepwise approach, and revealed that lower oral DI is an independent risk factor for postpartum GI.

A previous retrospective study also reported that oral DI in the antepartum 75-g OGTT was useful for identifying women with GDM at high risk of postpartum GI [12]. In addition, it was reported that among the Japanese-American adults, including males and non-pregnant women, the low oral DI was predictive of developing DM in the future [13]. DI represents a hyperbolic relationship between insulin secretion and insulin sensitivity [6,14]. Therefore, this parameter represents the insulin secretory capacity of pancreatic β cells adjusted for insulin sensitivity [13]. An adequate insulin secretory response of pancreatic β cells adapting to changes in insulin sensitivity might be significant for the maintenance of normal glucose tolerance during the postpartum period. Pregnant women with low oral DI on the antepartum 75-g OGTT may be at high risk not only for GI during the early postpartum period, but also for DM in the future.

On the other hand, previous retrospective studies in Japan demonstrated that

low II and II/fasting IRI ratio in the antepartum 75-g OGTT were associated with postpartum GI in patients with GDM [10,15]. Our previous prospective cohort study of 72 pregnant women with GDM, including 12 with postpartum GI, also demonstrated that a low II in the antepartum 75-g OGTT was an independent risk factor for developing GI during the early postpartum period [3]. In the present study, the levels of 0.5-h BG in antepartum 75-g OGTT in GI group were significantly higher than those in non-GI group, and oral DI in GI group was significantly lower than those in non-GI group. Whereas, there were no significant differences in FBG, FIRI, 0.5-h IRI and II between two groups. In addition, the numbers of women with GDM and postpartum GI in the present study (140 GDM and 22 postpartum GI) are almost two times larger than those in our previous study (72 GDM and 12 postpartum GI). The increase in the number of patients may lead to an increase in the number of GDM women with more impaired pancreatic β cell function, and therefore oral DI, but not II, may be selected as a risk factor for GI during the early postpartum period.

Previous studies evaluated associations between maternal clinical or laboratory findings of antepartum OGTT and postpartum GI. They demonstrated that higher FBG levels, higher AUC of glucose, lower fasting insulin concentration, decreased β cell

function, higher BMI prior to pregnancy, and family history of DM were risk factors for postpartum GI [16,17]. In addition, obesity and β cell function impairment were reported to be associated with type 2 DM at early postpartum [18]. In our present study, there were no clinical factors associated with postpartum GI, and oral DI was only associated with it. In these previous studies, not the new IADPSG criteria but previous one for GDM were used, and the race of the participants and the follow-up duration were different from those of our present study. Furthermore, not oral DI but HOMA-β and insulin secretion/insulin resistance disposition index calculated by 100-g OGTT were evaluated as indicators of pancreatic β cell function in these studies. These facts may influence the differences in results between previous studies and our study. In addition, postpartum GI in women with GDM may be more closely associated with β cell function impairment rather than the clinical background or characteristics of the patients.

There are some potential limitations in this study. The indications for 75-g OGTT in this study varied among the participants, therefore the GW at diagnosis of GDM varied, and the facts may influence the results of this study. In addition, the scale of the study was not large enough. Therefore, further studies are required to confirm the conclusions of this study.

This prospective cohort study demonstrated that a low oral DI on the antepartum 75-g OGTT was an independent risk factor for GI during the early postpartum period in women with GDM. Measurements of oral DI in pregnant women with GDM may be useful for identifying GDM women at high risk for DM in the future.

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Conflict of Interest

The authors declare no conflict of interest.

232

233 **Author Contributions**

234 All listed authors meet the criteria for authorship and have contributed to the acquisition
235 of data, supervision, manuscript writing and manuscript review.

236

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Figure legends

Figure 1. Flow diagram for the study participants

During the study period, 2370 pregnant women underwent screening for GDM and were enrolled in this study. Thirteen of the 251 (5.2%) pregnant women, who underwent 75-g oral glucose tolerance test (OGTT) due to a casual BG ≥100 mg/dL (5.5 mmol/L) at 10–14 gestational weeks (GW), were diagnosed with GDM. Ninety-nine of the 508 (19.5%) pregnant women, who underwent 75-g OGTT due to a casual BG ≥100 mg/dL (5.5 mmol/L) and/or 1-hr BG ≥140 mg/dL (7.8 mmol/L) in the 50-g glucose challenge test (GCT) at 24–28 GW, were diagnosed with GDM. Ten of the 83 (12.0%) pregnant women, who underwent 75-g OGTT due to the presence of polyhydramnios and/or heavy for date (HFD) on ultrasound examinations, were diagnosed with GDM. Eighteen of 54 (33.3%) pregnant women, who underwent 75-g OGTT due to risk factors for GDM, were diagnosed with GDM. Total one hundred forty of the 2370 (5.9%) pregnant women screened for GDM by our study protocol were diagnosed with GDM. Finally, one hundred fifteen women with GDM underwent75-g OGTT during the early postpartum period, and 22 of them (19.1%) were diagnosed with glucose intolerance (GI).

Abbreviations: BG, blood glucose; GW, gestational week; OGTT, oral glucose

316 intolerance test; GDM, gestational diabetes mellitus; DM, diabetes mellitus; HFD,
317 heavy for date; GI, glucose intolerance; IFG, impaired fasting glucose; IGT, impaired
318 glucose tolerance.

319

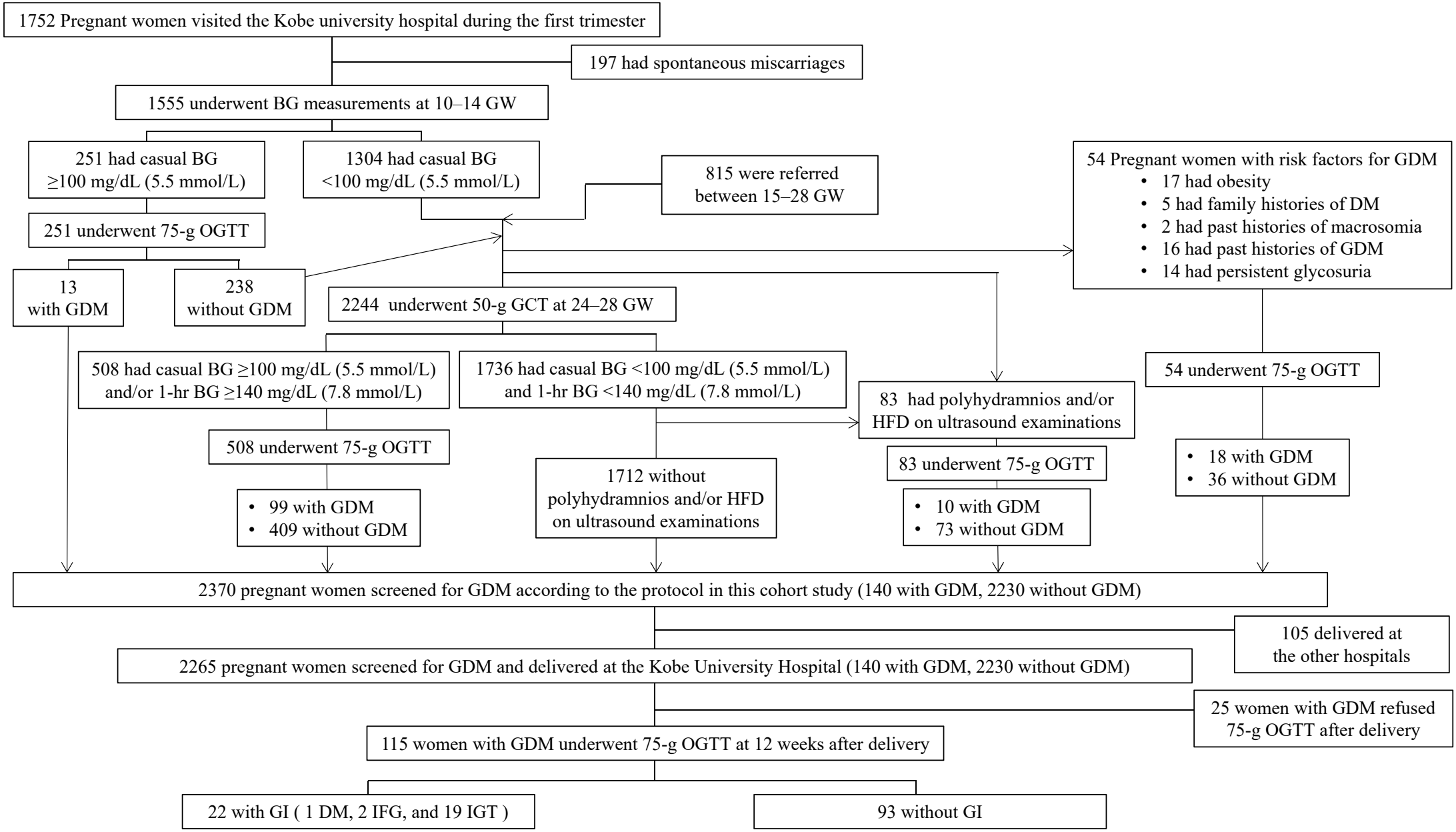
1752 Pregnant women visited the Kobe university hospital during the first trimester
197 had spontaneous miscarriages
1555 underwent BG measurements at 10–14 GW
251 had casual BG ≥100 mg/dL (5.5 mmol/L)
1304 had casual BG <100 mg/dL (5.5 mmol/L)
815 were referred between 15–28 GW
54 Pregnant women with risk factors for GDM
• 17 had obesity
• 5 had family histories of DM
• 2 had past histories of macrosomia
• 16 had past histories of GDM
• 14 had persistent glycosuria
251 underwent 75-g OGTT
13 with GDM
238 without GDM
2244 underwent 50-g GCT at 24–28 GW
508 had casual BG ≥100 mg/dL (5.5 mmol/L) and/or 1-hr BG ≥140 mg/dL (7.8 mmol/L)
1736 had casual BG <100 mg/dL (5.5 mmol/L) and 1-hr BG <140 mg/dL (7.8 mmol/L)
83 had polyhydramnios and/or HFD on ultrasound examinations
54 underwent 75-g OGTT
508 underwent 75-g OGTT
1712 without polyhydramnios and/or HFD on ultrasound examinations
83 underwent 75-g OGTT
• 18 with GDM
• 36 without GDM
• 99 with GDM
• 409 without GDM
• 10 with GDM
• 73 without GDM
2370 pregnant women screened for GDM according to the protocol in this cohort study (140 with GDM, 2230 without GDM)
105 delivered at the other hospitals
2265 pregnant women screened for GDM and delivered at the Kobe University Hospital (140 with GDM, 2230 without GDM)
25 women with GDM refused 75-g OGTT after delivery
115 women with GDM underwent 75-g OGTT at 12 weeks after delivery
22 with GI (1 DM, 2 IFG, and 19 IGT)
93 without GI

Table 1. Clinical characteristics and laboratory data of the subjects.

Variable	postpartum GI n=22	non-postpartum GI n=93	*P* values
Clinical findings of pregnant women			
Age (years)	37 (29–42)	37 (21–45)	0.9
Gravidity	2 (1–5)	2 (1–10)	0.3
Parity	1 (0–3)	0 (0–4)	0.3
BMI prior to pregnancy (kg/m^2)	24.1 (16.4–33.9)	22.3 (16.4–34.7)	0.1
Weight gain during pregnancy (kg)	5.0 (-9.0–13.2)	7.2 (-5–22.7)	0.1
Family history of DM	31.8%	38.7%	0.7
GW at diagnosis of GDM	28 (16–32)	29 (11–38)	0.4
Insulin therapy during pregnancy	36.4%	40.9%	0.9
Polyhydramnios	4.7%	4.3%	1.0
GW at delivery	38 (32–40)	38 (31–41)	0.1
Birth weight (g)	2865 (2064–3850)	2938 (1580–3934)	0.6
Birth weight > 90th percentile	4.7%	9.6%	0.7
Birth weight < 10th percentile	4.7%	11.8%	0.5
Diagnosis of HDP	27.2%	11.8%	0.1
Parameters in antepartum 75-g OGTT			
FBG (mg/dl)	84 (76–138)	82 (55–112)	0.2
0.5-hr BG (mg/dl)	155 (108–199)	145 (86–192)	<0.05
1-hr BG (mg/dl)	178 (123–226)	176 (120–235)	0.5
1.5-hr BG (mg/dl)	174 (123–222)	171 (119–249)	0.5
2-hr BG (mg/dl)	163 (122–206)	159 (86–248)	0.2
Fasting IRI (μU/ml)	8 (4–26)	7 (2–35)	0.2
0.5-hr IRI (μU/ml)	47 (20–115)	46 (7–243)	0.6
1-hr IRI (μU/ml)	58 (22–109)	61 (27–307)	0.3
1.5-hr IRI (μU/ml)	58 (18–146)	64 (20–340)	0.5
2-hr IRI (μU/ml)	69 (20–150)	75 (15–501)	0.6
AUC-glucose (mg min/dl)	18735 (15345–23820)	18180 (14880–23970)	0.2
AUC-insulin (μU min/ml)	6713 (2205–12105)	6420 (2835–30060)	0.6
AUC-insulin/glucose	0.3 (0.1–0.6)	0.3 (0.2–1.8)	0.3
HbA1c (%)	5.4 (4.8–6.2)	5.4 (4.9–6.2)	0.7
HOMA-IR	1.7 (0.8–8.9)	1.4 (0.4–7.8)	0.2
HOMA-β	140 (60–220)	127 (-1080–504)	0.8
Insulinogenic index	0.5 (0.2–1.5)	0.7 (0.0–3.6)	0.1
Oral disposition index	1.4 (0.5–2.2)	1.7 (0.7–3.5)	<0.01

Data are expresses as the median (range) or percentage. Abbreviations: GI, glucose intolerance; BMI, body mass index; DM, diabetes mellitus; GW, gestational week; GDM, gestational diabetes mellitus; HDP, hypertension disorder during pregnancy; OGTT, oral glucose tolerance test; FBG, fasting blood glucose; BG, blood glucose; IRI, immunoreactive insulin; AUC, area under the curve; HOMA, homeostasis model assessment; IR, insulin resistance.

Table 2. Results of univariate and multivariate logistic regression analyses.

Variable	Univariate analysis			Multivariable analysis		
	Odds ratio	95% CI	*P* values	Odds ratio	95% CI	*P* values
Clinical findings of pregnant women						
Age (years)	1.0	0.9–1.1	0.7			
Gravidity	0.8	0.6–1.2	0.3			
Parity	1.3	0.8–2.1	0.4			
BMI prior to pregnancy (kg/m^2)	1.1	1.0–1.2	0.2			
Weight gain during pregnancy (kg)	0.9	0.8–1.0	0.1			
Family history of DM	0.7	0.3–2.0	0.5			
GW at diagnosis of GDM	1.0	0.9–1.1	0.7			
Insulin therapy during pregnancy	0.8	0.3–2.2	0.7			
Polyhydramnios	1.1	0.1–10.0	1.0			
GW at delivery	0.8	0.6–1.0	0.1			
Birth weight (g)	1.0	0.9998–1.0	0.7			
Birth weight > 90th percentile	0.4	0.1–3.7	0.5			
Birth weight < 10th percentile	0.4	0.04–2.9	0.3			
Diagnosis of HDP	2.8	0.9–8.7	0.1			
Parameters in antepartum 75-g OGTT						
FBG (mg/dl)	1.0	1.0–1.1	0.04			
0.5-hr BG (mg/dl)	1.0	1.0–1.1	0.02	1.0	1.0–1.05	0.2
1-hr BG (mg/dl)	1.0	1.0–1.02	0.8			
1.5-hr BG (mg/dl)	1.0	1.0–1.03	0.5			
2-hr BG (mg/dl)	1.0	1.0–1.03	0.2			
Fasting IRI (μU/ml)	1.0	1.0–1.1	0.3			
0.5-hr IRI (μU/ml)	1.0	0.98–1.0	0.4			
1-hr IRI (μU/ml)	1.0	0.98–1.0	0.2			
1.5-hr IRI (μU/ml)	1.0	0.99–1.0	0.4			
2-hr IRI (μU/ml)	1.0	0.98–1.0	0.3			
AUC-glucose (mg min/dl)	1.0	1.0–1.005	0.1			
AUC-insulin (μU min/ml)	1.0	0.9998–1.0	0.3			
AUC-insulin/glucose	0.2	0.01–2.4	0.2			
HbA1c (%)	1.2	0.3–5.6	0.8			
HOMA-IR	1.3	0.9–1.7	0.1			
HOMA-β	1.0	0.997–1.0	1.0			
Insulinogenic index	0.3	0.1–1.3	0.1			
Oral disposition index	0.1	0.03–0.5	<0.01	0.2	0.04–0.7	<0.05

Abbreviations: CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; GW, gestational week; GDM, gestational diabetes mellitus; HDP, hypertension disorder during pregnancy; OGTT, oral glucose tolerance test; FBG, fasting blood glucose; BG, blood glucose; IRI, immunoreactive insulin; AUC, area under the curve; HOMA, homeostasis model assessment; IR, insulin resistance.